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Retinal Measurements by Spectral Domain Optical Coherence Tomography:

Normative Data and Associations in Adolescents

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Table of Contents

PREFACE

This thesis describes the candidate's work on the measurement of retinal parameters in adolescents using OCT. These retinal measurements were obtained from the older cohort of the Sydney Myopia Study (SMS, older cohort was predominantly 12 years of age) and all participants of the Sydney Adolescent Vascular and Eye Study (SAVES, age range 10 to 19 years). In the SMS time domain OCT technology was used, and these data were used to perform analysis of associations of retinal thickness. The SAVES examined retinal parameters with spectral domain OCT, and these data were used to determine the normative distribution of retinal parameters in a normal adolescent population, as well as assess associations of these parameters.

The first chapter of this thesis reviews existing publications of OCT measurements of retinal parameters in normal eyes. It provides normative data from these publications and comments on previous findings of variations of retinal thickness with age, ethnicity, axial length and myopia. Chapter 2 outlines the methodology of the thesis, encompassing the protocols for the SMS and the SAVES. Chapters 3 and 4 provide Cirrus HD-OCT measured retinal nerve fiber layer for a mixed ethnic population of young adults and children from the Sydney metropolitan area. Chapters 5 and 6 provide data and analysis for macular parameters. Together these four chapters are the first to describe normative spectral domain OCT values in such a large cohort, as well as the first studies to provide comprehensive childhood data using this technology.

Chapter 7 provides side-by-side macular thickness data for four distinct ethnic groups, and chapter 8 is a novel study describing ethnic differences in the association of retinal parameters with axial length. Chapters 9, 10 and 11 investigate how perinatal factors are associated with changes in retinal parameters in adolescence. Chapter 12 concludes the thesis with a brief discussion and the implications of the major findings. The exam booklet and the two questionnaire booklets for SAVES are included in the appendix.

Executive Summary

The **objectives** of this thesis were to:

1. Determine the distributions and develop a normative database for spectral domain OCT measured macular and optic disc parameters in healthy children and young adults
2. Investigate the association of gender and ethnicity with macular and optic disc parameters
3. Determine if OCT parameters are associated with AL and SER
4. Determine if prematurity and low birth weight are associated with macular and RNFL parameters
5. Investigate if an association exists between maternal diabetes and retinal parameters measured by OCT

The Sydney Childhood Eye Study comprises 3 separate studies, including the Sydney Myopia Study (SMS), the Sydney Paediatric Eye Disease Study (SPEDS) and the Sydney Adolescent Vascular and Eye Study (SAVES). SMS and SAVES were carried out in 2003 to 2005 and 2009 to 2011, respectively and conducted ocular exams on two cohorts of school children. Data from the school year 7 SMS children (predominantly 12 years old) and SAVES were utilised in the preparation of this thesis. During SMS 2367 Year 7 children were examined. During SAVES 2818 participants underwent examination.

As part of both of these studies Optical Coherence Tomography (OCT) scanning was performed. The first commercially available OCT machines applied time domain technology.

The newer spectral domain OCT allows faster scanning, with higher scanning density and higher scanning resolution than time domain OCT. In the SMS the time domain Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) was used, and in SAVES the spectral domain Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California, USA) was used.

Major findings from this thesis

1. **Normative values and associations of spectral domain OCT RNFL and optic disc measurements in young adults and children**

In the SAVES older cohort (aged 16 to 19 years) the mean value of average RNFL for this population was 99.4 ± 9.7μm with a range of 61 to 138μm. The RNFL was thickest at the inferior (128.5 ± 17.2μm) and superior (124.8 ± 15.9μm) quadrants. The average RNFL was normally distributed based on the Kolmogorov-Smirnov test. The mean disc area in this population was 1.98 ± 0.38mm^2 with a mean rim area of 1.50 ± 0.30 mm^2 and a mean CDR of 0.44 ± 0.18. CDRs ranged from 0.05 to 0.80. The temporal RNFL was found to be thinner in males as compared with females in data adjusted for age, height, AL and ethnicity (P = 0.0008). Females had smaller disc areas, cup volumes and cup disc ratios (all $P \leq 0.004$). Individuals of Caucasian (European) ethnicity had thinner RNFL parameters than East Asian children (all $P \leq 0.005$, data adjusted for age, sex, height, AL and clustered sampling) except for the nasal quadrant which was significantly thicker in Caucasians (P < 0 .0001). The optic disc rim area was smaller (mean difference 0.08mm^2, P = 0.0007) and optic disc area was greater (mean difference 0.14mm^2, P < 0.0001) in East Asian than in Caucasian children resulting in overall greater cup disc ratio in East Asian (mean difference 0.11, P < 0.0001). Increased AL and more severe myopia were associated with decreased RNFL thickness (P_{trend} < 0.0001).

In the younger cohort of the SAVES study (age range 10 – 15 years) the average RNFL was 100.3 ± 10.2μm. The pattern of relative quadrant thickness was similar to the older cohort. The disc area in this population had a mean value of 2.01 ± 0.38mm^2 and the rim area was 1.57 ± 0.32mm^2. The cup disc area ratio ranged from 0.05 to 0.82. There was no inter-sex difference in average RNFL; however girls had a significantly thinner nasal quadrant RNFL than boys in analysis adjusted for age, height, AL and ethnicity. Boys had marginally larger disc area (mean difference 0.07mm^2, P = 0.002) and cup volume (mean difference 0.02mm^3, P = 0.01) compared with girls, in analysis adjusted for age, height, AL and ethnicity. Average RNFL was thicker in East Asian children compared with white children (mean difference 6.1μm, CI 4.0 – 8.1, P < 0.0001, data adjusted for age, sex, height, AL and clustered sampling). Disc area was greater in East Asians compared with Caucasian, however rim area was reduced, resulting in greater cup to disc ratio in the East Asian children (mean difference 0.10, P < 0.0001).

AL was found to be negatively associated with average RNFL thickness measured by Cirrus HD-OCT (regression coefficient β = -2.63 μm/mm, P < 0.0001), while SER was positively associated with average RNFL (β = 1.45 μm/D, P<0.0001). Height had a weak positive association with average RNFL when adjusting for age, sex, axial length and ethnicity (β = 0.09 μm/cm, P = 0.04). Weight did not show any association with average RNFL thickness when adjusting for age, sex, height, axial length and ethnicity (P = 0.91).

2. **Normative values and associations of spectral domain OCT macular measurements in young adults and children**

In the older cohort of SAVES the mean thicknesses were 255 ± 20μm for the central macula, 322 ± 15μm for the inner macula and 280 ± 13μm for the outer macula. Males had greater macular parameters, with greatest intersex difference being found in the central macula, in analysis adjusted for covariates (mean difference 10.2 μm, $P < 0.0001$). Macular parameters were thicker in Caucasians than East Asians in both the central and inner macula (mean difference 11.9μm and 4.7μm, respectively, $P < 0.0001$ for both).

For the younger group (age range 10 – 15 years) the central macula had a mean thickness of 254 ± 19μm, the average inner thickness was 322 ± 14μm and average outer thickness was 280 ± 13μm. Relationships between girls and boys and between East Asians and Caucasians were similar to those seen in the older cohort.

AL was positively associated with central macular thickness in the older cohort (regression coefficient $\beta = 1.2$ μm/mm, $P = 0.03$) but not in the younger cohort. In both age groups AL was negatively associated with inner and outer macular thickness and SER was positively associated with inner and outer macular thickness.

3. **Ethnic differences in macular thickness**

In the 12 year old SMS cohort, the differences in Stratus OCT macular parameters between the four largest ethnic groups was assessed. Data were adjusted for age, gender, height, AL and cluster-sampling. The central macula was thicker in Caucasian children than East Asian, South Asian and Middle Eastern children (mean differences 9.0 μm, 12.1 μm and 6.5 μm respectively, all $P <0.0001$). The inner macula was thicker in the Caucasian compared with

East Asian and South Asian children (mean difference 3.0μm, P = 0.005 and 8.1μm, P < 0.0001). The inner macula was thinner in South Asian children compared with East Asian (mean difference 5.1μm, P = 0.002) and Middle Eastern children (5.5μm, P = 0.004). The average outer macula was significantly thicker in Caucasian than Middle Eastern and South Asian children (P =0.03 and P < 0.0001), respectively.

4. Impact of ethnicity on the correlation of retinal parameters with AL

In the SMS older cohort, using Stratus OCT, differences in the correlations of AL with retinal parameters amongst ethnic groups were found. Larger AL correlations were found for East Asians for average RNFL, inferior RNFL, outer macula and macular volume (r = -0.25, -0.36, -0.31, -0.35 and -0.31 respectively, P<0.001) than Caucasian children (r = -0.14, -0.20, -0.12, -0.17 and -0.13 respectively, P<0.001). A positive correlation of AL with temporal RNFL was found only in the South Asian and East Asian ethnic groups. A positive correlation of central macula and foveal minimum thickness with AL was found for Caucasian children.

5. Retinal thickness in offspring of diabetic pregnancies

Children from diabetic pregnancies had significantly thinner inner (264.9μm vs. 270.2μm, P = 0.007) and outer (231.9μm vs. 238.6μm, P = 0.0001) macular thickness and macular volume (6.75mm^3 vs. 6.92mm^3, P = 0.0003) compared with children from non-diabetic pregnancies. However, central macular thickness, foveal minimum thickness and RNFL parameters were not significantly different between the two groups.

6. **Impact of perinatal factors on retinal parameters measured by Stratus OCT**

Children with low birth weight (<2500g) had a thinner mean RNFL (98.2µm vs. 103.5µm P<0.0001) and a thicker mean foveal minimum (164.3µm vs. 158.5µm, P = 0.004) compared to children of normal birth weight (2500 – 4000g). With increasing birth weight, average RNFL thickness increased (mixed model coefficient β=2.97µm/kg, P<0.0001) and foveal minimum thickness decreased (β=-2.16µm/kg, P = 0.008). Children born before 32 weeks gestation had significantly thicker mean foveal minimum and central macular thickness (205.5µm vs. 193.4µm, P = 0.001) measurements compared to children born after 37 weeks gestation.

7. **Impact of prematurity on Cirrus HD-OCT measured macular parameters**

The central macula in those born at ≤32 weeks gestation was significantly greater than those born after 37 weeks (266.3µm vs. 251.7 µm, P=0.0007). The average cube thickness and average outer thickness were smaller in those born at ≤32 weeks gestation compared to those born at ≥37 weeks (P= 0.03 and 0.02 respectively). Similarly the cube volume was smaller in the ≤32 weeks gestation compared to those born at ≥37 weeks (P = 0.04).

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Candidate's Contributions

The thesis topics were jointly developed by the candidate and Professor Paul Mitchell. The candidate was directly involved in managing the Sydney Adolescent Vascular Study (SAVES) serving as Chief Medical Officer for the study. The candidate supervised study staff, transported and set up equipment, and examined participants in the study. The candidate dealt with all eye examination related concerns of participants and parents. The candidate managed the administrative staff involved in contacting schools and participants. The candidate gave presentations on eye anatomy and physiology to students at participating schools. The candidate assisted Professor Paul Mitchell in reporting examination findings to study participants. The candidate supervised data entry and data cleaning for the study. The candidate performed all literature review, oversaw statistical analysis and interpreted data for all material in this thesis and wrote the first draft for the thesis and associated publications.

Publications and Presentations

Published Articles

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3. **Tariq YM,** Pai A, Li H, Afsari S, Gole GA, Burlutsky G, Mitchell P. Prematurity is associated with foveal thickening. *Investigative Ophthalmology and Visual Science.* 2011;52:1709-1715

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15. **Tariq YM**, Li H, Burlutsky G, Mitchell P. Retinal Nerve Fiber Layer and Optic Disc Measurements by Spectral Domain OCT: Normative Values and Associations in Young Adults. *Eye.* 2012;26, 1563-1570

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2. **Tariq YM**, Samarawickrama C, Huynh SC, Burlutsky G, Mitchell P. Associations Between Axial Length and Spherical Equivalent Refraction with Macular and Retinal Nerve Fibre Layer Parameters. *Clinical and Experimental Ophthalmology.* 2009; 37(Suppl 1): A89 – A90.

3. **Tariq YM,** Samarawickrama C, Pai A, Burlutsky G, Mitchell P. Ethnic Differences in the Relationship of Axial Length with Macular and Retinal Nerve Fiber Layer Parameters. *Investigative Ophthalmology and Visual Science* 2010; 51: E-Abstract 1009

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1. Associations between Axial Length and Spherical Equivalent Refraction with Macular and Retinal Nerve Fiber Layer Parameters. *Westmead Association Hospital Week Research Symposium,* Sydney 2009 (poster)

2. Ocular Biometric Asymmetry in Adolescents. *Royal Australian and New Zealand College of Ophthalmologists 41st Annual Scientific Congress,* Brisbane 2009 (poster)

3. Associations between Axial Length and Spherical Equivalent Refraction with Macular and Retinal Nerve Fibre Layer Parameters. *Royal Australian and New Zealand College of Ophthalmologists 41st Annual Scientific Congress,* Brisbane 2009 (poster)

4. Ethnic Differences in the Relationship of Axial Length with Macular and Retinal Nerve Fiber Layer Parameters. *Association for Research and Vision in Ophthalmology Annual Meeting,* Fort Lauderdale, Florida 2010 (poster)

5. Association of Birth Parameters with OCT Measured Retinal Parameters. *Royal Australian and New Zealand College of Ophthalmologists 42nd Annual Scientific Congress,* Adelaide 2010 (paper)

6. Retinal thickness is decreased in offspring of diabetic pregnancies. *Royal Australian and New Zealand College of Ophthalmologists 42nd Annual Scientific Congress,* Adelaide 2010 (poster)

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8. Variation of Macular Thickness by Ethnicity Measured by Stratus OCT in Children. *Asia Association for Research and Vision in Ophthalmology,* Singapore 2011 (poster)

9. Ocular Associations of Low Birth Weight and Prematurity in 12-year-old Children. *Asia Pacific Academy of Ophthalmology Congress,* Sydney 2011 (paper)

10. Macular, Retinal Nerve Fibre Layer and Optic Disc Parameters Measured by Spectral Domain OCT in Normal Adolescent Eyes. *Association for Research and Vision in Ophthalmology 2011 Annual Meeting,* Fort Lauderdale, Florida 2011 (poster)

11. Spectral Domain OCT Measured Retinal Nerve Fiber Layer and Optic Disc Parameters in Children: Normative Data and Associations. *Royal Australian and New Zealand College of Ophthalmologists 43rd Annual Scientific Congress,* Canberra 2011(poster)

List of Tables

List of Figures

Abbreviations

ABS	Australian Bureau of Statistics
ACD	Anterior Chamber Depth
AL	Axial length
BMI	Body mass index
CDR	Cup Disc ratio
CI	Confidence interval
D	Dioptre
ETDRS	Early Treatment Diabetic Retinopathy Study
HRT	Heidelberg Retinal Tomography
K-S	Kolomogorov-Smirnov
LogMAR	Logarithm of the minimum angle of resolution
NHMRC	National Health and Medical Research Council
OCT	Optical Coherence Tomography
RNFL	Retinal nerve fibre layer
ROP	Retinopathy of prematurity
SAVES	Sydney Adolescent Vascular and Eye Study
SER	Spherical equivalent refraction
SMS	Sydney Myopia Study
SPEDS	Sydney Paediatric Eye Disease Study

Introduction

Spectral domain OCT is currently the most advanced commercially available application of OCT technology. It allows faster scanning and higher resolution images than time domain OCT technology.[1,2] The Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, CA) is a spectral domain OCT instrument that images the macula, optic disc and peripapillary RNFL. OCT is now a widely used for the diagnosis and monitoring of retinal and optic nerve disease.

Spectral domain OCT has shown particular utility in quantitatively monitoring RNFL loss in glaucoma.[3-5] It has also been shown to detect RNFL thickness changes in hereditary optic neuropathy and optic neuritis.[6,7] The technology has also shown great utility in the diagnosis and monitoring of macular diseases including diabetic macular oedema, age related macular degeneration, macular holes, epiretinal membranes and macular dystrophy.[8-12]

The current Cirrus HD-OCT internal database is based on measurements of individuals greater than 18 years of age. Clinicians examining structure with this instrument in children under the age of 18 years do not have a normative dataset with which to compare their measurements. Given the high resolution of this instrument, having comprehensive normative information allows clinicians to better delineate pathologic change from normal variation. OCT is especially useful in younger patients, given that it provides detailed information without having to dilate the pupil or having the patient fixate on bright lights.

OCT measured parameters are known to vary due to particular demographic[13-19] and ocular factors.[14,19-22] Spectral domain OCT has now superseded time domain OCT technology, but

most studies to have assessed variation in measured parameters have been performed using the older time domain Stratus OCT. As results using the Cirrus HD-OCT and Stratus OCT are not interchangeable,[23] studies assessing these relationships with Cirrus HD-OCT are needed. An adolescent population is ideal for this study as it is relatively free from ocular diseases which alter normal morphology (e.g., age related macular degeneration and glaucoma) or conditions affecting the clarity of the ocular media (e.g., cataract).

To utilize the full potential of this technology in determining the presence of pathological change, an understanding of the demographic variables that influence normal variation is required. To our knowledge, there are few published studies documenting Cirrus HD-OCT normative values from large population based samples. One of the purposes of this thesis is to report normative values of macular parameters measured by the Cirrus HD-OCT in a large adolescent population, and to determine factors associated with variation of these parameters.

Preterm birth and low birth weight are associated with a number of ophthalmic complications including retinopathy of prematurity (ROP), myopia, strabismus, amblyopia and cortical visual impairment.[24-29] Few studies have examined the impact of birth parameters on macular and RNFL thickness.[30-32] One of the objectives of this thesis is to determine OCT measured retinal structural changes associated with preterm birth and low birth weight.

The effects of maternal diabetes on the foetus are numerous.[33-36] Increased serum glucose concentrations in the mother has a secondary effect of causing excessive growth and a large-for-gestational-age foetus.[33] These neonates are more prone to asphyxia during vaginal delivery, hypoglycaemia, infant respiratory distress syndrome, cardiomyopathy and polycythemia.[34,35] During adolescence, children of diabetic pregnancies are more likely to be

obese, and to develop metabolic syndrome or type 2 diabetes.[36] One of the aims of this thesis is to investigate whether there are changes in retinal structure in children whose mothers have had diabetes during pregnancy.

CHAPTER 1

Brief Literature Review

The principle of OCT is to measure the properties of reflected light from retinal structures to create a detailed image of retinal structure. Time domain OCT technology measures the interference pattern created by two beams of light, one reflected from retinal layers and another from a reference mirror. Spectral domain OCT, is a newer technology which uses a spectrometer to detect the amplitudes of many optical frequencies simultaneously, without the need for a moving reference mirror. Therefore all the reflections from one A-scan can be calculated together (using a Fourier transformation) allowing a higher scanning speed than time domain OCT.[37] Higher scanning speed allows a higher scanning density and minimises movement artefact. Spectral domain in comparison to time domain also provides higher resolution scanning.[1,2]

The time domain OCT instruments include OCT1 (Humphrey-Zeiss Systems, California, USA), OCT 2000 (Humphrey Instruments, California, USA) and Stratus OCT (Carl Zeiss Meditec, California, USA). Spectral domain instruments utilised to measure retinal parameters include Cirrus HD-OCT (Carl Zeiss Meditec, California, USA), RTVue (Optovue Inc, California, USA), Spectralis (Heidelberg Engineering, Heidelberg, Germany), 3D OCT-1000 (Topcon Inc, Tokyo, Japan) and the V2.2OPKO (OPKO health Inc, Florida, USA).

RNFL values and associations

Normal Values

The RNFL is most often measured with a 3.4mm diameter scan circle centred on the optic disc. For the purposes of this review only scans of 3.4mm diameter will be compared. The commonly reported parameters are RNFL average thickness and quadrant specific thickness.

Table 1.1 presents the RNFL thickness reported by studies using healthy subjects. Using OCT1 and OCT 2000 studies found the RNFL average thickness in normal samples between 91 ± 14 and 133 ± 14µm.[38-48] Many of these studies also reported quadrant specific RNFL thickness.[41,42,44-48] In all these studies the superior and inferior quadrant were thicker than the nasal and temporal quadrants.

Stratus OCT RNFL measurements in samples of healthy eyes by 48 different studies are also seen in **Table 1.1**. The mean RNFL thicknesses in these studies ranged from 96 ± 12 to 114 ± 10µm.[13-15,19,20,23,49-86] There were 2 outlying studies showing smaller mean RNFL values of 80 ± 16µm[87] and 89 ± 11µm.[88]

In samples measured by Cirrus OCT the mean RNFL average thickness has ranged between 92 ± 10 and 102 ± 9µm.[23,84-86,89-93] Five of these studies provide quadrant specific RNFL, showing again that superior and inferior RNFL is thicker than nasal and temporal RNFL, however there is no consistency in relative thickness of between temporal and nasal RNFL or inferior and superior RNFL.[84,85,91,92,94]

Spectralis OCT studies have found mean RNFL average thicknesses between 93 ± 7 and 107 ± 13µm.[86,93,95,96] Using RTVue, mean RNFL average has been found to measure between 108 ± 12 and 113 ± 13µm.[86,92,97,98]

Age and RNFL

Previous OCT studies incorporating samples with a wide age range, are in agreement that RNFL thickness decreases with age, with a loss of between 2 and 4µm per decade.[14,41,45,47,73,80,87,90,95,99-102] This age related decrease is especially evident after 50 years of age.[73] Studies limited to younger populations did not find any association of RNFL thickness with age.[15,22,49]

Hirasawa et al[101] using scan circles with varying diameters, found that thinning of RNFL with age occurs at a greater rate closer to optic disc margin. Some studies have also shown that rate of thinning varies between RNFL quadrants, however these are inconsistent in their findings. Parikh et al[73] found that the inferior quadrant had a non-significant RNFL decay with age, whereas Sung et al[80] in their cohort found that the temporal quadrant RNFL had a non-significant decrease with age. Mok et al[45] found significant thinning in all quadrants with temporal quadrant having the least amount of thinning with age. Kanno et al[99] found that greatest age associated thinning in RNFL occurred in the inferior-temporal and superior-temporal segments.

Ethnicity and RNFL

Using Stratus OCT it has been shown that RNFL thickness varies in different ethnic groups. Budenz et al[14] measured RNFL thickness in Caucasians, Hispanics and Asians. Mean RNFL thickness in Caucasians (98 ± 11µm) was thinner than the mean values for Asians (106 ± 9µm; P = 0.043) and Hispanics (104 ± 12µm; P=0.022). In study of 6 and 12 year old Australian children, Samarawickrama et al[15] found that the RNFL was thicker in East Asian children compared with European Caucasian children across both age groups, by 3.2 to

12.1%. When this difference was examined by quadrants it was found that East Asians children had thicker RFNL in the non-nasal quadrants and the nasal RNFL was significantly thicker in the Caucasian children, this pattern was seen in both age groups. The implications of this finding were demonstrated by Kim et al[63] who found that in the non-nasal RNFL region, a normal Korean population has a false positive rate which is much lower than the expected 5%, which is a result of the Stratus OCT normative database being largely based on a non-Asian population.

Differences amongst quadrant specific RNFL thickness have been demonstrated between other ethnic groups as well, El-Dairi et al[19] found that superior quadrant and average RNFL thickness were significantly greater in black compared with Caucasian children ($P<0.001$). Girkin et al[103] reported that individuals of African descent had thicker RNFL in the superior, inferior and temporal quadrant compared with individuals of European descent.

Association of AL and myopia with RNFL

Hoh et al[40] used OCT1 to investigate the relationship of SER and AL with RNFL. They found that mean RNFL measured did not differ with myopic SER or AL. The OCT1 instrument utilized by this study applied a Littman-based formula to adjust for different scan sizes due to magnification.

Studies using the Stratus OCT have, however, found that AL and myopic SER are associated with thinning of the RNFL.[14,19-22,104,105] Using Stratus OCT, Budenz et al[14] reported that RNFL thickness decreased approximately by 2.2μm (95% CI, 1.1–3.4) for every 1mm increase in AL. Similarly, El Dairi et al[19] reported a 2.6μm reduction in RNFL for every 1mm

increase in AL in white children, however interestingly they did not find a significant association of AL and RNFL in black children.

With the Cirrus HD OCT, Wang et al[106] reported a negative correlation of AL (r=-0.322, p<0.001), and positive correlation of SER (r=0.291, p<0.001), with RNFL thickness. Bendschneider et al[95] used an separate spectral domain instrument, the Spectralis HRA + OCT, and found that a 1mm increase in AL produced a mean decrease in RNFL of 4.8µm (P<0.001).

Some recent spectral domain studies have found no relationship between RNFL and AL. Hirasawa et al[101] using the Topcon 3D OCT-1000 found that AL did not correlate with RNFL in multiple regression analysis (P>0.08). The reason for this discrepancy may be due to the magnification correction (modified Littman method) performed by the Topcon 3D OCT-1000. Support for these results has recently been found by Savini et al(BJO Epub doi:10.1136/bjo.2010.196782) who measured RNFL with Cirrus HD OCT and found that after applying the Littman correction for magnification the relationship of RNFL with AL disappeared. Similarly, using Cirrus HD OCT, Kang et al[90] also reported that the relationship of RNFL with SER disappeared when adjusting for magnification; and the negative relationship of AL with RNFL became positive after magnification adjustment. These findings suggest that the thinning of the RNFL with increased AL may in fact be related to magnification artefact. As AL increases the scanning circle projected onto the fundus is larger, therefore sampling the RNFL further from the disc margin (assuming similar disc sizes in these larger eyes) and Hirasawa et al[101] have shown that larger scanning circles

measure thinner RNFL. These observations taken together suggest that in eyes with a longer AL, OCT will measure a thinner RNFL.

When examining the relationship of quadrant RNFL thickness with AL and myopia it has been found that the superotemporal and inferotemporal RNFL bundles are shifted temporally in longer eyes.[89,104] This leads to temporal RNFL having either a positive relationship with AL/myopia[104,106] or the normal RNFL decrease with increasing AL/myopia is not seen in the temporal quadrant.[105] The findings of a study by Hwang et al(J Glaucoma Epub doi:10.1097/IJG.0b013e31820719e1) suggested this temporal retinal shift may be related to the temporal disc tilt associated with myopia.

Macular Values and Associations

Normal Values

For OCT1 and OCT 2000, the macular thickness was measured with a scan line of variable length consisting of 100 A-scans. These studies are difficult to compare as different studies have used various orientations and lengths of this scan line. However, a commonly reported parameter in these studies is foveal minimum thickness, which is taken as the thinnest point in the central macula, corresponding to the foveola. For normal eyes measured by OCT 1 and OCT 2000, mean foveal minimum thickness ranged from 133 ± 9 to 174 ± 21μm.[107-111]

For Stratus OCT and spectral domain instruments macular parameters are largely measured in a 6mm circular region centred on the fovea. This circular region is divided into a central 1mm diameter circle and two concentric rings with borders at diameters of 1mm, 3mm and 6mm.

The central circular area is termed the central macula. The two rings are called inner macula and outer macula. The two concentric rings are further divided into temporal, superior, nasal and inferior quadrants. This 9 region grid is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) map.[112] In addition there is a total macular volume which is the volume of retinal tissue of the 6mm diameter circular area. The Cirrus HD-OCT, in addition to the above parameters, provides an average thickness and volume for a 6mm × 6mm square region termed the macular cube thickness and macular cube volume.

Central macular thickness is the most commonly presented parameter in Stratus OCT studies. **Table 1.2** presents macular thickness values for normal individuals. The mean central macular thickness measured by Stratus OCT is reported as between 176 ± 18 and 214 ± 21μm.[16,17,19,56,58,59,66,70,74,80,85,103,113-131] Stratus OCT measured total macular volume means reported by these studies was between 6.8 ± 0.5 and 7.2 ± $0.3mm^3$.[16,19,56,58,59,74,85,115,116,119,122,125]

Studies which have provided Stratus OCT measurements of inner and outer macular regions have found that the inner macula is thicker than the central and outer macula. Within the inner macula the temporal quadrant is thinnest compared to the other 3 quadrants. The inferior and temporal quadrants are thinnest in the outer macula, while the nasal quadrant is generally thickest in both inner and outer macular regions.[16,17,19,60,66,70,80,85,103,114,115,117-119,122,124-126,128]

Using the Cirrus HD-OCT in normal populations the central macular thickness was found to be between 244 ± 19 and 276 ± 17μm.[85,117,126,128,130,132,133] Using Spectralis OCT investigators

reported normal central macular thickness means between 270 ± 23 and 288 ± 16µm.[118,127,130,134] Mean values for central macular thickness for RTVue were between 209 ± 22 and 256 ± 13µm[119,126-128,130] and for 3D OCT-1000 were between 216 ± 18 and 231 ± 16µm.[85,124,127,128,135] The spectral domain OCT findings of relative thickness within the inner and outer macula were similar to Stratus OCT.

Age and macular thickness

A number of studies have investigated the relationship of age with OCT-measured macular thickness in healthy individuals.[80,111,114,115,122,123,128,129,132,134,136,137] Of the studies that have found an association between age and macular thickness, all have reported a decrease in inner and outer macula with increasing age.[80,115,129,132,136,137] Eriksson et al[136] reported a decrease of between 0.26 and 0.46µm/year for all ETDRS areas however the significance for the central macula was marginal ($p = 0.04$). Sung et al[80] reported that overall macular thickness decreased 0.42µm/year. In contrast, the central macula/foveal thickness has been found to increase with age in some studies.[80,115,122,129]

However, there are other studies which have failed to find any association between age and macular thickness in any subfield.[111,114,123,128,134] The reasons why these studies may have failed to find any relationship could include small sample size,[114,128,134] not controlling for refractive error[123] or use of lower resolution OCT.[111] A limitation of all current studies investigating effects of ageing on macular OCT measurements is that they are cross-sectional in nature, whereas a longitudinal methodology would more suited to studying this relationship.

Ethnicity and macular thickness

Studies have found individuals of Caucasian (European) ethnicity have thicker macular parameters than those of African ethnicity.[17-19,103,116,122,134] The difference in macular thickness is greatest in the central subfield, where mean differences are between 10 and 20µm. Wagner-Schuman et al[138] have found that differences in the foveal morphology between ethnic groups appears to be the main reason for these findings. Studies examining populations of Asian ethnicity have also reported thinner central macular parameters in comparison to studies with Caucasian populations.[16,115,131,137]

Association of AL and myopia with macular parameters

Studies have found that the central macular thickness increases with increasing AL.[111,115,123,125,139,140] However other studies have failed to find this relationship.[16,17,19,132,135] The reason for discrepancy amongst these studies for this association is unclear. Many of the studies varied in the use of exclusion criteria for refractive error, the use of adjustment for confounding variables, different OCT instruments and application of a magnification correction. Generally the studies which found a correlation of central thickness with AL/SE had a wide range of refractive errors in their sample or a large sample size and did not apply a magnification correction.

It has also been found that OCT measured outer macular thickness and macular volume decreases with increasing AL or more myopic refractions.[16,18,125,132,140] This finding may be due to a "stretch effect" causing the thinning of the retinal tissues in elongated eyes. However these finding are in conflict with that of Ooto et al[135] who did not find an association with AL

and macular thickness using a the 3D OCT 1000. The correction of scan length by the 3D OCT 1000 instrument (which applies a magnification correction based on the AL of the eye) may be a factor influencing the lack of association of macular thickness with AL in this study.

In conclusion, there is a rapidly growing body of literature on normative OCT findings in different populations and the effects of age, ethnicity and AL on these parameters. This is a reflection of the importance of this new technology to clinicians and researchers. However the lack of consistency of results and the fact that different instruments and different populations produce varying results highlights the need for further study in this area.

Table 1.1 Normal values for RNFL thickness measured by OCT

Study	OCT	Country	N	Age, mean (Range) (years)	RNFL mean (µm)	Temporal RNFL (µm)	Superior RNFL (µm)	Nasal RNFL (µm)	Inferior RNFL (µm)
Carpineto et al 2003[38]	OCT1	Italy	24	53.1±4.6 (41-60)	123 ± 13				
Hoh et al 2000 [39]	Humphrey OCT	White 14 Black 3	17	27 – 72	90.86 ± 14.17				
Hoh et al 2006 [40]	Humphrey OCT	114 ethnic Chinese, 11 Malays, 7 Indians	132	21.2 ± 1.1 (19 – 24)	101.1 ± 8.2				
Kanamori et al 2003 [41]	Humphrey OCT	Japanese	144	46.3 (16 – 84)	123 ± 11.6	101 ± 18.5	148 ± 18.4	96 ± 19.2	146 ± 19.3
				<30 (n = 41)	128 ± 11.0	107 ± 18.3	150 ± 19.1	100 ± 20.7	151 ± 20.2
				31 – 51 n=35	127 ± 11.0	104 ± 17.0	158 ± 20.0	97 ± 19.1	147 ± 20.4
				51 – 70 n=58	120 ± 10.1	97 ± 18.5	143 ± 15.5	94 ± 19.0	144 ± 17.4
				>70 n=11	114 ± 9.3	90 ± 14.3	137 ± 14.7	93 ± 11.3	134 ± 16.6
Shin et al 2008 [42]	Humphrey OCT	Korean	30	41.4 ± 15.73 (20 – 73)	102.4 ± 16.96	81.73 ± 25.56	139.47 ± 22.25	60.70 ± 23.33	126.17 ± 23.02
Jones et al 2001[43]	Humphrey OCT 2000	UK (ENM)	15	30.8 (20 – 53)	127.87 ± 9.81				
Hougaard et al 2003[44]	OCT2000	Danish	100	20 - 45	104.4±9.9	80.1±12.9	126.1±13.3	79.6±13.5	129.5±14.0
Mok et al 2002 [45]	Humphrey OCT 2000	Hong Kong Chinese	129	24 – 78		98 ± 32	145 ± 24	87 ± 16	154 ± 26
			22	25 ± 2	119 ± 20	105 ± 21	154 ± 27	94 ± 16	158 ± 16
			25	35 ± 3	112 ± 20	96 ± 22	147 ± 26	88 ± 15	155 ± 15
			23	45 ± 3	117 ± 18	103 ± 23	150 ± 28	90 ± 17	161 ± 19
			22	53 ± 3	107 ± 19	90 ± 20	140 ± 24	81 ± 16	151 ± 14
			21	64 ± 3	109 ± 19	93 ± 21	146 ± 23	86 ± 16	152 ± 15
			16	75 ± 3	101 ± 18	88 ± 21	132 ± 20	82 ± 16	133 ± 17
Mrugacz et al 2005 [46]	Humphrey OCT 2000	Poland (ENM)	26	16.4 ± 4.8 (11 – 19)	132 ± 24.5	85 ± 21.3	142 ± 23.5	79 ± 25.6	122 ± 24.2
Nouri-Mahdavi et al 2004[48]	OCT 2000	US (mixed)	50	56.7 ± 8.7 (46 – 77)	128.4 ± 15.4	103.6 ± 19.5	153.6 ± 20.7	106.1 ± 24.7	150.1 ± 19.1
Varma et al.	Humphrey	Latino	312	51.9 ± 9.8	132.7 ± 14.4	102.5 ± 19.0	157.7 ± 17.8	109.3 ± 19.1	159.8 ± 18.9

2003[47]	OCT 2000			(40 – 79)					
				40 – 49	136.3 ± 13.2	106.0 ± 18.9	161.9 ± 17.0	111.6 ± 19.2	163.7 ±15.8
				50 - 59	132.1 ± 13.8	101.2 ± 19.1	155.6 ± 18.0	110.1 ± 18.3	159.8 ± 17.0
				60 – 69	128.1 ± 12.9	98.5 ± 16.8	153.8 ± 12.6	105.0 ± 19.7	155.1 ± 19.9
				70 +	118.5 ± 17.6	89.9 ± 17.7	143.1 ± 21.7	98.4 ± 15.4	139.2 ± 30.0
Ahn et al 2005[49]	Stratus	Korean study (ENM)	72 right	12.6 (9 – 18)	106.8 ± 13.0	85.0 ± 14.9	132.7 ± 23.9	75.6 ± 13.6	133.3 ± 25.3
				9	103.71				
				10	106.75				
				11	107.25				
				12	105.84				
				13	103.87				
				14	104.53				
				15	106.54				
				17	101.87				
				18	108.81				
Anton et al 2007[87]	Stratus	Spain	55	60.5 ± 12.4	79.70 ± 16.4		103.21 ± 26.1		97.25 ± 26.0
Budenz 2007 [14]	Stratus	America	328	47.4 (18 – 85)	100.1 ± 11.6	69.0 ± 12.7	124.2 ± 17.9	80.9 ± 18.1	126.1 ± 17.8
			58	18 – 29	103.7 ± 9.7				
			45	30 – 39	104.7 ± 10.4				
			74	40 - 49	99.9 ± 12.2				
			71	50 – 59	99.4 ± 12.7				
			43	60 – 69	97.0 ± 10.8				
			37	70 - 85	94.1 ± 10.0				
		Caucasian	206		98.1 ± 10.9				
		Hispanic	80		103.7 ± 11.6				
		African American	27		101.1 ± 14.0				
		Asian	11		105.8 ± 9.2				
		Asian Indian	3		107.7 ± 9.9				
Budenz 2005 [50]	Stratus	US (ENM)	88	53 ± 18 (19 – 88)	104.8 ± 10.4	74.8 ± 14.0	131.4 ± 17.1	79.0 ± 16.1	134.6 ± 19.0
Budenz 2005[51]	Stratus	US (mixed)	109	42.8 ± 14.6 (19 – 88)	104.8 ± 10.7	75.1 ± 17.2	130.9 ± 18.2	79.8 ± 17.2	133.4 ± 18.7

Carpineto et al 2005[88]	Stratus	Italian study (ENM)	30	29.4 (20 – 40)	89.3 ± 10.8				
Chen et al 2005 [52]	Stratus	Taiwanese	62	45.4 ± 10.4	113.0 ± 13.4				
El Dairi et al 2009[19]	Stratus	America	286	8.6 ± 3.1 (3 – 17)	108 (92 – 125)	78 (56 – 105)	143 (112 – 177)	83 (56 – 120)	129 (102 – 160)
		Caucasian	154		106 (90 – 122)	78 (55 – 106)	137 (111 – 167)	81 (57 – 115)	127 (99 – 160)
		Black	114		111 (96 – 126)	76 (56 – 102)	150 (122 – 182)	85 (52 – 118)	131 (103 – 159)
			85	(3 – 6)	109 (94 – 126)	77 (58 – 109)	143 (112 – 178)	84 (53 – 124)	131 (103 – 163)
			120	(7 – 10)	107 (90 – 123)	79 (55 – 101)	138 (113 – 174)	81 (59 – 115)	128 (99 – 158)
			79	(11 – 17)	109 (93 – 124)	80 (60 – 106)	144 (111 – 173)	84 (57 – 112)	129 (102 – 160)
Feuer et al 2011 [53]	Stratus	US	425	46 ± 15 (18 – 85)	104.7 ± 10.8				
Fisher et al 2006[54]	Stratus	US 88% Caucasian	36	38 ± 10	105 ± 12				
Girkin et al 2010[103]	Stratus	European descent	290	45.1±13.3	100.6 ± 10.9	120.9 ± 17.5	128.2 ± 17.4	71.5 ± 12.6	80.8 ± 16.3
		African descent	315	47.7±15.9	103.7 ± 10.7	66.5 ± 11.1	128.8 ± 84.3	84.3 ± 17.2	135.1 ± 16.3
Gupta et al 2007[55]	Stratus	American (ENM)	25 eyes	6 – 13	100.0 ± 13.2	73.6 ± 4.3 CI	122 ± 4.5 CI	76.4 ± 3.3 CI	132 ±3.9 CI
Gurses-Ozden et al 2004[56]	Stratus	American	10	32 ± 11.2 (21 – 52)	98.0 ± 14.4	74.7 ± 15.1	119.7 ± 23.9	75.8 ± 23.9	121.5 ± 22.4
Gyatsho et al 2008[57]	Stratus	Indian	48	54.40 ± 4.11	101.52 ± 10.13	65.92 ± 14.66	123.21 ± 15.55	87.85 ± 17.40	128.73 ± 13.15
Hsu and Tsai 2008[58]	Stratus	Taiwanese	52	31.2 ± 16.2 (10 – 53)	108.1 ± 19.3	73.2 ± 15.6	128.1 ± 18.1	85.2 ± 18.9	145.8 ± 24.4
Hsu et al 2008[59]	Stratus	Taiwanese	39	F 31.2 ± 19.9 (11 – 46) M 30.1 ± 15.2 (13 – 44)		73.4 ± 15.7	129.2 ± 18.2	85.3 ± 18.8	145.9 ± 24.5
Huynh et al 2008[60]	Stratus	Mixed	2132	11.1 – 14.4	103.6 ± 10.6	74.6 ± 12.8	129.7 ± 17.5	82.0 ± 16.7	128.3 ± 18.6
Huynh et al	Stratus	Mixed	1369	6.71	103.7 ± 11.4	75.7 ± 14.7	129.5 ± 20.6	81.7 ± 19.6	127.8 ± 20.5

2006[20]									
		White	909		102.7 (101.9 – 103.6) CI	75.1 (74.2 – 76.0)	127.9 (126.4 – 129.5)	81.9 (80.7 – 83.0)	126.1 (124.7 – 127.5)
		East Asian	213		107.7 (106.4 – 108.9) CI	81.9 (79.8 – 83.9)	136.6 (134.3 – 139.0)	77.4 (75.9 – 78.9)	134.5 (132.0 – 137.0)
Kang et al 2010[13]	Stratus	Korean	103	53.5 (19 – 70)	108.3 ± 10.3				
Kee et al 2006[61]	Stratus	Korea	42	8.5 (4 – 17)	108.8 ± 11.3	82.7 ± 16.1	134.8 ± 22.5	77.6 ± 20.5	136.7 ± 20.8
Kim et al 2007[62]	Stratus	Korean	49	55.9 ± 11.7 34–81	101.7 ± 10.9	77.8 ± 11.0	123.8 ± 16.7	76.4 ± 14.9	128.6 ± 17.9
Kim et al 2008[63]	Stratus	Korean	137	52.0 ± 13.4 19–81					
Larsson et al 2009[64]	Stratus	Sweden white	56	10.1±3.0 (5-16)	98.4 ±7.9				
Leung et al 2010[22]	Stratus	Hong Kong Chinese	104	Median: 9.75 6 - 17	113.5 ± 9.8	87.3 ± 15.4	146.3 ± 16.3	78.3 ± 16.1	142.4 ± 18.4
Leung et al 2005[66]	Stratus	Hong Kong Chinese	46	50.5 ± 14.2	106.44 ± 11.15	78.26 ± 13.34	132.48 ± 17.21	77.26 ± 17.26	137.24 ± 14.85
Leung et al 2004[67]	Stratus	Hong Kong	107	53.0 ± 11.8	106.83 ± 10.73				
Manassakorn et al 2008[137]	Stratus OCT	Thailand	250	44 ± 12 (20 to 77)	109.3 ± 0.7	75.1 ± 0.7	136.0 ± 1.0	83.6 ± 1.0	142.4 ± 1.1
Martinez et al 2008[68]	Stratus	Spain	53	28.0 ± 8.1 (18 – 49)	104.6 ± 14.4	70.8 ± 12.4	119.1 ± 17.9	92.7 ± 21.8	136.2 ± 23.1
Medeiros et al 2004[69]	Stratus	US (ENM)	66	65 ± 8	97.5 ± 9.68	68.0 ± 13.7	119.8 ± 15.7	77.9 ± 19.6	124.3 ± 16.3
Medeiros et al 2005[70]	Stratus	US (ENM)	78	65 ± 9	96.5 ± 9.90	67.6 ± 13.1	118.6 ± 16.0	76.1 ± 19.6	123.8 ± 16.5
Monteiro et al 2008 [71]	Stratus	Brazil	30	36.2 ± 12.2 (20 – 69)	107.89 ± 17.80	74.50 ± 12.73	131.77 ± 19.02	80.40 ± 13.79	134.37 ± 18.90
Park et al 2005[72]	Stratus	Korea	121	43.20 ±13.90		85.21 ± 17.92	137.45 ± 19.97	89.46 ± 22.17	138.10 ± 20.81
Parikh et al 2007[73]	Stratus	Indian	187	33.0 ± 19.7 5–75	97.27 ± 11.3	63.61 ± 12.36	124.79 ± 18.19	80.44 ± 17.39	120.20 ± 18.75
			59	< 20	100.15 ± 10.8	68.1 ± 11.38	128.53 ± 15.9	82.67 ± 17.36	121 ± 22.7
			49	20 – 34	98.76 ± 12.7	66.18 ± 14.31	127.82 ± 19.1	79.89 ± 19.41	121 ± 17.76

			34	35 – 50	97.17 ± 10	59.36 ± 7.43	125.35 ± 20.4	79.56 ± 17.93	124 ± 17.8
			45	≥ 51	92.28 ± 9.56	59.48 ± 10.72	117.31 ± 16.4	77.45 ± 15.11	114 ± 13.1
Paunescu et al 2004[74]	Stratus		10	30.5 ± 7.4 (23-43)	98-99 ± 9				
Peng et al 2008[75]	Stratus	Taiwanese	162	41.3 ± 20 (6 – 74)	108.7 ± 9.4	82.4 ± 17.8	133.9 ± 18.0	82.6 ± 16.0	135.8 ± 16.3
Ramakrishnan et al 2006[76]	Stratus	Indian	118	45.2 ± 13.56 (21 – 74)	105 ± 38.79	66.38 ± 17.37	138.2 ± 21.74	85.71 ± 21	129.1 ± 25.67
Salchow et al 2006[77]	Stratus	American	92	9.7 ± 2.7 (4 – 17)	108.0 ± 11.4	72.5 ± 13.4	135.4 ± 19.3	83.0 ± 18.0	136.9 ± 16.9
Samarawickrama et al 2010[15]	Stratus	Caucasian	762	6 (CI 6.7 – 6.8)	102.99 (102.15 – 103.82)	75.09 (74.12 – 80.10)	128.25 (126.79 – 129.70)	82.19 (80.90 – 83.48)	126.43 (124.92 – 127.94)
		East Asian	155	6 (CI 6.4 – 6.5)	106.90 (105.22 – 108.58)	82.11 (80.10 – 84.11)	135.64 (132.68 – 138.60)	76.61 (73.95 – 79.27)	133.08 (130.04 – 136.12)
		Caucasian	1050	12 (CI 12.7 – 12.8)	103.33 (102.55 – 104.11)	73.04 (71.91 – 74.16)	127.97 (126.64 – 129.29)	84.12 (82.75 – 85.50)	128.14 (126.81 – 129.47)
		East Asian	216	12 (CI 12.6 – 12.8)	105.72 (104.36 – 107.09)	81.83 (80.6 – 83.60)	135.84 (133.57 – 138.10)	74.43 (72.20 – 76.67)	130.80 (128.43 – 133.16)
Sehi et al 2007[78]	Stratus	Mixed	10	39 ± 8	100.3 ± 8.8		121.6 ± 12.6		124.3 ± 16.2
Sony et al 2004[79]	Stratus	Indian	146	44.6 ± 16.1 20–70	104.27 ± 8.51	67.10 ± 12.77	131.09 ±14.31	85.93 ± 17.85	132.34 ± 14.70
Sung et al 2009[80]	Stratus	American	124	47.5 ± 15.9 (18 – 85)	100.8 ± 10.5				
			41 eyes	18 – 29	107.4 ± 8.8	74.3 ± 11.2	132.7 ± 17.2	86.1 ± 14.4	136.4 ± 15.4
			30 eyes	30 – 39	103.7 ± 9.3	77.6 ± 19.2	129.8 ± 13.0	77.9 ± 13.1	129.8 ± 13.0
			56 eyes	40 - 49	102.4 ± 9.0	69.6 ± 9.8	127.1 ± 14.6	85.2 ± 15.1	127.5 ± 15.2
			57 eyes	50 – 59	98.3 ± 10.6	64.7 ± 11.6	123.9 ± 16.2	81.4 ± 16.3	123.3 ± 17.8
			42 eyes	60 – 85	93.4 ± 9.2	71.3 ± 13.4	114.0 ± 14.8	70.7 ± 15.6	117.6 ± 15.0
Tzamalis et al 2009[81]	Stratus	Switzerland (all Caucasian)	20	34.2 ± 10.87 (22-61)	104.54 ±11.33	77.18 ± 15.02	128.35 ± 16.7	76.41 ± 17.38	136.22 ± 16.81
Wollstein et al 2005[82]	Stratus	American (ENM)	37	51.5 ± 11.9	96.33 ± 11.77	65.05 ± 12.92	118.08 ± 17.91	79.86 ± 19.44	122.19 ± 18.78
Yamada et al	Stratus	Japanese	100	46.8 ± 18.3	108 ± 13.5				

2006[83]				(8 – 78)					
Bendschneider et al 2010[95]	Spectralis	Germany	170	Approx 20-79	97.2 ± 9.7	68.8 ± 11.1	118.0 ± 14.5	76.4 ± 15.0	123.7 ± 16.4
Hirasawa et al 2010[101]	3DOCT1000	Japan	251	≥20	101.9 ± 8.4	78.6 ± 13.3	123.9 ± 13.6	79.6 ±13.6	125.5 ± 13.1
Hong et al 2010 [89]	Cirrus	Korean	269	21.3 (19 – 26)	98.6 ± 8.7				
Hong et al 2011[84]	Cirrus	Korean	59	46.5±12.2 (20-80)	95±12	73±14	118±19	68±12	121±21
	Stratus	Korean			100±14	75±15	120±21	78±17	115±32
Huang et al 2010[85]	Stratus	China	60	40.9±10.2 (20-60)	110.7±9.4	81.3±11.9	142.2±16.6	82.6±13.7	136.4±16.6
	Cirrus				101.5±8.5	71.6±10.0	128.8±16.3	70.3±10.5	135.2±14.9
	3DOCT1000				106.8±6.6	75.3±9.8	132.6±13.3	86.0±11.9	133.1±10.7
Kang et al 2010 [90]	Cirrus	Korean (incl myopia)	269	21.3±1.7 (19-26)	98.2±8.6				
Kanno et al 2010[99]	EG SCANNER (time domain)	Japanese	460	44.0 (20 – 84)	111.3 ± 9.5				
Knight et al 2009[23]	Stratus	US (ENM)	29	55.7 ± 12.1 36 – 83	99.4 ± 13.2				
	Cirrus				92.0 ± 10				
Leung et al 2010[96]	Spectralis		76	48.76 ± 13.54	104.46 ± 10.14				
Li et al 2011[97]	RTVue	China	79	43.9±17.9	107.9±12.3	83.0±10.8	138.2±19.1	74.4±13.9	136.0±17.5
Mansoori et al 2010[141]	V2.2OPKO	India	65	42.0±14.8	113.4±10	72.8±12.1	137.9±16.0	100.4±13.1	142.0±18.1
Rao et al 2011[98]	RtVue (3.45mm)	Indian	60	47±13, 22 – 74	108.4 (106.6 – 110.3)	75.8 (74.3– 77.3)	134.4 (131.4– 137.4)	83.6 (81.1– 86.1)	139.7 (136.7– 142.6)
Mohammad Salih 2010et al [91]	Cirrus	Malaysia	49	26.5±6.2 (21 to 45)	94.3±8.6	75.9±16.1	119.2±16.8	64.9±9.8	117.1±16.8
Savini et al 2010 [92]	RTvue	Italy (white)	23	47±17	105.9±14.6	78.1±10.1	128.4±22.5	77.6±15.6	137.2±22.0
	Cirrus		23		95.2±12.5	67.1±9.6	119.7±18.2	70.2±11.5	124.0±22.5

Seibold et al 2010 [86]	Stratus	US	40	37.1±11.0 (21 to 61)	110.1±12.8	75.8±13.0	133.5±16.7	87.6±16.9	143.6±19.9
	Cirrus				96.7±10.9	64.9±10.4	123.5±16.2	74.9±10.3	132.0±18.9
	Spectralis				106.6±12.8	78.5±14.2	131.4±18.5	78.1±13.1	137.4±19.0
	RTVue				112.8±13.2	88.2±19.4	135.8±17.5	86.8±13.1	148.1±20.3
Sung et al 2009[142]	Stratus	Korean	60	51.3 ± 12.6	110.6 ± 10.5				
	Cirrus				97.3 ± 8.8				
Wu et al 2010[93]	Spectralis	America 78% white	45	66.2±17.0 (20-90)	92.7±7.2	70.4±12.0	108.3±12.4	73.3±11.9	117.3±13.4

Table 1.2 Normal values for macular thickness measured by OCT

Study	OCT	N	Country/Ethnicity	Age, years (mean/range)	Foveal min (μm)	Central Macula (μm)	Inner Macula (μm)		Outer Macula (m)	
Cagini et al 2009[113]	Stratus	60	Italy	70.4 ± 7.6	186.8 ± 34.0	213.0 ± 33.3	263.6 ± 23.2		230.9±21.2	
Chan et al 2006[114]	Stratus	37	USA	22 – 77 median 43	182 ± 23	212 ± 20	Temp	251 ± 13	Temp	210 ± 14
							Sup	255 ± 17	Sup	239 ± 16
							Nas	267 ± 16	Nas	246 ± 14
							Inf	260 ± 15	Inf	210 ± 13
Duan et al 2010[115]	Stratus	2230	Chinese	46.4 ± 9.9	150.3 ± 18.1	176.4 ± 17.5	AV	255.3 ± 14.9	Av	237.7 ± 12.4
							Temp	246.7 ± 16.7	Temp	227.0 ± 13.1
							Sup	261.6 ± 16.2	Sup	240.0 ± 13.5
							Nas	252.9 ± 19.1	Nas	258.5 ± 14.5
							Inf	260.0 ± 15.5	Inf	225.5 ± 13.3
		641		30-39	146.1 ± 17.5	173.3 ± 16.9	256.2 ± 14.7		239.0 ± 12.1	
		679		40-49	148.9 ± 16.8	176.4 ± 16.7	257.3 ± 15.0		239.3±12.6	
		690		50-59	152.8 ± 18.1	177.8 ± 17.9	254.5 ± 14.5		237.2±11.9	
		176		60-69	157.9 ± 19.9	180.9 ± 18.8	249.7 ± 15.3		231.8±11.7	
		44		≥70	162.5 ± 19.0	183.9 ± 16.6	247.0 ± 12.0		227.0±10.5	
El-Ashry et al 2008[116]	Stratus	200eyes	British	38 ± 12	173 ± 23	203 ± 24				
				21-36	162 ± 24					
				37-51	171 ± 25					
				52-66	174 ± 28					
				67-81	178 ± 12					
		24	Indian		176.31 ± 15					
		7	Black		159.14 ± 15					
		6	Oriental		150.33 ± 4					
		63	White		173.44 ± 21					

El-Dairi et al 2009[19]	Stratus	286	USA (mixed)	8.59 ± 3.11 (3 – 17)		189 (149-233)	Temp	261 (241-286)	Temp	224 (202-248)
							Sup	274 (250-297)	Sup	241 (218-263)
							Nas	270 (247-295)	Nas	259 (235-286)
							Inf	270 (247-295)	Inf	236 (215-263)
		114	Black			176 (147-214)	Temp	258 (239-285)	Temp	223 (204-241)
							Sup	269 (249-292)	Sup	240 (217-262)
							Nas	266 (246-286)	Nas	258 (236-280)
							Inf	266 (246-286)	Inf	235 (215-255)
		154	White			198 (160-237)	Temp	263 (241-286)	Temp	224 (202-248)
							Sup	276 (251-298)	Sup	241 (219-262)
							Nas	273 (250-296)	Nas	259 (235-287)
							Inf	273 (250-296)	Inf	236 (214-264)
				3 – 6		186 (149-236)	Temp	259 (238-284)	Temp	227 (204-248)
							Sup	274 (252-297)	Sup	243 (219-266)
							Nas	268 (242-294)	Nas	262 (240-287)
							Inf	268 (242-294)	Inf	240 (216-265)
				7 – 10		196 (148-226)	Temp	263 (241-285)	Temp	225 (202-249)
							Sup	276 (248-297)	Sup	241 (217-263)
							Nas	272 (249-295)	Nas	258 (234-286)
							Inf	272 (249-295)	Inf	237 (214-263)
				11 – 17		192 (156-234)	Temp	262 (242-289)	Temp	222 (203-244)
							Sup	273 (254-295)	Sup	241 (224-262)
							Nas	272 (253-295)	Nas	258 (237-282)
							Inf	272 (253-295)	Inf	233 (212-252)
Geitzenauer et al 2010[117]	Cirrus	48	27 White, 8 Hispanic, 2 Black, 15 Asian	38.4 ± 15.5 (21-75)		256.1 ± 18.6	Temp	308.6 ± 15.1	Temp	260.8 ± 12.6
							Sup	323.8 ± 15.4	Sup	279.8 ± 13.0
							Nas	325.3 ± 15.9	Nas	296.8 ± 14.6
							Inf	318.6 ± 15.2	Inf	267.7 ± 12.3
	Stratus					196.7 ± 18.6	Temp	258.1 ± 14.2	Temp	217.8 ± 12.6
							Sup	272.1 ± 17.1	Sup	240.3 ± 13.4
							Nas	270.1 ± 17.8	Nas	254.9 ± 14.1
							Inf	268.7 ± 18.1	Inf	226.3 ± 15.4
Girkin et al	Stratus		African Descent	315	47.7 ± 15.9	184.4 ± 20.2	Temp	253.4 ± 15.7	Temp	217.8 ± 15.0

2010[103]							Sup	266.2 ± 16.8	Sup	233.4 ± 15.6
							Nas	264.7 ± 17.7	Nas	249.5 ± 17.1
							Inf	263.1 ± 16.7	Inf	225.7 ± 15.1
			European Descent	290	45.1 ± 13.3	200.8 ± 20.0	Temp	259.2 ± 14.7	Temp	218.6 ± 14.7
							Sup	272.2 ± 15.4	Sup	235.0 ± 14.5
							Nas	272.2 ± 16.5	Nas	253.2 ± 15.2
							Inf	269.2 ± 15.1	Inf	228.1 ± 13.8
Goebel and Gross et al [143]	OCT2000	30	Germany	53 ± 20	153 ± 15	Total Macular average:225 ± 23 µm	0.5mm scan radius		1mm scan radius	
							Temp	217± 25	Temp	249 ± 19
							Sup	221 ± 25	Sup	270 ± 17
							Nas	233 ± 29	Nas	268 ± 20
							Inf	220 ± 27	Inf	269 ± 18
Grover et al 2009[134]	Spectralis	50	USA	20-84	227.3 ± 23.2	270.2 ± 22.5	Temp	322.6 ± 16.5	Temp	320.1 ± 15.4
							Sup	336.0 ± 20.6	Sup	329.6 ± 16.4
							Nas	335.0 ± 19.3	Nas	339.5 ± 16.9
							Inf	334.9 ± 16.7	Inf	325.4 ± 16.6
		19		20-40		275.2±24.2	Temp	324.9 ± 20.9	Temp	322.1 ± 15.9
							Sup	340.6 ± 21.0	Sup	333.3 ± 17.8
							Nas	338.7 ± 23.6	Nas	342.3 ± 19.0
							Inf	337.3 ± 18.9	Inf	327.9 ± 18.7
		20		41-60		269.4±22.1	Temp	324.3 ± 12.7	Temp	321.5 ± 16.3
							Sup	333.8 ± 22.9	Sup	330.0 ± 16.1
							Nas	334.9 ± 16.3	Nas	340.8 ± 17.0
							Inf	337.4 ± 15.1	Inf	325.9 ± 17.6
		11		≥61		263.0±20.2	Temp	315.5 ± 13.0	Temp	314.1 ± 11.9
							Sup	332.2 ± 15.3	Sup	322.4 ± 13.0
							Nas	328.9 ± 16.0	Nas	332.5 ± 10.7
							Inf	326.3 ± 13.7	Inf	320.0 ± 9.7
		28	White			272.7 ± 20.8				
		11	Asian			279.5 ± 27.4				
		11	Black			256.5 ± 16.9				
Grover et al 2010[118]	Stratus	36	US	20 – 69	166.9 ± 20.9	202.3 ± 19.6	Temp	255.7	Temp	257.5
							Sup	270.8	Sup	269.5
							Nas	265.4	Nas	277.4
							Inf	264.7	Inf	268.9

	Spectralis				225.1 ± 17.1	271.4 ± 19.6	Temp	326.8	Temp	324.6
							Sup	343.3	Sup	334.3
							Nas	339.4	Nas	344.8
							Inf	338.8	Inf	330.8
Gurses-Ozden et al 2004[56]	Stratus	10	USA	32 ± 11.2 (21-52)		184.1 ± 25.7				
Hagen et al 2011[133]	Cirrus 200x200	17	Austria	43.1 ± 14.9		262.7 ± 19.4	Temp	310.7 ± 14.4	Temp	259.4 ± 12.7
							Sup	322.7 ± 16.4	Sup	274.7 ± 11.9
							Nas	326.0 ± 14.2	Nas	295.7 ± 13.4
							Inf	319.8 ± 14.9	Inf	270.9 ± 10.9
	Cirrus 512x128					265.8 ± 18.1	Temp	311.2 ± 14.2	Temp	260.2 ± 12.5
							Sup	323.1 ± 16.5	Sup	275.7 ± 12.0
							Nas	326.3 ± 14.3	Nas	295.5 ± 13.5
							Inf	320.8 ± 13.9	Inf	271.7 ± 10.7
Hsu et al 2008[58]	Stratus	52	Taiwanese	31.2 ± 16.2 (10 – 53)	171.0 ± 9.4	192.5 ± 18.0	252.4 ± 7.0		228.8 ± 10.0	
Hsu et al 2006[59]	Stratus	39	Taiwanese	30.4 ± 16.1 (11-46)	171.4 ± 9.5	192.4 ± 17.2	252.3 ± 7.1		228.7 ± 10.1	
Huang et al 2009[119]	Stratus	32	Chinese	42.7±9.4 (21-55)	164.7 ± 25.9	193.7±22.2	Temp	263.8 ± 17.2	Temp	226.6 ± 15.2
							Sup	274.6 ± 19.3	Sup	244.3 ± 17.6
							Nas	269.1 ± 21.6	Nas	261.8 ± 15.5
							Inf	271.5 ± 17.3	Inf	232.6 ± 13.3
	RTVue-100				175.7 ± 16.8	208.6 ± 21.7	Temp	238.7 ± 13.2	Temp	238.7 ± 13.3
							Sup	252.6 ± 16.0	Sup	252.6 ± 16.0
							Nas	257.4 ± 17.6	Nas	257.4 ± 17.6
							Inf	239.6 ± 15.9	Inf	239.6 ± 15.9
Huang et al 2011[85]	Stratus	60	Chinese	40.9 ± 10.2 (20 – 60)	158.5 ± 20.2	191.2 ± 16.5	Temp	264.95 ± 12.02	Temp	224.29 ± 12.92
							Sup	277.29 ± 13.04	Sup	244.64 ± 11.82
							Nas	272.59 ± 14.96	Nas	264.64 ± 12.74
							Inf	275.78 ± 12.00	Inf	233.56 ± 14.07
	Cirrus					244.2 ± 18.7	Temp	307.40 ± 13.49	Temp	264.01 ± 12.94
							Sup	320.13 ± 14.08	Sup	283.82 ± 11.27
							Nas	322.21 ± 15.15	Nas	298.23 ± 12.17
							Inf	317.86 ± 12.71	Inf	268.61 ± 13.59

	Topcon 3D OCT1000				181.04 ± 14.35	221.8 ± 16.0	Temp Sup Nas Inf	286.16 ± 11.77 299.62 ± 11.88 301.72 ± 13.24 296.04 ± 11.65	Temp Sup Nasal Infer	240.52 ± 11.54 256.81 ± 10.53 273.57 ± 12.00 245.69 ± 11.50
Huynh et al 2006[16]	Stratus	1543	White 1009, East Asian 245, 63 Middle Eastern	6.7 ± 0.4	161.1 ± 19.4	193.6 ± 17.9	Av Temp Sup Nas Inf	264.3 ± 15.2 256.2 ± 16.5 269.7 ± 15.1 264.8 ± 18.7 266.7 ± 15.1	Av Temp Sup Nas Inf	236.9 ± 13.6 223.1 ± 15.2 239.5 ± 13.9 254.1 ± 17.9 230.9 ± 14.1
		789 boys			161.2 (159.3-163.1)	194.2 (192.3-196.1)	Av Temp Sup Nas Inf	264.9 (263.3-266.5) 256.7 (255.0-258.3) 270.3 (268.5-272.0) 265.5 (263.4-267.5) 267.3 (265.9-268.7)	Av Temp Sup Nas Inf	235.6 (234.1-237.2) 222.0 (220.4-223.7) 239.6 (238.1-241.1) 254.7 (252.8-256.7) 231.5 (230.1-233.0)
		754 girls			158.6 (157.1-160.2)	189.3 (187.9-190.8)	Av Temp Sup Nas Inf	262.5 (261.4-263.7) 254.2 (252.7-255.6) 269.0 (267.7-270.3) 262.7 (261.3-264.0) 264.5 (263.4-265.7)	Av Temp Sup Nas Inf	236.8 (235.4-238.1) 221.3 (220.1-222.5) 239.6 (238.1-241.1) 254.7 (252.8-256.7) 231.5 (230.1-233.0)
		1009	White		163.0 (161.8–164.3)	196.0 (194.9-197.1)	Av Temp Sup Nas Inf	265.2 (264.3–266.0) 257.0 (256.2–257.9) 270.2 (269.3–271.0) 265.6 (264.6–266.6) 267.9 (266.9–268.9)	Av Temp Sup Nas Inf	237.5 (236.6–238.3) 224.1 (223.1-225.1) 239.8 (238.8–240.7) 254.4 (253.2–255.5) 231.6 (230.6–232.6)
		245	East Asian		154.9 (152.6–157.1)	186.7 (184.7-188.7)	Av Temp Sup Nas Inf	262.3 (260.9–263.8) 254.8 (253.7–256.0) 268.6 (267.0–270.2) 263.1 (260.7–265.4) 263.3 (261.7–264.8)	Av Temp Sup Nas Inf	237.0 (235.4–238.6) 222.7 (221.0-224.3) 241.0 (238.7–243.2) 254.5 (252.5–256.5) 230.1 (228.7–231.5)
Huynh et al 2008[60]	Stratus	2068	Australian (mixed)	11.1 – 14.4	161.6 ± 19.9	197.4 ± 18.7	Av Temp Sup Nas Inf	271.9 ± 15.0 263.0 ± 15.5 275.8 ± 15.2 275.0 ± 17.1 274.1 ± 15.1	Av Temp Sup Nas Inf	239.5 ± 13.5 225.9 ± 14.8 242.3 ± 13.9 258.4 ± 16.4 231.5 ± 14.4
Kakinoki et al	Stratus	50	Japan	49.9 ± 18.0	Mean macular thickness 197.2 ± 17.8					

2009[121]				(22 – 78)						
	Cirrus				Mean macular thickness 257.6 ± 19.6					
Kashani et al 2010[122]	Stratus	48	American	41 ± 10	156.9 ± 3.2	194.5 ± 2.7	Temp Sup Nas Inf	259.7 ± 2.4 274.9 ± 2.1 273.3 ± 2.0 270.5 ± 2.5	Temp Sup Nas Inf	222.7 ± 1.8 242.3 ± 2.8 257.0 ± 2.2 229.3 ± 2.6
Kelty et al 2008[17]	Stratus	83	American	36.8 ± 12.1 (22 – 75)		205 ± 27				
		31	African American	37.7 ± 11.2		185 ±17	Temp Sup Nas Inf	267 ± 18 278 ± 19 277 ± 18 281 ± 18	Temp Sup Nas Inf	227 ± 17 248 ± 18 266 ± 19 242 ± 17
		52	Caucasian	36.2 ± 12.7		217 ± 25	Temp Sup Nas Inf	275 ± 23 290 ± 20 290 ± 23 290 ± 19	Temp Sup Nas Inf	233 ± 20 252 ± 19 272 ± 20 245 ± 31
Konno et al 2001[107]	OCT2000	24 eyes			155.1 ± 14.9					
Leung et al 2005[66]	Stratus	46	Hong Kong Chinese	50.5 ± 14.2		186.2 ± 23.1	Av Temp Sup Nas Inf	263.83 ± 17.88 254.70 ± 15.54 266.24 ± 25.27 268.30 ± 19.10 266.06 ± 17.79		
Leung et al 2008[124]	Stratus	35	Hong Kong Chinese	36.4 ± 12.6	155.4 ± 15.8	195.6 ± 17.2	Temp Sup Nas Inf	275.1 ± 12.8 292.0 ± 13.2 288.0 ± 12.5 286.5 ± 12.9	Temp Sup Nas Inf	235.1 ± 13.3 258.4 ± 14.9 278.4 ± 15.3 247.3 ± 14.0
	3D OCT (Topcon)					216.4 ± 18.0	Temp Sup Nas Inf	277.1 ± 12.0 297.2 ± 14.4 294.2 ± 16.5 288.4 ± 13.7	Temp Sup Nas Inf	244.3 ± 13.3 257.5 ± 13.2 276.6 ± 15.9 259.5 ± 14.7
Luo et al 2006[125]	Stratus	104	Singapore Chinese	11.5 ± 0.5 years (11 – 12)	157.0 ± 19.2		Temp Sup Nas Inf	255.4 ± 13.4 271.4 ± 14.3 266.2 ± 16.2 261.8 ± 13.2	Temp Sup Nas Inf	214.6 ± 13.5 234.5 ± 13.2 254.6 ± 14.9 230.2 ± 14.1

		39 no myopia			152.3 ± 19.1		Temp Sup Nas Inf	259.4 ± 11.9 275.3 ± 13.7 270.5 ± 14.8 265.1 ± 13.7	Temp Sup Nas Inf	220.7 ± 12.3 239.0 ± 13.6 261.2 ± 15.4 238.7 ± 13.4
		43 low myopia			156.3 ± 18.8		Temp Sup Nas Inf	254.5 ± 14.8 270.3 ± 14.8 265.8 ± 16.8 260.8 ± 13.3	Temp Sup Nas Inf	212.5 ± 13.0 233.1 ± 11.8 251.8 ± 12.9 225.8 ± 11.0
		22 moderate myopia			167.2 ± 17.3		Temp Sup Nas Inf	250.0 ± 11.4 266.0 ± 12.8 259.0 ± 15.3 257.7 ± 11.3	Temp Sup Nas Inf	207.6 ± 12.7 228.7 ± 12.8 247.9 ± 13.6 223.2 ± 13.4
Manassakorn et al 2008[137]	Stratus OCT	250	Thailand	44 ± 12 (20 – 77)		183.2 ± 1.3	Temp Sup Nas Inf	259.0 ± 1.0 269.4 ± 1.0 271.5 ± 1.1 272.6 ± 1.0	Temp Sup Nas Inf	222.2 ± 0.9 243.1 ± 1.0 260.7 ± 1.0 229.2 ± 0.9
Medeiros et al 2005[70]	Stratus	78	USA	65 ± 9		201 ± 28	Temp Sup Nas Inf	257 ± 19 269 ± 19 269 ± 21 265 ± 19	Temp Sup Nas Inf	218 ± 18 236 ± 17 247 ± 18 224 ± 16
Menke et al 2009[126]	Stratus	14 (28 eyes)	Switzerland	32 ± 4		214 ± 21	Temp Sup Nas Inf	268 ± 13 280 ± 13 283 ± 14 273 ± 13	Temp Sup Nas Inf	229 ± 14 250 ± 17 233 ± 15 256 ± 18
	Cirrus					266 ± 20	Temp Sup Nas Inf	311 ± 12 327 ± 13 323 ± 11 317 ± 13	Temp Sup Nas Inf	272 ± 21 287 ± 16 267 ± 12 292 ± 16
	RTVue-100 FDOCT					231 ± 23	Temp Sup Nas Inf	283 ± 12 291 ± 14 290 ± 12 285 ± 13	Temp Sup Nas Inf	239 ± 12 251 ± 15 235 ± 14 250 ± 15
Neubauer et al 2001[108]	OCT	21 eyes	Germany	54	153					
Ooto et al	3-D OCT-	248	Japanese	20 – 77		221.9 ± 18.8	Temp	284.86 ± 13.96	Temp	243.59 ± 12.26

2010[135]	1000						Sup Nas Inf	296.73 ± 14.51 299.22 ± 15.28 293.51 ± 14.47	Sup Nas Inf	257.12 ± 12.87 273.44 ± 14.07 246.69 ± 13.00
Otani et al 1999[109]	OCT2000	10	Japan		133.4 ± 9.3					
Paunescu et al 2004[74]	Stratus	10	US (8 white)	30.5 ± 7.4 (23 – 43)	177.7 ± 28.7	205.8 ± 19.5				
Pierro et al 2010[127]	Stratus	18	Italy	29 – 56		202.9 ± 13.6				
	Spectral OCT/SLO					213.0 ± 10.0				
	3D OCT1000					224.4 ± 18.2				
	RTVue-100					233.2 ± 10.3				
	Cirrus HD OCT					253.9 ± 9.7				
	SOCT Copernicus					172.7 ± 7.9				
	Spectralis HRA+OCT					273.2 ± 8.3				
Sanchez-Tocino et al 2002[110]	OCT 1	44	Spain	52 (21-79)	145.1 ± 15.8	Sup 267 ± 18	Inf 264 ± 16	Tem 242 ± 18	Nas 258 ± 20	
Song et al 2010[132]	Cirrus HD OCT	198	Korea	55.6 ± 16.4 (17– 83)		253.92 ± 24.18	Av Temp Sup Nas Inf	313.38 ± 19.22 304.17 ± 25.58 317.45 ± 19.80 320.24 ± 18.63 311.66 ± 20.15	Av Temp Sup Nas Inf	272.23 ± 14.60 257.86 ± 20.27 274.77 ± 14.98 291.86 ± 17.88 264.43 ± 15.86
Sull et al 2010[128]	Stratus	40	22 White, 13 Asian, 3 Hispanic, 2 Black	36.1 ± 15.9 (20–82)		203 ± 17	Temp Sup Nas Inf	262 ± 14 276 ± 13 278 ± 13 274 ± 11	Temp Sup Nas Inf	219 ± 12 239 ± 13 255 ± 14 225 ± 14
	Cirrus 512					262 ± 16	Temp	306 ± 10	Temp	255 ± 9

	x 128					Sup	320 ± 12	Sup	274 ± 13
						Nas	323 ± 12	Nas	293 ± 13
						Inf	316 ± 11	Inf	264 ± 11
	RTVue MM5 5x5mm^2 grid				267 ± 15	Temp	317 ± 9	Temp	283 ± 11
						Sup	331 ± 12	Sup	296 ± 14
						Nas	330 ± 11	Nas	305 ± 14
						Inf	327 ± 10	Inf	289 ± 13
	RTVue MM6 6mm 12 radial lines				256 ± 15	Temp	308 ± 13	Temp	265 ± 10
						Sup	324 ± 11	Sup	278 ± 13
						Nas	324 ± 11	Nas	291 ± 14
						Inf	318 ± 10	Inf	267 ± 12
	3D OCT - 1000 Radial				227 ± 17	Temp	279 ± 10	Temp	233 ± 10
						Sup	292 ± 12	Sup	248 ± 13
						Nas	294 ± 12	Nas	264 ± 13
						Inf	287 ± 10	Inf	238 ± 11
	3D OCT-1000 3D Macular				231 ± 16	Temp	280 ± 10	Temp	234 ± 16
						Sup	293 ± 12	Sup	249 ± 13
						Nas	296 ± 12	Nas	266 ± 13
						Inf	288 ± 10	Inf	240 ± 12
Sung et al.2009[80]	Stratus	226 eyes of 124	American (83% Caucasian)	47.5 ± 15.9 (18 – 85)					
		41 eyes		18 – 29	192.9±19.4	Temp	262.3 ± 15.0	Temp	225.4 ± 14.3
						Sup	277.6 ± 14.8	Sup	248.8 ± 15.3
						Nas	274.4 ± 13.6	Nas	265.3 ± 12.7
						Inf	276.4 ± 13.0	Inf	236.7 ± 12.2
		30 eyes		30 – 39	205.5±21.8	Temp	268.6 ± 15.2	Temp	227.1 ± 14.2
						Sup	281.0 ± 13.2	Sup	244.2 ± 14.3
						Nas	282.0 ± 16.6	Nas	261.3 ± 11.1
						Inf	280.9 ± 16.0	Inf	232.7 ± 13.3
		56 eyes		40 - 49	198.2±23.4	Temp	257.6 ± 15.2	Temp	219.6 ± 14.4
						Sup	270.5 ± 13.3	Sup	238.9 ± 13.5
						Nas	270.3 ±15.7	Nas	253.6 ± 15.4
						Inf	270.5 ± 14.6	Inf	227.7 ± 14.8
		57 eyes		50 – 59	207.1±28.3	Temp	257.6 ± 17.2	Temp	214.0 ± 15.4
						Sup	270.2 ± 16.9	Sup	234.9 ± 14.3

							Nas	272.3 ± 18.4	Nas 250.5 ± 16.0
							Inf	268.7 ± 17.7	Inf 222.0 ± 16.0
		42 eyes		60 – 85		203.4±18.9	Temp	252.5 ± 11.8	Temp 210.2 ± 11.9
							Sup	263.6 ± 14.8	Sup 229.6 ± 15.8
							Nas	265.4 ±14.7	Nas 241.0 ± 16.1
							Inf	262.1 ± 14.1	Inf 218.0 ± 15.5
Wagner Schuman et al 2011[138]	Cirrus	47 male		25.7 ± 6.3		264.5±22.8	Temp	316.2 ± 16.4	Temp 265.5 ± 15.0
							Sup	328.2 ± 15.6	Sup 281.0 ± 15.7
							Nas	331.4 ± 18.0	Nas 301.6 ± 14.9
							Inf	326.8 ± 17.5	Inf 273.9 ± 14.2
		43 female		30.0 ± 10.9		253.6±193	Temp	308.4 ± 12.7	Temp 258.1 ± 11.0
							Sup	322.4 ± 13.9	Sup 278.6 ± 13.3
							Nas	322.9 ± 14.9	Nas 297.9 ± 12.7
							Inf	317.8 ± 13.6	Inf 267.6 ± 11.6
		60	Caucasian	28.9 ± 8.4		266.3±18.2	Temp	313.7 ± 15.4	Temp 261.0 ± 13.5
							Sup	325.8 ±15.5	Sup 278.5 ± 14.1
							Nas	329.3 ± 17.1	Nas 299.3 ± 15.0
							Inf	323.4 ± 16.8	Inf 271.1 ± 13.1
		30	African American	25.6 ± 9.9		245.2±21.9	Temp	310.1 ± 14.6	Temp 263.8 ± 14.0
							Sup	324.7 ± 14.2	Sup 282.5 ± 15.2
							Nas	323.4 ± 16.4	Nas 300.9 ± 11.5
							Inf	320.6 ± 15.2	Inf 270.6 ± 14.0
Wakitani et al 2003[144]	OCT2000	55 AL <25mm	Japan	48.9 ± 17.4	A164 ± 19	B213 ± 14	C233 ± 13		
		95 AL 25-26.99mm		46.3 ± 14.8	A 168 ± 22	B 213 ± 18	C 232 ± 15		
		53 AL ≥27mm		42.9 ± 15.9	A 169 ± 21	B 210 ± 19	B 228 ± 16		
Wexler et al 2010[129]	Stratus	107	Norwegian	42.4 ± 11.8 (21 - 63)	178±22	213±16	272±15(2.22mm diam)		274±14 (3.45mm diam)
Wolf-Schnurrbusch et al 2009[130]	Stratus	20	Switzerland	37.1 ± 12.8 (25 - 63)		213 ± 19			
	Spectralis					288 ± 16			

	HRA+OCT								
	Spectral OCT/SLO				243 ± 25				
	Cirrus HD OCT				276 ± 17				
	SOCT Copernicus				246 ± 23				
	RTVue-100				245 ± 28				
Wong et al 2005[111]	OCT 2000	60 male	Hong Kong	42.3±16.4 (13-81)	174 ± 21	203 ± 23			
	OCT 2000	57 female		38.6±16.1 (16-79)	168 ± 23	189 ± 20			
Zhang et al 2011 [131]	Stratus	720	Chinese	8.6 ± 1.6 (6 – 13)	178.5 ± 15.6	Temp Sup Nas Inf	257.1 ± 13.0 267.7 ± 13.7 260.4 ± 14.7 261.1 ± 13.5	Temp Sup Nas Inf	223.3 ± 12.8 241.8 ±12.8 259.3 ± 13.8 234.2 ± 13.9

CHAPTER 2

Methods

The following chapter contains the overall methodology used in this project. Methods which are specific to individual papers are found in subsequent chapters.

The Sydney Myopia Study (SMS) is a population-based survey that aimed to evaluate childhood ocular conditions. The study methods have been described in detail previously.[16,20,60,145] The participants were recruited and tested in schools in the Sydney metropolitan area. Schools were selected with a proportional mix of public and private or religious schools, and stratified according socio-economic status. The examinations included year 1 students (median age 6 years) from 34 primary schools and year 7 students (median age 12 years) from 21 secondary schools. The examinations were conducted during 2004-2005.

The Sydney Adolescent Vascular and Eye Study (SAVES) is a follow-up of SMS, conducted between 2009 and 2011. As part of the SAVES study, 20 high schools initially involved in SMS were re-visited and students in grades 11 or 12 were offered the opportunity to participate. This formed the older cohort of the study. The younger cohort of the study was tested at 13 primary schools and 30 high schools. At the primary schools all children in school year 6 were invited to participate. At the high schools only children that were part of the SMS were invited to participate.

Each participant under age 18 years was required to provide written consent from one parent, and those participants over 18 years of age were permitted to consent independently. The study followed the tenets of the Declaration of Helsinki. The study was approved by the Human Research Ethics Committee, University of Sydney and the New South Wales Department of Education and Training.

Examination

The ocular examination was conducted on both eyes of each participant by a group consisting of ophthalmologists, other medical practitioners, optometrists and orthoptists. Visual acuity (VA) was assessed monocularly with a logarithm of minimal angle of resolution (logMAR) chart, read at 244 cm (8 feet). Subjective refraction was performed to determine best corrected VA in children whose presenting VA was <0.02 logMAR units. Measurement of axial length (AL), anterior chamber depth (ACD) and keratometry were performed using the IOLMaster (Carl Zeiss, Germany). Five measures of both AL and anterior chamber depth and three measures of keratometry were performed. ACD was measured after cycloplegia.

The cornea was anaesthetized with 1% amethocaine hydrochloride. Cycloplegia was obtained with 1% cyclopentolate and 1% tropicamide eye drops. Cycloplegia was determined adequate when the pupil was ≥6mm in diameter and fixed. 2.5% phenylephrine was administered in those slow to dilate.

Cycloplegic autorefraction and keratometry with Canon RK-F1 (Canon, Japan) was then performed 30 minutes after instillation of drops, to generate 5 valid readings of refraction in each eye and one keratometry reading in each eye. After pupil dilation, digital retinal photographs centered on the optic disc and macula were obtained in both eyes using a fundus camera (Canon CF-60UVi fundus camera, CF-DA camera adapter, EOS-10D digital camera; Canon Inc, USA).

Stratus Optical Coherence Tomography (SMS)

The Stratus OCT (OCT3; Carl Zeiss Meditec, Dublin, California) obtains cross-sectional retinal tomographic scans, which have been found to be highly reproducible.[50,74] OCT scans were conducted after cycloplegia using the 'fast' scan protocol, to measure macular and peripapillary RNFL parameters.

The macular scans consisted of six radial scans each with 128 A-scans over a 6mm distance (visual angle 20.94 degrees [Durbin M, Carl Zeiss Meditec, personal communication, 2010]). This macular thickness map was divided into 3 concentric areas with diameters of 1mm, 3mm and 6mm, termed the central, inner and outer macula respectively. In addition the foveal minimum (the retinal thickness at the central point where the six radial scans intersect) and the total macular volume (an approximation of the volume of the macular area of 6mm diameter) were calculated by the Stratus OCT software. Averages of 5 scans were used in analysis.

The peripapillary RNFL was scanned with 256 A-scans arranged as a 3.46mm diameter circle (visual angle 12.08 degrees) centered on the optic disc. The Stratus OCT calculates average RNFL thickness and quadrant specific thickness based on an average of 3 circular scans. For both scan types the OCT instrument will assume a standard AL (24.46 mm) and refraction (0 D).

Cirrus HD-OCT Optical Coherence Tomography (SAVES)

Scans of retinal thickness and the optic disc parameters were performed using a Cirrus HD-OCT 4000, which performs low-coherence interferometry with an 840nm superluminescent light emitting diode to produce high-resolution tomograms. A single operator performed

scans on both eyes of each participant. The operator was required to ensure adequate pupil alignment, optimal fundus focus and illumination as well as centration of the optic disc or macula before each scan. Scans were repeated in an attempt to obtain signal strengths ≥8/10 and to avoid blink or eye movement artifacts.

Data for RNFL and optic disc parameters were acquired using the "Optic Disc Cube 200 x 200" protocol, after pupil dilation. This protocol scans a 6mm square grid ("cube") by acquiring a series of 200 horizontal scan lines each composed of 200 A-scans. RNFL thickness was calculated by layer-seeking algorithms for the entire cube. 256 specific A-scans aligned in a circle of 3.46mm diameter centered on the optic disc are extracted to provide RNFL thickness data in clock hours and quadrants. This circle is automatically placed by the software. In some cases where the operator deemed the circle to be eccentrically located, it was manually moved to be centered on the optic disc before data were exported for analysis.

The OCT software provides calculation of optic nerve head parameters. The software delineates the disc edge by the termination of Bruch's membrane. The neuroretinal rim width and area are determined by measuring the amount of neuroretinal tissue within the boundaries of the optic nerve. By defining disc edge and rim area the software can then calculate optic disc rim and optic cup area. The total area of the optic disc is the sum of the rim and cup areas. The average cup-disc ratio (CDR) is the square root of the ratio of the area of the cup to the area of the disc. The vertical CDR is the ratio of vertical cup diameter to vertical disc diameter. Cup volume is the volume between the plane created by the cup outline at the vitreous interface and the posterior surface of the optic nerve head.

Macula parameters were measured using the "Macular Cube 200 x 200" protocol, after pupil dilation. This protocol scans a 6mm square grid ("cube") by acquiring a series of 200 horizontal scan lines each composed of 200 A-scans. The cube scan analysis automatically finds the inner limiting membrane and the retinal pigment epithelium. These layers provide the delineation for calculation of the macular thickness and volume measurements. The volume and the average thickness of retinal tissue defined by these layers and the 6mm by 6mm square are called the Cube volume and Cube average thickness respectively. Also provided is the thickness within segments of a circular map known as the ETDRS Grid (derived from the Early Treatment Diabetic Retinopathy Study[112]). This is segmented into three concentric circles with diameters of 1mm, 3mm and 6mm. The central 1mm circular region is labeled central macular thickness. The two concentric rings are the inner macula and the outer macula and are further sub-divided into temporal, superior, nasal and inferior quadrants. We determined the average inner macula and average outer macula thickness by calculating an average of the four quadrants. The volume of the whole 6mm circular region is labeled Total ETDRS Volume.

Questionnaires

A comprehensive 193-item questionnaire was completed by parents. Questions included covered demographic information, ocular and general medical history and birth parameters. In Australia, health professionals record birth variables, including birth weight, length and head circumference in a booklet ("Blue Book"), which is provided to parents. The study questionnaire requested that parents provide this data. The questionnaire also specifically

asked whether the mother has diabetes or had developed diabetes during pregnancy and whether her child had been diagnosed with diabetes.

Ethnicity was self reported by the participants' parents by choosing from a list of ethnicities including Caucasian (European), East Asian, Indian/Pakistani/Sri Lankan, African, Melanesian/Polynesian, Middle Eastern, Indigenous Australian, South American and other.

Definitions

A child was considered to belong to a specific ethnic group if both parents self-identified with a common ethnicity; otherwise the child was classified as having mixed ethnicity. Based on the World Health Organisation definition [146] children less than 2,500g were deemed as low birth weight and for the purposes of this study we created a category of high birth weight for children >4000g. Gestational duration was divided into premature (≤32 weeks), modest prematurity (33 – 36 weeks) and normal (≥37 weeks).

CHAPTER 3

Retinal Nerve Fiber Layer and Optic Disc Measurements in Young Adults

Related publication:

Tariq YM, Li H, Burlutsky G, Mitchell P. Retinal Nerve Fiber Layer and Optic Disc Measurements by Spectral Domain OCT: Normative Values and Associations in Young Adults. *Eye.* 2012; 26(12):1563-70

Abstract

Purpose: To determine normative values and associations of retinal nerve fibre layer (RNFL) and optic disc parameters in normal eyes measured by spectral domain optical coherence tomography (OCT).

Methods: In a population based setting 1521 young adults were examined as part of the Sydney Adolescent Vascular and Eye Study (SAVES). Their mean age was 17.3 ± 0.6 years. RNFL and optic disc parameter measurements were made using Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, CA).

Results: The average RNFL was found to be 99.4±9.6µm. RNFL thickness was least for the temporal quadrant (69.9 ± 11.2 µm), followed by the nasal (74.3 ± 12.8µm), superior (124.7 ± 15.7µm) and inferior (128.8 ± 17.1µm) quadrants. The mean disc area in this population was 1.98 ± 0.38mm^2 with a mean rim area of 1.50 ± 0.30mm^2 and a mean cup/disc ratio of 0.44 ± 0.18. Multivariate adjusted RNFL thickness was marginally greater in East Asian than in white participants (100.1 µm vs. 99.5 µm; $P = 0.0005$). The RNFL was thinner with greater axial length ($P_{trend} < 0.0001$), less positive spherical equivalent refractions ($P_{trend} < 0.0001$), smaller disc area and cup area ($P_{trend} < 0.0001$) and larger cup/disc ratio ($P_{trend} = 0.02$).

Conclusion: This study documents normative values for the RNFL and optic disc measured using Cirrus HD-OCT in young adults. The values and associations reported in this study can inform clinicians on the normal variation in RNFL and optic disc parameters.

Introduction

In glaucoma, thinning of the RNFL is known to occur before the onset of detectable visual field loss.[147,148] Optical coherence tomography (OCT) is an imaging modality which can be used to non-invasively measure retinal parameters. It is of great use in diagnosis and monitoring of diseases affecting retinal and optic nerve structure and can also be used to detect RNFL thinning in glaucomatous eyes.[149]

Spectral domain OCT is currently the most advanced commercially available application of OCT technology. It allows faster scanning and higher resolution images than time domain OCT technology.[1,2]. The Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, CA) is a spectral domain OCT instrument that scans the optic disc and peripapillary RNFL in a $6mm^2$ area consisting of 200 x 200 scanning grid. The instrument software has an in-built normative database in order to compare with RNFL parameters. RNFL and optic disc parameters, however, are known to vary due to particular demographic[13-15] and ocular factors. [14,19-22] Most studies to have assessed variation in these parameters have been performed using the older time domain Stratus OCT. As results using the Cirrus HD-OCT and Stratus OCT are not interchangeable,[23] studies assessing these relationships with Cirrus HD-OCT are needed.

The purpose of this study is to determine normal values for Cirrus HD-OCT measured RNFL and optic disc parameters in a large population based sample of young adults aged 16 to 19 years, and to determine whether demographic and ocular factors impact on these measurements. We believe that this young population is ideal for such investigations as they are relatively free of confounding ocular disease.

Specific Methods

Statistical analysis was performed using SAS, Version 9.2 (SAS Institute, Cary NC). For the purposes of this report only scans of the right eye with signal strengths greater than 7 were used in analysis. The Kolmogorov-Smirnov (K-S) test was used to assess for normality of the distributions. Paired t-tests were used to compare RNFL quadrant data. For comparison of parameters between sex and ethnicity, mixed linear models[150] were employed adjusting for age, height, AL and sex/ethnicity with the school attended included as a random effect. In assessing the relationships of RNFL thickness with AL, refraction and optic disc parameters, these parameters were divided into quintiles with the median values of each quintile group used to determine P_{trend}.

Results

Of 2,294 students offered examinations, 1,550 (67.6%) students between the ages of 16 and 19 years had OCT scanning performed. Of these, 9 participants were excluded because of signal strengths <8 for optic disc scans; 5 were excluded because of ocular pathology, including retinitis pigmentosa, posterior staphyloma and prior optic nerve injury, and another 15 were excluded because their best corrected visual acuity was 20/40 or worse, leaving 1521 with OCT scans included in analysis. **Table 3.1** presents baseline characteristics from the sample. The mean age of the sample was 17.3 ± 0.6 years and 49.6% were male.

Table 3.2 presents the distributions of RNFL and optic disc parameters. The average RNFL for this population was 99.4 ± 9.7µm with a range of 61 to 138µm. The inferior RNFL quadrant was the thickest at 128.5 ± 17.2µm followed by the superior quadrant at 124.8 ± 15.9µm. The two thinnest quadrants were the nasal RNFL at 74.2 ± 12.6µm and the temporal

RNFL at 69.9 ± 11.6μm. These differences in thickness between RNFL quadrants were highly statistically significant (P<0.0001). The thickest RNFL clock hour segments were at the 7 (inferotemporal) and 11 (superotemporal) o'clock positions, with the thinnest at the 3 (nasal) and 9 (temporal) o'clock positions. Average RNFL, superior RNFL, the 11 and 12 o'clock segments were found to be normally distributed based on the Kolomogorov-Smirnov test. Other RNFL parameters had a non-normal distribution with a positive skew, except for clock hours 7 and 11 which had a negative skew. The mean disc area in this population was 1.98 ± 0.38mm^2 with a mean rim area of 1.50 ± 0.30 mm^2 and a mean CDR of 0.44 ± 0.18. CDRs ranged from 0.05 to 0.80. Disc parameters were not normally distributed based on the Kolomogorov-Smirnov test.

In **Table 3.3**, sex differences in RNFL thickness and optic disc parameters are presented. Females had a thicker temporal RNFL compared with males in data adjusted for age, height, AL and ethnicity (P =0.0008). Females also had smaller disc areas, smaller cup volumes and smaller CDRs (all $P \leq 0.004$). **Figure 3.1A** presents clock hour RNFL thickness for males and females and shows that the gender differences occur mainly in the temporal and superior clock hours (unadjusted data).

In **Table 3.4**, differences between East Asian and white participants are presented. The white group had thinner RNFL parameters except for the nasal quadrant, in data adjusted for age, height and AL(all P <0.05). The East Asian group was found to have smaller rim areas with larger disc areas, resulting in larger cup volumes and CDRs (all $P \leq 0.0007$). In **Figure 3.1B**, RNFL thickness for the two ethnic groups is presented, demonstrating a thicker RNFL temporally and superiorly in the East Asian group (unadjusted data).

Figure 3.2 demonstrates the relationship of RNFL to AL and refraction adjusted for age, sex, height and ethnicity. Both greater AL and more myopic refraction showed a significant trend with decreased RNFL thickness (P_{trend} <0.0001). Figure 3 presents the relationship between RNFL and optic disc parameters. Increasing optic disc rim and disc areas were found to be associated with greater average RNFL thickness (P_{trend} <0.0001). Larger CDR was associated with lower average RNFL thickness (P_{trend} = 0.02).

Discussion

In this study, we report normative values for RNFL thickness and optic disc parameters measured by Cirrus HD-OCT in a large population-based sample of young adults. We found that the average RNFL and superior RNFL were normally distributed. However, optic disc parameters did not have normal distributions. We also found significant associations between Cirrus HD-OCT measured RNFL thickness and ethnicity, axial length and optic disc parameters.

Based on our literature search, no large population based studies of RNFL and optic disc parameters measured by Cirrus HD-OCT have been reported. The largest OCT study to date is by Hong et al[89] who examined 269 (96% male) normal Korean military personnel aged 19 to 26 years; an average RNFL thickness of 98.2 ± 8.6 μm was reported, which is very similar to our value in males of 98.8 ± 9.8 μm and slightly less than our value for East Asians of 100.1 ± 9.4 μm. This study did not present quadrant or clock hour RNFL thickness or optic disc data.

In Table 3.5, values for OCT measured RNFL thickness in large studies is presented. The studies by Bendschneider et al[95] using Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) and Hirasawa et al[101] using the spectral domain Topcon 3D OCT1000 (Tokyo, Japan), report values remarkably similar to those found in our study. We would expect these two studies to measure thinner values as they included older populations by comparison with our study, and it is known that RNFL thickness decreases with age.[14,41,95] It should be noted, however, that measurements obtained using either the Spectralis HRA+OCT or Topcon OCT are not interchangeable with those using the Cirrus HD-OCT.[85,151] The Stratus OCT normative studies presented in Table 5 also have values within 10μm of those presented in our study, which is within the limit of resolution of time domain OCT.[14,152] Meaningful comparison with Stratus measurements, however, is difficult due to differences in the scanning pattern and segmentation algorithms.

We are not aware of previous large population studies of optic disc parameters using Cirrus HD-OCT. Large studies (n>100) that measured normal disc size using Stratus OCT[19,60,153-156] have reported disc areas between 2.34±0.41 and 2.63±0.55mm^2 which are larger than our value of 1.98±0.38mm^2. These studies also report cup-disc area ratios between 0.17±0.11 to 0.37±0.20, which are substantially smaller than our value of 0.44±0.18. These discrepancies are most likely due to differences in the scanning pattern and optic disc and cup delineation algorithms between Stratus and Cirrus OCT.

The Cirrus HD-OCT has an in-built database based on the measurement of 284 subjects aged 19 to 84 years. The instrument provides an age-specific (down to the age of 18) normal range based on the 5th to 95th percentile values developed on a linear fit of the data obtained from

these individuals. When we compared our 5th to 95th percentile values with those for the Cirrus normal range for an 18 year old, we found remarkably similar values (**Table 3.6**). As differences between our limits and the Cirrus in-built database are less than 10µm, our findings therefore provide a validation of the accuracy of the Cirrus normal range for this age group.

The RNFL thickness profile measured by OCT has a double hump configuration, showing thicker superior and inferior quadrants than the nasal and temporal quadrants.[20,22,47,77,157] We found the inferior RFNL quadrant to be the thickest and the temporal RNFL to be thinnest which is in concordance with the characteristic configuration of the neuroretinal rim, termed the ISNT rule,[157-159] although the difference between superior and inferior quadrants and between temporal and nasal quadrants was less than 5µm. In conflict with our findings, some other studies have reported the superior quadrant to be the thickest and the nasal to the be the thinnest.[22,41,46] It has been reported that the peak elevation points of the RNFL profile become more temporally deviated in higher myopia[90] and in eyes with longer AL[89] so that differences in myopia prevalence between the studied populations could have contributed to the reported differences in relative thickness between RNFL quadrants.

Our study found only small to non-significant sex differences in RNFL thickness with the Cirrus HD-OCT, similar to findings from studies using time domain OCT.[14,60,105] However, we did find very small, but statistically significant, gender differences in optic disc parameters. Most previous studies have reported a lack of association of sex with optic disc parameters.[158,160,161] However, larger optic disc size has previously been reported in males,[162,163] consistent with our finding of a slightly larger disc area in males. The average

CDR gender difference of 0.05 is not likely to be of any clinical relevance, particularly since the more sensitive parameter of RNFL thickness did not differ between sexes.

In the present study, we found that the average, temporal, superior and inferior RNFL was thicker in East Asians than in whites. However this difference was of a small magnitude, and the nasal RNFL was thinner in East Asians. Ethnic differences in RNFL thickness were previously reported with older time domain OCT.[13-15] The thinner nasal RNFL in East Asians could be explained by the greater prevalence of myopia in this population, which may be associated with a temporal shift in the arcuate nerve fibre bundles.[89]

We found that the East Asian group had larger disc areas, smaller rim areas and hence larger CDRs than the white sample. In support of our findings, Wang et al[164] using optic disc photographs reported larger disc size in a Chinese population than in white populations. Also in the SMS, using time domain OCT, we reported that at both 6 and 12 years of age, East Asian children had larger CDRs compared with white children.[15]

We found that increasing AL and more myopic refraction was associated with thinner average RNFL. This is in agreement with previous Cirrus HD-OCT studies.[13,106], as well as in a study using the Spectralis HRA+OCT.[95] Many previous studies using the time domain Stratus OCT instrument also reported thinner RNFL with increasing AL or myopic refraction.[14,19-22] Using the Topcon spectral domain OCT, Hirasawa et al[101] did not find a relationship with average RNFL thickness or AL in multiple regression analysis. One reason for this discrepancy could be the adjustment for optic disc size in their analysis. As previously suggested,[14,144] RNFL thinning in eyes with longer AL may be due to a

magnification effect. The larger projected scan circle in these eyes would alter RNFL measurement further from the disc margin, where the RNFL is thinner.[165] Regardless of the true relationship between RNFL and AL, it should be noted in clinical practice when using Cirrus HD-OCT that thinner RNFL values will be found in myopic eyes or eyes with longer AL. To account for this effect, a mathematical adjustment for scan enlargement may be utilized by clinicians for patients with very long eyes.[90]

Both larger disc and rim area were found to be associated with increased RNFL thickness and conversely, increasing CDR was associated with decreased RNFL thickness. Utilizing a spectral domain OCT instrument (OPKO/OTI Spectral OCT/SLO), Mansoori et al[141] found no significant association between disc area and RNFL thickness, in conflict with our findings. The reasons for their reported lack of association may be due to the differences in disc margin delineation between the two OCT instruments, or the small sample size of their study (n=65). Our studies also differed with respect to age, with their study including a wider age range of 13 to 79 years. However, Mansoori et al[141] reported significantly greater RNFL thickness with increasing rim area and lesser RNFL thickness with increasing CDR, in agreement with our findings. The association of a thinner RNFL with increasing CDR is in keeping with the traditional assumption made during clinical assessment of the optic disc for glaucoma screening.

In agreement with our results, a study using Topcon spectral domain OCT[101] and studies with the Stratus time domain OCT[14,166] have reported increasing RNFL thickness (measured using a 3.4 mm scanning circle) is associated with larger optic disc area. However these finding may not relate to an actual anatomic relationship as they are not unanimously

supported by human histologic studies.[167,168] The fixed diameter of OCT RNFL scanning may introduce an artefact of thicker RNFL measurement in eyes with larger discs, as the RNFL is sampled closer to the disc margin. Hirasawa et al[101] used the spectral domain Topcon OCT instrument to study the association of RNFL thickness with different sized scanning circles, and reported that optic disc area was negatively correlated with mean RNFL thickness in the smaller scanning circles (2.2 and 2.5mm diameter) and positively correlated with mean RNFL thickness in the larger scanning circles (3.4, 3.7 and 4.0 mm). This suggests that there may be an even more complex relationship between disc area and RNFL thickness.

Strengths of this study include its large population based sample of young adults without confounding ocular disease and the use of uniform examination techniques. A potential weakness of this study is that the scan data are presented without adjustment for scan magnification effects, which could produce abnormal results in individuals at the extremes of AL or refraction. However, as most clinicians rely principally on the raw output of the Cirrus HD-OCT without further calculation, our results may be applied directly to clinical scenarios.

In conclusion, we have presented normative values for Cirrus HD-OCT 4000 measured RNFL and optic disc parameters in a very large population-based sample aged 16 to 19 years. We further report that RNFL thickness is significantly associated with ethnicity, AL and optic disc parameters. The values and associations reported in this study can inform clinicians about normal variations in RNFL thickness and optic disc parameters as measured using the Cirrus HD-OCT and may help to better delineate normal variation from pathologic changes.

Table 3.1 Characteristics of Participants

Characteristic	**All (n = 1521)**	**White (n = 841)**	**East Asian (n = 301)**
Age, years	17.3 ± 0.6*	17.4 ±0.48	17.4 ± 0.7
Male *n*, (%),	755 (49.6)	448 (53.3)	129 (42.9)
Ethnicity *n*, (%)			
White	841 (55.3)		
East Asian	301 (19.8)		
South Asian	101 (6.6)		
Middle Eastern	133 (8.7)		
Other	145 (9.5)		
SER, D	0.08 ± 1.56†	0.55 ± 1.02	-1.12 ± 2.12
AL, mm	23.7 ± 0.9‡	23.5 ± 0.8	24.1 ± 1.2
Height, cm	169.4 ± 9.6	171.9 ± 9.5	164.9 ± 8.7
Weight, kg	66.2 ± 22.0	67.6 ± 14.8	61.5 ± 38.8

D = Diopter
* range = 16 – 19 years
† range = -8.0 – 6.3 D
‡ range = 20.8 – 28.2 mm

Table 3.2 Distribution of RNFL and Optic Disc Parameters (n = 1521)

	Mean (SD)	Median	Range	Kurtosis	Skew	K-S
RNFL, µm						
Average RNFL	99.4 (9.7)	99.0	61 – 138	0.34	0.15	0.12
Temporal	69.8 (11.5)	68.5	40 – 135	2.41	0.95	<0.01
Superior	124.8 (15.9)	124.3	61 – 186	0.31	0.18	>0.15
Nasal	74.3 (12.6)	73.2	31 – 117	0.28	0.38	<0.01
Inferior	128.5 (17.2)	127.7	53 – 214	0.82	0.25	<0.01
Clock Hour 9 temporal	54.1 (9.1)	53.2	31 – 136	6.62	1.43	<0.01
Clock Hour 10	83.6 (15.7)	82.1	41 – 157	0.85	0.67	<0.01
Clock Hour 11	139.7 (22.2)	139.8	64 – 213	-0.05	-0.07	>0.15
Clock Hour 12 superior	123.2 (26.5)	122.8	48 – 208	-0.18	0.10	>0.15
Clock Hour 1	111.6 (20.7)	109.8	50 – 184	0.01	0.29	<0.01
Clock Hour 2	94.7 (18.6)	94.1	42 – 156	-0.01	0.26	0.02
Clock Hour 3 nasal	58.2 (11.2)	56.8	8 – 114	1.34	0.77	<0.01
Clock Hour 4	70.0 (15.6)	68.8	19 - 141	0.65	0.56	<0.01
Clock Hour 5	104.8 (22.6)	103.0	33 - 191	0.30	0.51	<0.01
Clock Hour 6 inferior	139.5 (28.1)	138.2	52 - 259	0.23	0.21	<0.01
Clock Hour 7	141.3 (22.4)	142.7	61 - 250	0.43	-0.11	0.01
Clock Hour 8	71.9 (15.6)	69.9	38 – 169	3.36	1.23	<0.01
Optic Disc						
Rim area (mm^2)	1.50 (0.30)	1.47	0.50 – 2.82	0.80	0.54	<0.01
Disc area (mm^2)	1.98 (0.38)	1.94	1.01 – 4.29	1.50	0.84	<0.01
Cup Disc Area Ratio	0.44 (0.18)	0.47	0.05 – 0.80	-0.50	-0.57	<0.01
Vertical Cup Disc Ratio	0.42 (0.17)	0.45	0.05 – 0.84	-0.34	-0.54	<0.01
Cup Volume (mm^3)	0.13 (0.14)	0.09	0 – 1.12	5.83	1.96	<0.01

RNFL = retinal nerve fibre layer
K-S = Kolmogorov-Smirnov (<0.05 not normally distributed)

Table 3.3 Sex-Specific Differences in RNFL Thickness and Optic Disc Parameters

	Girls* Mean ± SD N = 766	Boys* Mean ± SD N = 755	Difference† (Girls - Boys) Mean (95% CI)	P
RNFL (µm)				
RNFL Average	99.9 ± 9.6	98.8 ± 9.8	1.1 (-0.19 – 2.5)	0.09
Temporal	71.0 ± 12.0	68.7 ± 11.0	2.7 (1.1 – 4.2)	0.0007
Superior	124.9 ± 15.7	124.8 ± 16.0	-0.3 (-2.5 – 1.9)	0.79
Nasal	74.2 ± 12.4	74.4 ± 12.8	0.9 (-0.8 – 2.7)	0.30
Inferior	129.8 ± 17.3	127.2 ± 17.1	1.9 (-1.5 – 5.2)	0.28
Optic Disc				
Rim area (mm^2)	1.52 ± 0.29	1.48 ± 0.31	0.03 (-0.006 – 0.08)	0.09
Disc area (mm^2)	1.97 ± 0.37	1.99 ± 0.38	-0.08 (-0.13 – -0.02)	0.004
Cup Disc Ratio	0.42 ± 0.18	0.46 ± 0.18	-0.05 (-0.08 – -0.03)	<0.0001
Vertical Cup Disc Ratio	0.40 ± 0.17	0.44 ± 0.17	-0.05 (-0.08 – -0.03)	<0.0001
Cup Volume (mm^3)	0.12 ± 0.12	0.15 ± 0.16	-0.06 (-0.07 – -0.04)	<0.0001

RNFL = retinal nerve fibre layer
*raw data
†adjusted for age, height, axial length and ethnicity

Table 3.4 Ethnicity-Specific Differences of RNFL Thickness and Optic Disc Parameters

	White* Mean ± SD N = 841	East Asian* Mean ± SD N = 301	Difference† (East Asian - White) Mean (95% CI)	P
RNFL (µm)				
RNFL Average	99.5 ± 9.8	100.1 ± 9.4	2.6 (1.1 – 4.0)	0.0005
Temporal	68.6 ± 10.5	75.7 ± 13.7	5.3 (3.6 – 7.1)	<0.0001
Superior	124.1 ± 15.4	126.9 ± 16.7	6.2 (3.9 – 8.6)	<0.0001
Nasal	76.5 ± 12.3	68.7 ± 12.1	-4.9 (-6.8 – -3.0)	<0.0001
Inferior	129.0 ± 17.8	129.2 ± 16.2	3.7 (1.1 – 6.2)	0.005
Optic Disc				
Rim area (mm^2)	1.53 ± 0.31	1.42 ± 0.25	-0.08 (-0.12 – -0.03)	0.0007
Disc area (mm^2)	1.94 ± 0.36	2.04 ± 0.38	0.14 (0.08 – 0.20)	<0.0001
Cup Disc Ratio	0.40 ± 0.18	0.51 ± 0.14	0.11 (0.08 – 0.13)	<0.0001
Vertical Cup Disc Ratio	0.39 ± 0.18	0.48 ± 0.14	0.09 (0.06 – 0.11)	<0.0001
Cup Volume (mm^3)	0.11 ± 0.13	0.17 ± 0.14	0.06 (0.03 – 0.08)	<0.0001

RNFL = retinal nerve fibre layer
* raw data
† adjusted for age, sex, height, axial length and clustered sampling.

Table 3.5 Reports of RNFL Thickness Values Measured by OCT in Large Studies (n>100)

Paper	**OCT**	**OCT type**	**Country**	**N**	**Age mean (range), years**	**Average RNFL, µm**	**Temporal RNFL, µm**	**Superior RNFL, µm**	**Nasal RNFL, µm**	**Inferior RNFL , µm**
Current study	Cirrus	SD	Australia	1521	17.3 (16 – 19)	99.4 ± 9.7	69.8 ± 11.5	124.8 ± 15.9	74.3 ± 12.6	128.5 ± 17.2
Hong,Seung et al[16]	Cirrus	SD	Korea	269	21.3 (19 – 26)	98.6 ± 8.7				
Hirasawa et al[18]	Topcon	SD	Japan	251	≥20	101.9 ± 8.4	78.6 ± 13.3	123.9 ± 13.6	79.6 ±13.6	125.5 ± 13.1
Bendschneider et al[17]	Spectralis	SD	Germany	170	Approx 20-79	97.2 ± 9.7	68.8 ± 11.1	118.0 ± 14.5	76.4 ± 15.0	123.7 ± 16.4
Huynh et al[24]	Stratus	TD	Australia	2132	11.1 – 14.4	103.6 ± 10.6	74.6 ± 12.8	129.7 ± 17.5	82.0 ± 16.7	128.3 ± 18.6
Huynh et al[9]	Stratus	TD	Australia	1369	6.71	103.7 ± 11.4	75.7 ± 14.7	129.5 ± 20.6	81.7 ± 19.6	127.8 ± 20.5
El Dairi et al[10]	Stratus	TD	America	286	8.6 (3 – 17)	108 (92 – 125)	78 (56 – 105)	143 (112 – 177)	83 (56 – 120)	129 (102 – 160)
Budenz et al[7]	Stratus	TD	America	328	47.4 (18 – 85)	100.1 ± 11.6	69.0 ± 12.7	124.2 ± 17.9	80.9 ± 18.1	126.1 ± 17.8

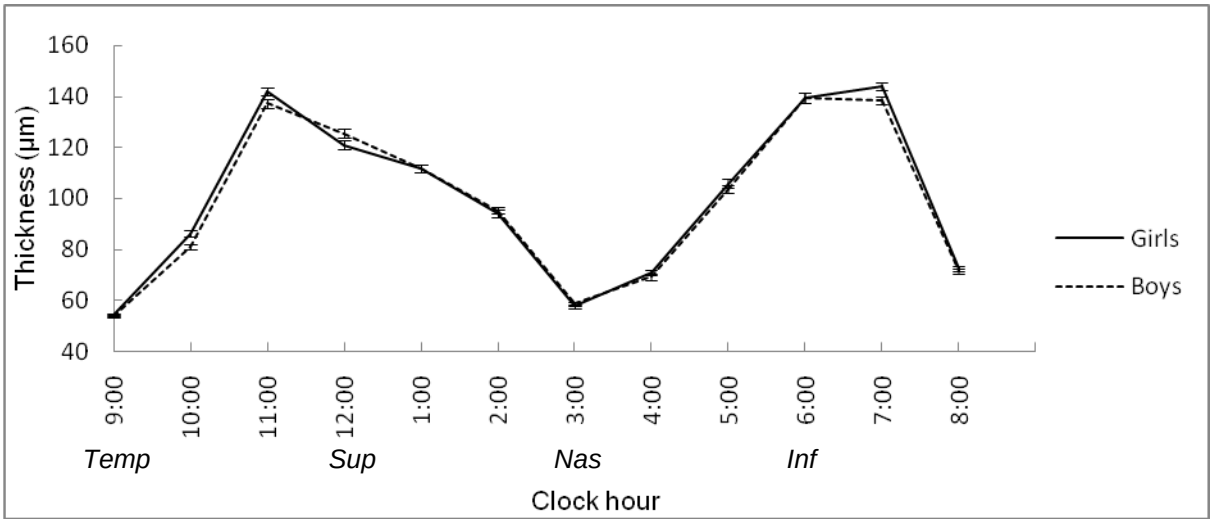
RNFL = retinal nerve fibre layer, SD = Spectral domain, TD = Time domain

Table 3.6 Normal Limits (5^{th} – 95^{th} percentiles) of RNFL Parameters in Comparison with Cirrus Normal Range

RNFL parameter (μm)	Current Study	Cirrus In-built Normal Range (18 year old)
Average RNFL thickness	84 – 115	85 – 112
Temporal	53 – 90	50 – 87
Superior	100 – 152	102 – 149
Nasal	55 – 96	55 – 91
Inferior	102 – 157	105 – 154
Clock Hour 9 temporal	41 – 69	39 – 70
Clock Hour 10	60 – 112	61 – 109
Clock Hour 11	102 – 176	98 – 165
Clock Hour 12 superior	81 – 168	84 – 169
Clock Hour 1	80 – 148	87 – 148
Clock Hour 2	65 – 127	65 – 122
Clock Hour 3 nasal	43 – 79	42 – 71
Clock Hour 4	47 – 99	47 – 92
Clock Hour 5	72 – 145	77 – 140
Clock Hour 6 inferior	95 – 186	103 – 180
Clock Hour 7	104 – 176	101 – 175
Clock Hour 8	51 – 101	47 – 95

RNFL = retinal nerve fibre layer

A



B

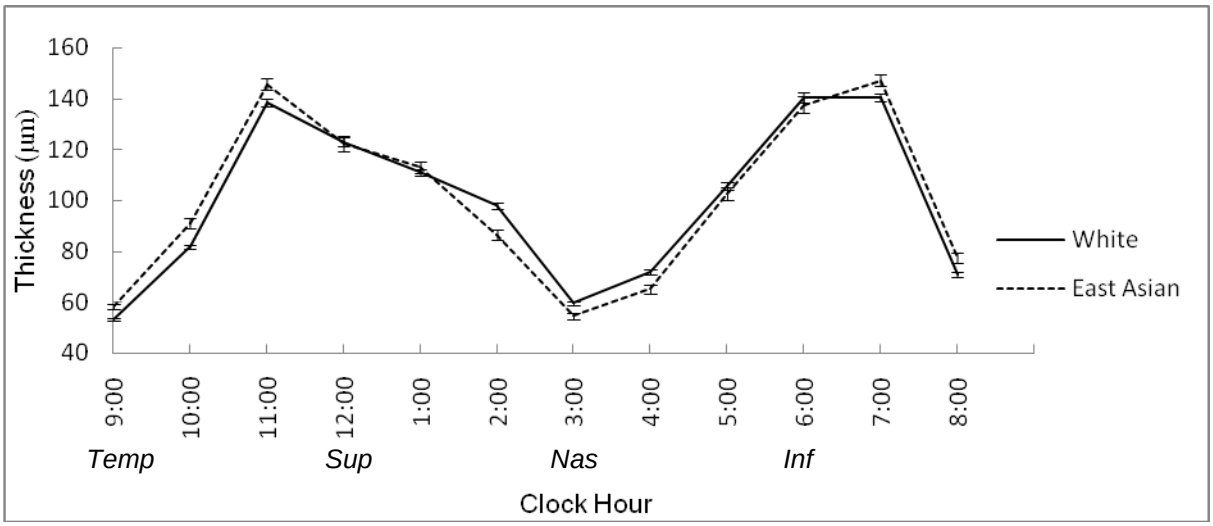
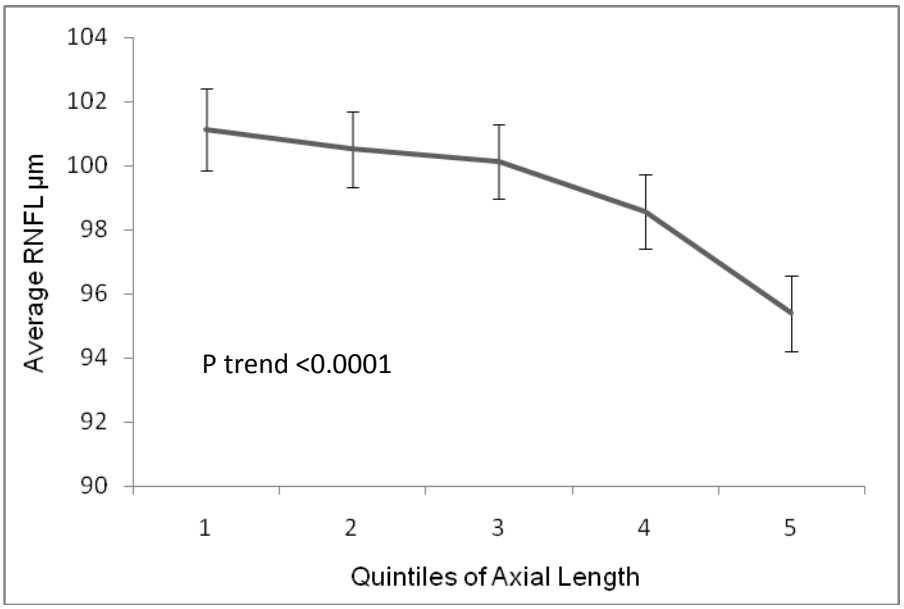


Figure 3.1: Graphs showing (A) gender and (B) ethnic differences in peripapillary retinal nerve fibre layer mean thickness by clock hours in right eyes. Error bars in both figures are 95% confidence intervals. Inf = inferior; nas = nasal; sup = superior; temp = temporal.

A



B

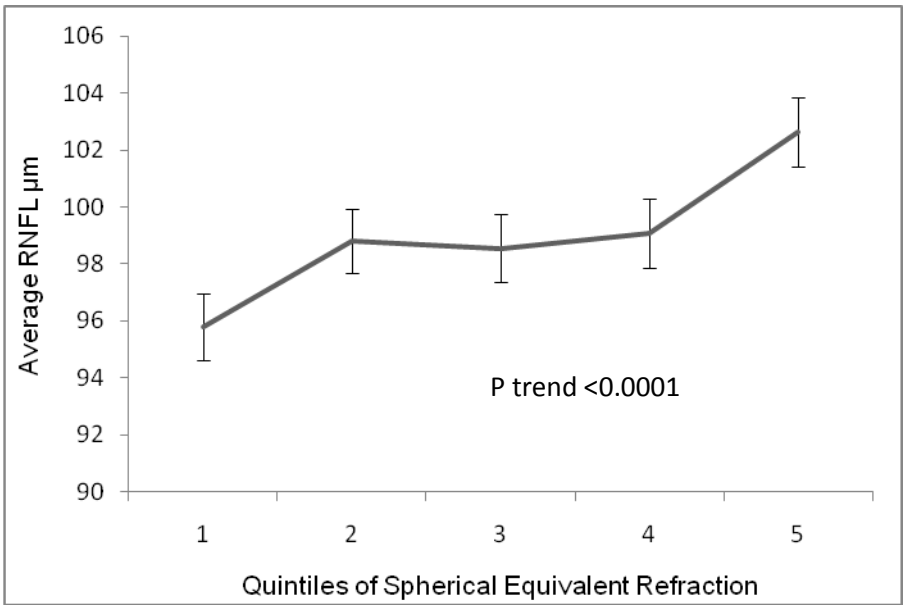
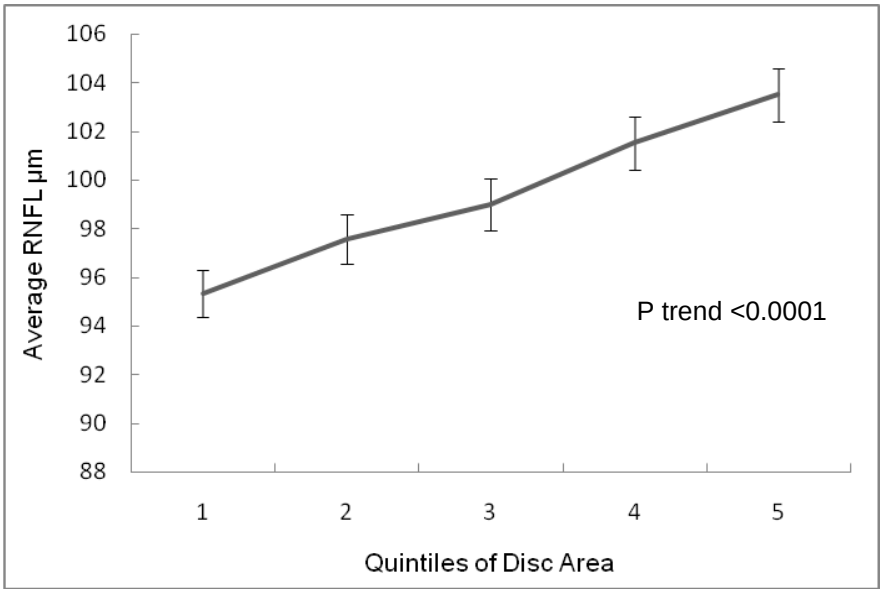
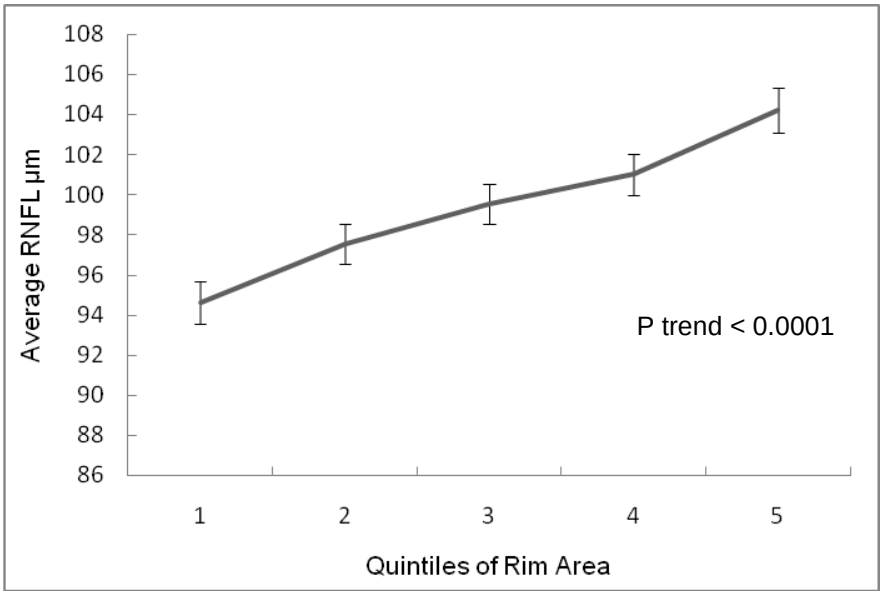


Figure 3.2: Relationship of average RNFL thickness to (**A**) quintiles of axial length (**B**) quintiles of spherical equivalent refraction. Error bars representing 95% confidence interval.
Axial Length Quintiles (mm): 1 = 20.8 – 22.89, 2 = 22.9 – 23.4, 3 = 23.4 – 23.8, 4 = 23.8 – 24.3, 5 = 24.3 – 28.2
Spherical Equivalent Quintiles (D): 1 = -8.0 - -0.6, 2 = -0.6 – 0.3, 3 = 0.3 – 0.6, 4 = 0.6 – 0.9, 5 = 1.0 – 6.3

A


106
104
102
100
98
96
94
92
90
88
Average RNFL µm
P trend <0.0001
1
2
3
4
5
Quintiles of Disc Area

B


108
106
104
102
100
98
96
94
92
90
88
86
Average RNFL µm
P trend < 0.0001
1
2
3
4
5
Quintiles of Rim Area

C

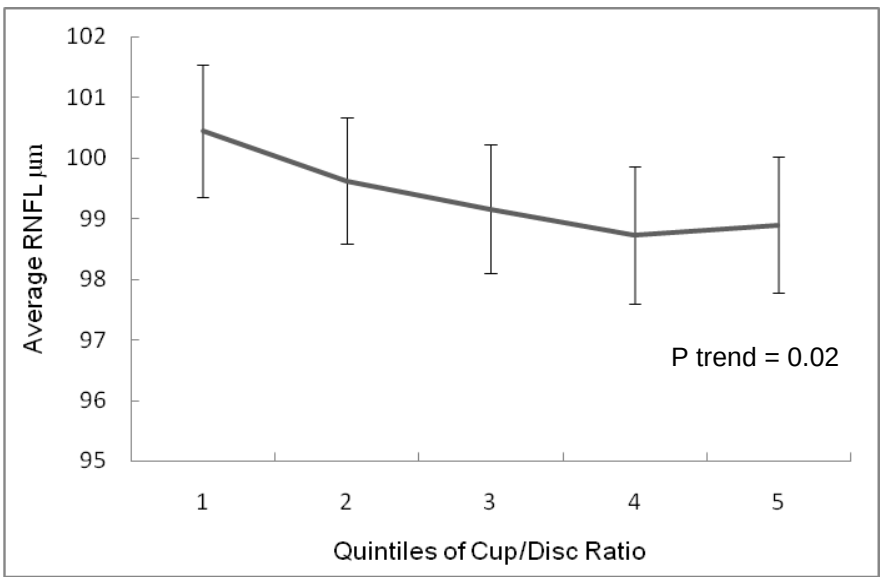

102
101
100
99
98
97
96
95
Average RNFL µm
P trend = 0.02
1
2
3
4
5
Quintiles of Cup/Disc Ratio

Figure 3.3: Relationship of average RNFL thickness to (**A**) quintiles of disc area (**B**) quintiles of rim area (**C**) quintiles of cup/disc ratio. Error bars representing 95% confidence interval.

Disc area quintiles (mm^2): 1 = 1.0 – 1.7, 2 = 1.7 – 1.8, 3 = 1.8 – 2.0, 4 = 2.0 – 2.3, 5 = 2.3 – 4.3
Rim area quintiles (mm^2): 1 = 0.5 – 1.2, 2 = 1.2 – 1.4, 3 = 1.4 – 1.5, 4 = 1.5 – 1.7, 5 = 1.7 – 1.9
Cup disc ratio quintiles: 1 = 0.1 – 0.3, 2 = 0.3 – 0.4, 3 = 0.4 – 0.5, 4 = 0.5 – 0.6, 5 = 0.6 – 0.8

CHAPTER 4

Retinal Nerve Fibre Layer and Optic Disc Parameters in Children

Abstract

Purpose: To determine the normative values for retinal nerve fibre layer thickness (RNFL) and optic disc parameters measured by Cirrus HD-OCT in children and the factors associated with variation of these parameters.

Methods: School children were given comprehensive eye examinations as part of the Sydney Adolescent Vascular and Eye Study from 2009 to 2011. Retinal and optic disc parameters were measured with Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California, USA). In addition, visual acuity assessment, autorefraction, ocular biometry measurement and dilated fundus examinations were also performed. Analysis comparing parameters between groups and in linear models were adjusted for age, sex, height, ethnicity and axial length.

Results: A total of 1069 participants were included in analysis, with a mean age of 12.5 ± 1.0 years (range 10 – 15 years) and 51.9% male. The average RNFL was found to be 100.3 ± 10.2μm. The disc area in this population had a mean value of 2.01 ± 0.38mm^2 and the rim area was 1.57 ± 0.32mm^2. Boys had larger disc areas, cup volumes and cup-to-disc ratios than girls (all $P \leq 0.02$). East Asian children had thicker average RNFL compared with Caucasian children with a difference of 6.1μm (95% confidence interval 4.4 – 8.1 μm, $P < 0.0001$). Average RNFL was found to be negatively associated with axial length (regression coefficient $\beta = -2.63$ μm/mm, $P < 0.0001$) and positively associated with spherical equivalent refraction ($\beta = 1.45$ μm/diopter, $P<0.001$).

Conclusion: This study provides normative RFNL and optic disc data for Cirrus HD-OCT in children.

Introduction:

Optical coherence tomography (OCT) is now a widely used imaging method for the diagnosis and monitoring of retinal and optic nerve disease. It has shown particular utility in quantitatively monitoring retinal nerve fibre layer (RNFL) loss in glaucoma.[3-5] It has also been shown to detect change in RNFL in hereditary optic neuropathy and optic neuritis.[6,7]

Spectral domain OCT has now superseded time domain OCT technology, providing high resolution OCT scanning with higher scan resolution and higher scanning density allowing more detailed measurement. Cirrus HD-OCT is one such commercially available spectral domain instrument. To utilize this instrument to detect pathologic change, normal values and an understanding of factors associated with variation of these measurements are required.

The current in-built Cirrus HD-OCT database does not provide normal ranges for individuals under 18 years of age. The purpose of this study is to assess normal RNFL and optic disc parameters in a population based sample of 10 to 15 year old children. A secondary purpose is to assess the variation of RNFL parameters with sex, ethnicity, ocular biometry and optic disc parameters.

Specific Methods

Statistical analysis was performed using SAS, Version 9.2 (SAS Institute, Cary NC). For the purposes of this report only scans of the right eye with signal strengths greater than 7 were used in analysis. The Kolmogorov-Smirnov (K-S) test was used to assess for normality of distributions. The paired t-test was used to compare RNFL quadrant data. For comparisons of

parameters between sex and ethnicity, mixed linear models[150] were employed adjusting for age, height, AL and sex/ethnicity with the school attended included as a random effect. Mixed linear models were also used to examine associations of average RNFL with axial length, spherical equivalent refraction, height and weight (adjusting for age, sex and ethnicity). To assess relationship of RNFL thickness with optic disc parameters, these parameters were divided into quintiles with the median values of each quintile group used to determine P_{trend}.

Results:

A total of 1618 school children were offered eye examinations. OCT optic disc cube scanning was performed on 1081 (66.8%) of these children. Of these 3 children were excluded due to signal strength less than 8. A further 8 participants were excluded due to visual acuity worse than 20/30. Another child was excluded due to Coats' disease in the left eye, leaving 1069 participants for analysis. The average age was 12.5 ± 1.0 years (range 10 – 15 years) and 51.9% of participants were male. Further characteristics of the participants are included in **Table 4.1**.

Table 4.2 presents the RNFL and optic disc parameters for this sample. The average RNFL was found to be 100.3 ± 10.2µm. The inferior and superior quadrants were thickest at 129.7 ± 17.3µm and 125.9 ± 17.4µm, respectively. The nasal and temporal RNFL was thinner at 74.2 ± 12.8µm and 71.3 ± 11.4µm, respectively. These differences in thickness between the quadrants were found to be statistically significant (all P<0.0001). The RNFL thickness was greatest at clock hour segments 7 (inferotemporal) and 11 (superotemporal), and least at the 3 (nasal) and 9 (temporal) segments. The disc area in this population had a mean value of 2.01

± 0.38mm^2 and the rim area was 1.57 ± 0.32mm^2. The cup disc area ratio ranged from 0.05 to 0.82.

The sex differences in quadrant RNFL thickness are presented in **Table 4.3**. Girls had a significantly thinner nasal quadrant RNFL than boys in analysis adjusted for age, height, axial length and ethnicity. There was no inter-sex difference in average RNFL or in the other quadrants. Boys had larger disc areas, cup volumes and cup disc ratios than girls (all $P \leq 0.02$) however the magnitudes of these differences were small.

In **Table 4.4** ethnicity specific differences are provided. East Asian children had thicker average RNFL compared with white children with a difference of 6.1µm (95% CI 4.4 – 8.1 µm, $P < 0.0001$), after adjusting for age, sex, height and AL. The East Asian children had thicker temporal, superior and inferior RNFL and thinner nasal RNFL compared with white children. In **Figure 4.1** the clock hour RNFL is presented for these two ethnic groups, displaying that the RNFL thickness is greater in the temporal, superior and inferior clock hours in East Asians. The optic disc area, cup disc ratio and cup volume was greater in East Asian children (all $P < 0.0001$, table 4).

Average RNFL was found to be negatively associated with AL after adjusting for age, sex, height and ethnicity (regression coefficient $\beta = -2.63$ µm/mm, $P < 0.0001$). In analysis adjusting for age, sex, height and ethnicity SER was positively associated with average RNFL ($\beta = 1.45$ µm/D, $P < 0.0001$). Height had a weak positive association with average RNFL when adjusting for age, sex, AL and ethnicity ($\beta = 0.09$ µm/cm, $P = 0.04$). Weight did not show any association with average RNFL thickness when adjusting for age, sex, height,

AL and ethnicity (P = 0.91). We also found with increasing disc area and rim area the average RNFL increased (P trend < 0.0001) and with increasing cup disc ratio average RNFL decreased (P trend = 0.003).

Discussion

This study presents normative Cirrus HD-OCT RNFL and optic disc measurements for a large population-based cohort of children. Also we report variations in RNFL and optic disc parameters by sex and ethnicity. Average RNFL was found to decrease with increasing AL and more hyperopic refractions. Associations between RNFL and disc parameters were also found in this cohort.

To our knowledge there are no Cirrus HD-OCT studies presenting information on normal childhood values for RNFL (Pubmed Search keywords: child, Cirrus, spectral domain, retinal nerve fibre layer). The Cirrus HD-OCT provides normal data corresponding to the age of the patient being examined down to the age of 18 years. This is derived from testing of 284 normal individuals aged between 19 – 84 years of age. In **Table 4.5** we provide a comparison of the 5^{th} to 95^{th} percentiles from our population (age range 10 to 15 years) to the normal values for an 18 year old from the Cirrus HD-OCT database. The largest differences are at the lower limit at 1 o'clock, which is 9µm lower in our population, and the upper limit at 11 o'clock, which is 13µm higher in our population. Differences of this magnitude are not likely to be of any clinical significance, suggesting that for RNFL parameters the Cirrus HD-OCT normal values could be applicable to younger individuals.

For the optic nerve there are few studies [3,169,170] documenting normal values measured by Cirrus HD-OCT. The largest of these studies by Mwanza et al [3] examined 146 healthy eyes and reported a mean disc area of 1.83 ± 0.35 mm^2, a mean rim area of 1.27 ± 0.21 mm^2, a mean cup disc ratio of 0.51 ± 0.16 with a mean cup volume of 0.16 ± 0.14 mm^3. Our population of children had larger discs and smaller cups compared with this adult population.

A significant intersex difference in RNFL was only found in the nasal quadrant, with boys having a slightly thicker RNFL in this region. All other quadrants and average RNFL thickness was not significantly difference between the sexes. The lack of association of RNFL with sex has been shown in studies using time domain OCT [14,60,79,105] and spectral domain OCT.[95,98,101] We found disc area, cup disc ratio and cup volume to be significantly smaller in girls compared with boys. The magnitude of the differences were small. The finding of larger optic discs in males has been previously reported,[162,163] however other studies have failed to find a difference.[158,160,161] A recent study using spectral domain OCT failed to find an intersex difference in optic disc parameters.[98] Because the magnitude of differences in optic disc parameters between sexes is small only studies with very large sample sizes would be able to detect this difference.

The average RNFL in our East Asian population was thicker than in our white population. Studies utilizing time domain OCT have also reported ethnic differences in RNFL difference.[13,15] We found that in the nasal quadrant the white population had a thicker RNFL than the East Asian population. This difference in the RNFL thickness distribution across quadrants could be due to the higher rates of myopia and increased axial length in the East

Asian population, which is associated with a temporal shift in the arcuate nerve fibre bundles.[89]

The East Asian population had larger disc areas, cup volumes and cup disc ratios compared with the white population. It has previously been shown using different imaging modalities that disc size is smaller in white compared with East Asian populations.[164,171,172] Although the cup-disc-ratio is traditionally used as a marker for RNFL thickness, the East Asian population had thicker average RNFL but also had greater cup disc ratios and cup volumes compared with the white children, which can be explained by larger disc size in the East Asian population.[173]

Increasing axial length and more myopic refractive error was associated with thinner average RNFL. This has been shown in previous Cirrus HD-OCT studies in adults[13,91,106,174]. This RNFL thinning with larger AL may be a result of the magnification of the scanning zone resulting in a sampling of RNFL thickness further from the disc, resulting in a thinner RNFL measurement.[165]

We found that increasing average RNFL thickness was associated with an increase in disc area. This relationship of disc area and RNFL thickness has been reported in previous time domain OCT studies.[14,175,176] Studies examining this relationship using spectral domain OCT have shown varying results. Rao et al[98] using RTVue and Mansoori et al[141] using Spectral OCT/SLO did not find an association of disc area with RNFL thickness. However, Benschneider et al[95] using Spectralis HRA + OCT did report a positive association of disc area and RNFL thickness, which is in agreement with our findings. The reason for this

positive association may be due to the sampling of the RNFL closer to the disc margin in eyes with larger discs, as it has been shown that RNFL is thicker closer to the disc margin.[165] Our finding of a positive association of average RNFL with rim area, and a negative association with cup disc ratio is in keeping with the normal anatomic relationships between these parameters.

Strengths of this study include a large population based sample with uniform examination techniques and adjustment for confounding variables. Also the use of young population which previously has not been examined with this imaging modality is a strength of this study. The young age of the sample means that there is clear ocular media and very little ocular morbidity allowing unhindered examination of normal parameters. A low participation rate of 66.8% is a weakness of this study.

In conclusion, this study presents normative values for RNFL parameters measured by Cirrus HD-OCT. These parameters were found to vary by sex, ethnicity and ocular biometry. Values and relationships presented in this study will aid clinicians in distinguishing normal variation from pathologic change in younger patients.

Table 4.1 Characteristics of Participants

Characteristic	**All*** **(n = 1069)**	**White** **(n = 664)**	**East Asian** **(n = 236)**
Age, years	12.5 ± 1.0†	12.7 ± 1.0	11.9 ± 0.7
Male *n*, (%),	555 (51.9)	326 (49.1)	121 (51.3)
SER, D	0.46 ± 1.32	0.81 ± 1.00	-0.62 ± 1.63
AL, mm	23.5 ± 0.8	23.3 ± 0.8	24.0 ± 0.9
Height, cm	155.3 ± 9.2	156.7 ± 9.2	150.8 ± 7.8
Weight, kg	48.2 ± 12.2	49.0 ± 11.9	43.3 ± 10.1

* Includes 664 white, 236 East Asian, 47 Middle Eastern, 14 South Asian and 108 from other ethnicities
D = Diopter
†range = 10 – 15 years

Table 4.2 Distribution of RNFL and Optic Disc Parameters (n = 1069)

	Mean (SD)	Median	Range	Kurtosis	Skew	K-S
RNFL, µm						
Average RNFL	100.3 ± 10.2	99.9	65.5 – 145.2	0.92	0.28	<0.01
Temporal	71.3 ± 11.4	70.1	42.0 – 127.7	2.05	0.93	<0.01
Superior	125.9 ± 17.4	124.6	57.9 – 240.4	2.07	0.45	<0.01
Nasal	74.2 ± 12.8	73.5	39.5 – 126.6	0.42	0.42	0.02
Inferior	129.7 ± 17.3	129.5	81.0 – 192.1	0.22	0.20	0.04
Clock Hour 9 temporal	54.5 ± 8.4	53.8	31.6 – 90.9	1.11	0.69	<0.01
Clock Hour 10	84.6 ± 15.6	82.5	48.5 – 158.9	2.17	1.00	<0.01
Clock Hour 11	141.0 ± 22.2	141.2	67.3 – 272.9	1.14	0.21	0.12
Clock Hour 12 superior	124.2 ± 27.7	122.5	41.3 – 266.2	0.61	0.34	0.07
Clock Hour 1	112.6 ± 22.3	111.7	38.1 – 191.9	0.22	0.28	<0.01
Clock Hour 2	96.1 ± 96.1	95.2	41.2 – 180.5	0.60	0.40	0.05
Clock Hour 3 nasal	57.7 ± 11.4	56.4	33.4 – 100.7	0.42	0.59	<0.01
Clock Hour 4	68.8 ± 15.5	67.6	34.5 – 137.0	0.15	0.48	<0.01
Clock Hour 5	104.3 ± 22.6	101.8	39.7 – 204.6	0.56	0.55	<0.01
Clock Hour 6 inferior	140.2 ± 27.44	140.2	64.2 – 218.4	-0.28	0.02	>0.15
Clock Hour 7	144.6 ± 23.9	145.0	70.3 – 246.9	0.63	0.11	0.12
Clock Hour 8	74.8 ± 16.8	72.3	31.6 – 158.0	1.80	1.05	0.08
Optic Disc						
Rim area (mm^2)	1.57 ± 0.32	1.56	0.39 – 3.76	2.66	0.64	<0.01
Disc area (mm^2)	2.01 ± 0.38	2.02	0.53 – 3.85	0.93	0.52	<0.01
Cup Volume (mm^3)	0.11 ± 0.13	0.07	0 – 1.05	7.00	2.13	<0.01
Cup Disc Area Ratio	0.42 ± 0.17	0.44	0.05 – 0.82	-0.57	-0.42	<0.01
Vertical Cup Disc Ratio	0.40 ± 0.17	0.42	0.04 – 0.88	-0.40	-0.42	<0.01

RNFL = retinal nerve fibre layer, SD = standard deviation
K-S = Kolmogorov-Smirnov (<0.05 not normally distributed)

Table 4.3 Sex-Specific Differences of RNFL and Optic Disc Parameters

	Difference† (Girls - Boys) Mean (95% CI)	P
RNFL (µm)		
RNFL Average	-0.9 (-2.0 – 0.4)	0.16
Temporal	0.9 (-0.5 – 2.2)	0.21
Superior	-1.2 (-3.4 – 0.9)	0.27
Nasal	-2.6 (-4.2 – -1.1)	0.0008
Inferior	-0.8 (-3.0 – 1.3)	0.43
Optic Disc		
Rim area (mm^2)	-0.01 (-0.05 – 0.02)	0.59
Disc area (mm^2)	-0.07 (-0.12 – -0.03)	0.002
Cup Volume (mm^3)	-0.02 (-0.04 – -0.01)	0.01
Cup Disc Ratio	-0.03 (-0.05 – -0.005)	0.02
Vertical Cup Disc Ratio	-0.02 (-0.05 – -0.005)	0.02

RNFL = retinal nerve fibre layer, SD = standard deviation
†adjusted for age, height, axial length and ethnicity

Table 4.4 Ethnicity-Specific Differences of RNFL and Optic Disc Parameters

	Difference† (East Asian - White) Mean (95% CI)	P
RNFL (µm)		
RNFL Average	6.1 (4.0 – 8.1)	<0.0001
Temporal	6.3 (4.1 – 8.4)	<0.0001
Superior	11.2 (7.8 – 14.6)	<0.0001
Nasal	-3.8 (-6.0 – -1.6)	0.0008
Inferior	10.9 (7.8 – 14.0)	<0.0001
Optic Disc		
Rim area (mm^2)	-0.05 (-0.10 – 0.01)	0.09
Disc area (mm^2)	0.18 (0.10 – 0.25)	<0.0001
Cup Volume (mm^3)	0.07 (0.04 – 0.09)	<0.0001
Cup Disc Ratio	0.10 (0.06 – 0.13)	<0.0001
Vertical Cup Disc Ratio	0.08 (0.05 – 0.12)	<0.0001

RNFL = retinal nerve fibre layer, SD = standard deviation
† adjusted for age, sex, height, axial length and clustered sampling

Table 4.5 Normal Limits (5^{th} – 95^{th} percentiles) of Retinal Nerve Fibre Parameters in Comparison with Cirrus Normal Range

Parameter (µm)	**Current Study**	**Cirrus for 18 year old**
Average RNFL	85 – 117	85 – 112
Temporal	55 – 92	50 – 87
Superior	100 – 155	102 – 149
Nasal	55 – 96	55 – 91
Inferior	102 – 158	105 – 154
Clock Hour 9 temporal	42 – 69	39 – 70
Clock Hour 10	63 – 113	61 – 109
Clock Hour 11	105 – 178	98 – 165
Clock Hour 12 superior	81 – 172	84 – 169
Clock Hour 1	78 – 151	87 – 148
Clock Hour 2	65 – 130	65 – 122
Clock Hour 3 nasal	41 – 79	42 – 71
Clock Hour 4	46 – 96	47 – 92
Clock Hour 5	71 – 143	77 – 140
Clock Hour 6 inferior	96 – 185	103 – 180
Clock Hour 7	107 – 183	101 – 175
Clock Hour 8	53 – 107	47 – 95

RNFL = retinal nerve fibre layer

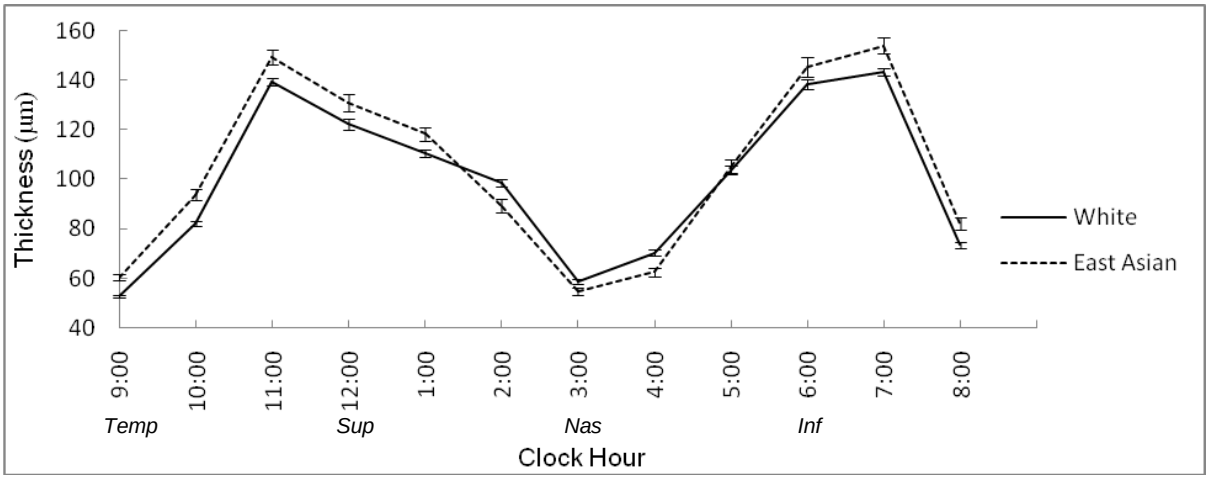


Figure 4.1: Graphs showing ethnic differences in peripapillary retinal nerve fibre layer mean thickness by clock hours in right eyes. Error bars are 95% confidence intervals. Inf = inferior; nas = nasal; sup = superior; temp = temporal.

CHAPTER 5

Macular Measurements in Young Adults

Abstract

Purpose: To determine the normative distribution of macular parameters measured by spectral domain optical coherence tomography (OCT) in a young adult population and determine the variation of these parameters by gender, ethnicity and ocular parameters.

Methods: The Sydney Adolescent Vascular and Eye Study carried out eye examinations on grade 11 and 12 school students during 2009 and 2010. Macular parameters were measured using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). In addition, visual acuity, cycloplegic autorefraction and optical biometry measurements were performed.

Results: The number of participants included in analysis was 1529. The average age of the sample was 17.3 ± 0.55 years (range 16 to 19) and 49.9% were male. The central subfield had a mean thickness of 255.3 ± 20.3μm and a range of 196 to 332 μm. Mean values for the average cube thickness, average inner thickness, average outer thickness and total cube volume were 284.1 ± 12.7μm, 322.4 ± 15.4μm, 279.7 ± 13.1μm and 10.2 ± 0.5mm^3, respectively. Males had significantly larger parameters than females and Caucasians had a thicker central and inner subfield than East Asians (all $P < 0.05$). Axial length was positively associated with central subfield thickness ($P = 0.03$) and negatively associated with inner and outer subfield thickness (both $P < 0.0001$). Inner and outer subfield thickness and cube volume were positively associated with spherical equivalent refraction (all $P < 0.0001$) and height (all $P<0.05$).

Conclusion: This study provides normative macular values and associations for this Australian young adult population.

Introduction

Macular morphology measured by optical coherence tomography (OCT) can guide clinicians and researchers in the diagnosis and treatment of a number of ocular diseases.[177-180] There are now several instruments employing spectral domain OCT technology to map macular topography with high resolution. However the results from separate spectral domain instruments or the older time domain OCT cannot be used interchangeably.[85,117-119,126,181] Also, macular parameters measured by OCT have been found to vary by ethnicity.[16-19] Therefore it is helpful to have instrument specific normative databases from different population samples that can guide clinicians in determining normal variation from pathologic change.

The Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, California, USA) is a spectral domain OCT that can perform 27,000 A-scans per second with an axial resolution of 5µm. This increased scanning density and axial resolution allows this technology to provide more detailed information on macular morphology, especially in the outer macular regions where the Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) only scanned a few points.

To our knowledge, there are no published studies documenting Cirrus HD-OCT normative values from large population based samples. The purpose of this study is to report normative values of macular parameters measured by the Cirrus HD-OCT in a large Australian population of young adults, and to determine factors associated with variation of these parameters.

Specific Methods:

Statistical analysis was performed using SAS, Version 9.2 (SAS Institute, Cary NC). For the purposes of this report only scans of the right eye with signal strengths ≥ 8 were used in analysis. The Kolmogorov-Smirnov (K-S) test was used to assess for normality of the distributions. Paired t-tests were used to compare macular quadrant data. For comparisons of parameters between genders and ethnicity, mixed linear models[150] were employed adjusting for covariates (age, height, AL and cluster sampling). Mixed linear models were also used to test associations of AL, refraction and height with macular parameters.

Results

Of 2,258 students offered examinations, 1,561 (69.1%) students between the ages of 16 and 19 years had macular OCT scanning performed. Of these, 10 were excluded due to signal strengths <8 and a further 5 participants were excluded due to ocular pathology, including retinitis pigmentosa, posterior staphyloma and optic nerve injury. Another 17 participants were excluded due to a best corrected visual acuity of 20/40 or worse, leaving 1529 participants with data for analysis. In **Table 5.1** baseline characteristics for the whole group and for the two predominant ethnic categories is presented. The average age of the sample was 17.3 ± 0.55 years and 49.9% were male.

In **Table 5.2** data on the distribution of macular parameters are presented. The central subfield had a mean thickness of 255.3 ± 20.3μm and a range of 196 to 332 μm. The average cube thickness was 284.1 ± 12.7μm, average inner thickness was 322.4 ± 15.4μm and average outer thickness was 279.7 ± 13.1μm . Within the inner subfield the temporal

quadrant was thinnest followed by inferior, superior and nasal quadrant. The quadrants in the outer subfield had the same temporal < inferior < superior < nasal pattern of relative thickness. The total cube volume was 10.2 ± 0.5mm^3 and the total ETDRS volume was 8.1 ± 0.4mm^3. Of all these parameters only cube volume met Kolmogorov-Smirnov criteria for normality. In **Figure 5.1** we present frequency histograms for central, inner and outer macular subfield thickness and cube volume, all of which appear to demonstrate normal distributions.

The gender specific values for macular parameters are presented in **Table 5.3**. Males had significantly larger parameters than females in data adjusted for age, height, AL and ethnicity. The difference was greatest in the central subfield (10.2µm, P<0.0001), smaller differences were seen in the inner (7.7µm, P<0.0001) and outer (3.4 µm, P = 0.0002) subfields. These differences were also reflected in the volume parameters.

Differences in macular parameters between Caucasian and East Asian participants are presented in **Table 5.4**. In data adjusted for age, sex, height and AL, Caucasians had a thicker central and inner subfield than East Asians. The difference in the central subfield was 11.9µm (P<0.0001) and in the inner subfield the difference was 4.7µm (P<0.0001). The outer subfield and volume parameters did not demonstrate a significant difference between Caucasians and East Asians.

In a model adjusting for age, sex, height and ethnicity, AL was positively associated with central subfield thickness (regression coefficient β = 1.2 µm/mm, P = 0.03) and negatively associated with inner and outer subfield thickness (β = -2.5 and -3.7 µm/mm respectively,

both P < 0.0001). Cube volume was also negatively associated with AL (β = -0.11mm^3/mm, P<0.0001). In models adjusting for age, sex, height and ethnicity, spherical equivalent refraction was positively associated with inner and outer subfield thickness (β = 1.70 and 2.02 μm/D respectively, both P < 0.0001) and cube volume (β = 0.06 mm^3/D, P < 0.0001). In models adjusting for age, sex, AL and ethnicity, height was positively associated with inner and outer subfield thickness and cube volume (β = 0.15 μm/cm, 0.09 μm/cm and 0.0004 mm^3/cm respectively, all P < 0.05).

Discussion

In this study we report normative values for macular parameters and describe macular topography as measured by Cirrus HD-OCT in a very large population-based sample of young adults aged 16 to 19 years. We report significant associations of Cirrus HD-OCT measured macular parameters with gender, ethnicity, AL, spherical equivalent refraction and height.

The 5th to 95th percentile limits in the current study data set are remarkably similar to the normal limits for an 18 year old in the Cirrus in-built database (**Table 5.5**). The difference is most marked in the central macula, in which the normal limits differ by 9μm. These differences would likely be explained by ethnic or AL disparities between our samples. The Cirrus in-built normative database is based on 282 individuals aged 19 to 84 years, with a mixed ethnic composition. The age specific values in the Cirrus dataset is derived from a linear fit to the normative data curve based on age. A methodology which would likely result in values less accurate to those derived from a restricted age sampling, as in our study.

The macula profile measured by OCT displays a thin region at the fovea surrounded by a thicker rim resulting in the central and outer macular subfields being thinner than the inner subfield. This relationship has previously been found in OCT studies.[16,19,60,115,134,135,138,182] In the inner and outer subfields we found the nasal quadrant to be the thickest, followed by superior, inferior and temporal. In the inner subfield the nasal and superior quadrants were of very similar thickness with <1 μm difference. This pattern of relative thickness has been consistently found using Cirrus HD-OCT [117,126,128,133,138,182] and other spectral domain instruments.[85,118,119,124,126,134]

We found that all macular parameters were larger in males compared with females. Many previous studies have reported central and inner macula to be thicker in males compared with females,[16,60,115,135,138,182] however these studies did not report consistent relationships in the outer macular subfield. Wagner Schuman et al[138] and Song et al,[182] both using Cirrus HD-OCT, did not find superior and nasal outer macular thickness to be significantly different between males and females. Ooto et al[135] using 3D OCT 1000 did not find a significant intersex difference in outer quadrant superior, nasal and inferior thickness. In Stratus OCT studies, superior outer macular thickness was not found to be significantly different between sexes.[16,60,115] To our knowledge, the current study is the first to report that males have thicker outer macular thickness in all quadrants compared with females. Since the magnitude of difference in outer macular thickness between sexes is small, high resolution OCT is needed to detect this difference and a large sample size is needed to demonstrate statistical significance, therefore studies with smaller samples or using poorer resolution OCT have failed to find this relationship.

In this population we were able to demonstrate a difference in central macular thickness between individuals of Caucasian (European) and East Asian ethnicity. The central and inner subfield thickness in the Caucasian group was greater than that of the East Asian group. Using Stratus OCT in a 6 year old cohort, we previously reported thicker central and inner macular parameters in Caucasian compared with East Asian children, which is in agreement with our current findings.[16] In contrast with these findings, Grover et al[134] using Spectralis OCT (Heidelberg Engineering, Vista, California, USA) reported that central macular thickness was 279.5 ± 27.4μm in Asian (n=11) and 272.7 ± 20.8 μm in Caucasian (n=28) participants, the difference did not reach statistical significance. The low numbers and wide age range of participants in their study and the use of a different OCT instrument could be reasons for the discrepancy with our results. We are unaware of any studies directly comparing macular thickness in East Asian and Caucasian populations using Cirrus HD-OCT. However, Cirrus HD-OCT studies in East Asian populations[85,182] have reported thinner central macular values than studies in Caucasian populations[126,138], which adds weight to our current findings. The difference in central macular thickness found between these two ethnic groups could be a result of anatomic variation between individuals of different races, and it has been suggested that it is not simply thickness that differs between races but rather the actual shape of the foveal pit.[138]

Using the Cirrus HD-OCT we found that there is a significant increase in central macular thickness with increasing AL and decreasing spherical equivalent refraction. This positive relationship of central macular thickness with AL has been previously reported using time domain OCT[111,115,123,125,139,140], however not all studies have found this relationship.[17,144] With Cirrus HD-OCT Song et al[182] (n=198) found no relationship between AL or refraction with central macular thickness. One reason for this discrepancy could be that larger sample sizes

are needed to demonstrate this relationship. Another factor could be the ethnicities of our samples are different and differences in the foveal pit morphology could account for the disparity of results.[183] The reason for increasing central macular thickness measurement with increasing AL is unknown. We propose that the central subfield scanning area in eyes with longer AL encroaches on the thickened perifoveal region and thus produces larger central macular thickness measurements as a result. Ooto et al[135] also investigated the effect of AL on macular thickness measured by spectral domain OCT (3D OCT 1000). After adjusting for scan length magnification they found no association between AL and macular thickness in any of the ETDRS subfields, which also suggests that the relationship of axial length and macular thickness may be an artifact of the scan magnification.

We found inner and outer subfield thickness decreased with increasing AL and more myopic refractions. This is consistent with findings of larger populations using Stratus OCT.[16,125,140] Song et al [182] using Cirrus HD-OCT were able to find a correlation between increasing AL and outer subfield macular thickness, however they did not find any association with inner macular thickness. A possible explanation for this finding is that there is a finite amount of retinal substance which needs to spread over a larger area in elongated eyes leading to a thinner retina. Alternatively, this finding may be due to an artifact of increased scanning diameter as suggested by the results of Ooto et al using scan length adjustment.[135] We are unaware of any commercial software that adjusts the retinal scan area for AL, and until such software becomes available clinicians using the Cirrus HD-OCT should consider the effects of AL on macular measurements.

The strengths of this study include a large population based sample, uniform examination technique and the lack of ocular morbidity in this young population allowing us to demonstrate normal anatomical relationships. However the use of this population may also be seen as a limitation as the demonstrated relationships may not be applicable to older cohorts. Sung et al[80] have found a thinning of the inner and outer subfields with increasing age, presumably due to the loss of ganglion cells and retinal nerve fibre layer axons, and an age related thickening of the central macula has also been described.[115]

In conclusion, this study describes normal macular thickness values for a young adult population as measured by Cirrus HD-OCT. The macular thickness is found to vary with sex, ethnicity, AL and refraction. The normative values and relationships described can help clinicians in discriminating normal variation from pathologic change.

Table 5.1 Characteristics of Participants

Characteristic	**All (n = 1529)***	**Caucasian (n = 842)**	**East Asian (n = 306)**
Age, years	17.3 ± 0.55	17.4 ± 0.5	17.4 ± 0.7
Male *n*, (%),	763 (49.9)	450 (53.4)	134 (43.8)
SER, D	0.1 ± 1.6	0.6 ± 1.0	-1.1 ± 2.2
AL, mm	23.7 ± 0.9	23.5 ± 0.8	24.1 ± 1.2
Height, cm	169.4 ± 9.6	172.0 ± 9.4	165.0 ± 8.7
Weight, kg	65.8 ± 14.9	67.7 ± 14.7	59.6 ± 12.8

D = Diopter; SER = Spherical equivalent refraction; AL = Axial length

*Includes South Asian (n = 102), Middle Eastern (n = 134) and other (n= 145) ethnicities.

Table 5.2 Distribution of Macular Parameters (n = 1529)

	Mean (SD)	Median	Range	Kurtosis	Skew	K-S
Thickness (µm)						
Central Subfield	255.3 (20.3)	255	196 – 332	0.16	0.21	0.03
Average Cube	284.1 (12.7)	284	234 – 325	0.28	-0.03	0.03
Average Inner	322.4 (15.4)	322	268 - 367	0.0007	-0.06	0.02
Inner Temporal	312.4 (15.6)	312	255 – 356	0.10	-0.10	0.03
Inner Superior	327.1 (15.6)	327	271 – 374	0.10	-0.02	0.03
Inner Nasal	327.8 (16.3)	327	272 – 378	-0.09	-0.01	0.02
Inner Inferior	322.2 (15.8)	322	268 – 366	-0.01	-0.06	0.02
Average Outer	279.7 (13.1)	280	223 – 323	0.40	-0.03	0.02
Outer Temporal	263.6 (13.2)	264	200 – 305	0.49	-0.10	0.03
Outer Superior	283.2 (13.7)	283	228 – 332	0.37	0.05	0.03
Outer Nasal	301.7 (15.5)	301	249 – 355	0.37	0.12	0.04
Outer Inferior	270.3 (13.8)	270	213 – 312	0.35	-0.01	0.03
Volume (mm^3)						
Cube	10.2 (0.5)	10.2	8.4 – 11.7	0.25	-0.03	0.06
Total ETDRS	8.1 (0.4)	8.1	6.7 – 9.4	0.31	-0.04	0.02

ETDRS = Early Treatment of Diabetic Retinopathy Study (6mm circular grid)
K-S = Kolmogorov-Smirnov (<0.05 not normally distributed)

Table 5.3 Gender-Specific Differences of Macular Parameters

	Males* **Mean ± SD** **n = 763**	**Females*** **Mean (SD)** **n = 766**	**P***	**Difference†** **Mean (95% CI)**	**P†**
Thickness (µm)					
Central Subfield	261.6 (19.7)	249.0 (18.8)	<0.0001	10.2 (7.4 – 12.9)	<0.0001
Average Cube	286.1 (12.1)	282.0 (13.0)	<0.0001	3.7 (1.9 – 5.5)	<0.0001
Average Inner	326.9 (14.4)	317.9 (15.1)	<0.0001	7.7 (5.6 – 9.8)	<0.0001
Inner Temporal	317.3 (14.3)	307.6 (15.3)	<0.0001	8.0 (5.9 – 10.1)	<0.0001
Inner Superior	331.3 (14.6)	322.9 (15.9)	<0.0001	7.5 (5.4 – 9.6)	<0.0001
Inner Nasal	332.4 (15.4)	323.2 (16.0)	<0.0001	8.2 (6.0 – 10.4)	<0.0001
Inner Inferior	326.6 (15.0)	317.8 (15.3)	<0.0001	7.1 (5.0 – 9.2)	<0.0001
Average Outer	281.4 (12.6)	278.0 (13.5)	<0.0001	3.5 (1.7 – 5.3)	0.0002
Outer Temporal	266.9 (12.2)	260.4 (13.4)	<0.0001	6.4 (4.6 – 8.1)	<0.0001
Outer Superior	284.1 (12.8)	282.3 (14.6)	0.01	2.4 (0.5 – 4.3)	0.01
Outer Nasal	281.4 (12.6)	278.0 (13.5)	0.0003	3.4 (1.2 – 5.7)	0.002
Outer Inferior	271.6 (13.7)	269.1 (13.8)	0.0005	1.9 (0.0 – 3.7)	0.05
Volume (mm^3)					
Cube	10.3 (0.4)	10.2 (0.5)	<0.0001	0.13 (0.07 – 0.20)	<0.0001
Total ETDRS	8.2 (0.4)	8.1 (0.4)	<0.0001	0.13 (0.08 – 0.18)	<0.0001

*raw data

†adjusted for age, height, axial length and ethnicity

ETDRS = Early Treatment of Diabetic Retinopathy Study (6mm circular grid)

Table 5.4 Ethnic Differences of Macular Parameters

	Caucasian* **Mean ± SD** **n = 842**	**East Asian*** **Mean ± SD** **n = 306**	**P***	**Difference†** **Mean (95% CI)**	**P†**
Thickness (µm)					
Central Subfield	260.7 (20.1)	247.7 (18.2)	<0.0001	11.9 (8.8 – 15.1)	<0.0001
Average Cube	286.0 (12.5)	281.1 (12.8)	<0.0001	1.9 (-0.1 – 3.9)	0.06
Average Inner	325.5 (14.9)	317.0 (15.1)	<0.0001	4.7 (2.4 – 7.0)	<0.0001
Inner Temporal	315.4 (14.9)	307.8 (15.6)	<0.0001	3.8 (1.5 – 6.1)	0.001
Inner Superior	329.9 (15.3)	322.2 (15.3)	<0.0001	4.1 (1.8 – 6.4)	0.0006
Inner Nasal	331.0 (16.0)	322.5 (15.6)	<0.0001	4.8 (2.4 – 7.3)	0.0001
Inner Inferior	325.7 (15.2)	315.7 (15.3)	<0.0001	6.0 (3.6 – 8.3)	<0.0001
Average Outer	281.3 (13.0)	277.3 (13.5)	<0.0001	0.8 (-1.3 – 2.8)	0.45
Outer Temporal	265.5 (12.7)	261.0 (13.9)	<0.0001	0.6 (-1.4 – 2.6)	0.57
Outer Superior	284.1 (13.6)	282.3 (14.2)	0.05	1.2 (-3.4 – 0.9)	0.26
Outer Nasal	302.8 (15.8)	299.4 (15.1)	0.0009	1.1 (-1.4 – 3.5)	0.38
Outer Inferior	272.7 (13.6)	266.3 (14.2)	<0.0001	2.8 (0.7 – 4.9)	0.01
Volume (mm^3)					
Cube	10.3 (0.5)	10.1 (0.5)	<0.0001	0.07 (0.0 – 0.1)	0.07
Total ETDRS	8.2 (0.4)	8.1 (0.4)	<0.0001	0.05 (0.0 – 0.1)	0.05

*raw data

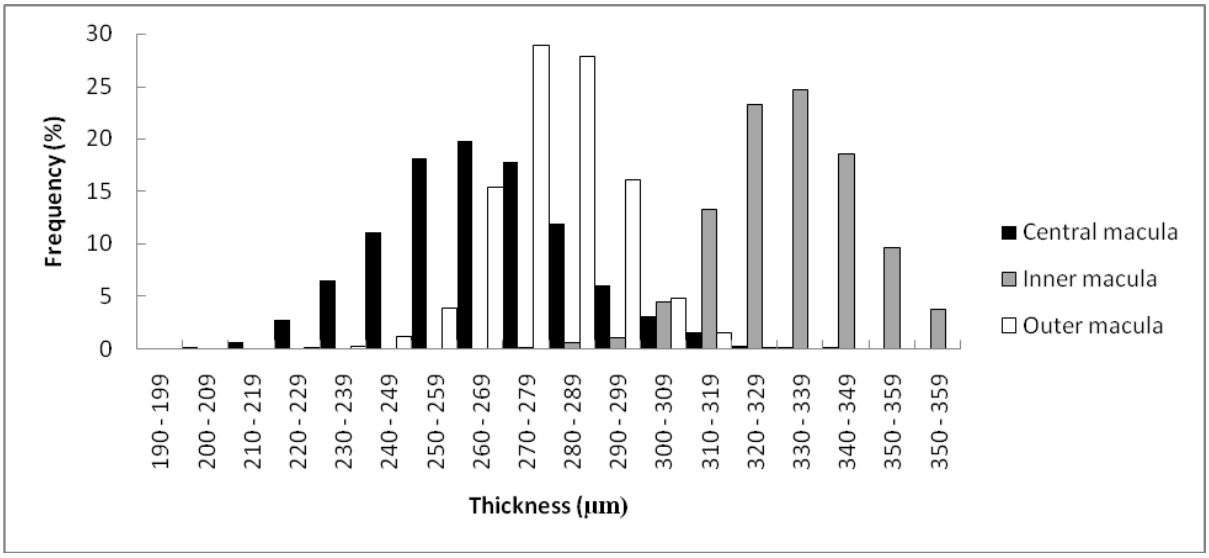
†adjusted for age, sex, height and axial length

ETDRS = Early Treatment of Diabetic Retinopathy Study (6mm circular grid)

Table 5.5 Normal Limits (5^{th} – 95^{th} percentiles) of Macular Parameters in Comparison with Cirrus In-built Dataset

	Current Study	**Cirrus in-built database for 18 year old**
Thickness (µm)		
Central Subfield	222 – 291	214 – 282
Average Cube	264 – 305	263 – 301
Inner Temporal	286 – 337	285 – 333
Inner Superior	301 – 353	302 – 349
Inner Nasal	302 – 354	300 – 350
Inner Inferior	297 – 347	296 – 342
Outer Temporal	242 – 284	242 – 280
Outer Superior	261 – 305	259 – 303
Outer Nasal	278 – 328	280 – 327
Outer Inferior	248 – 293	249 – 289
Cube volume (mm^3)	9.5 – 11.0	9.5 – 10.8

A



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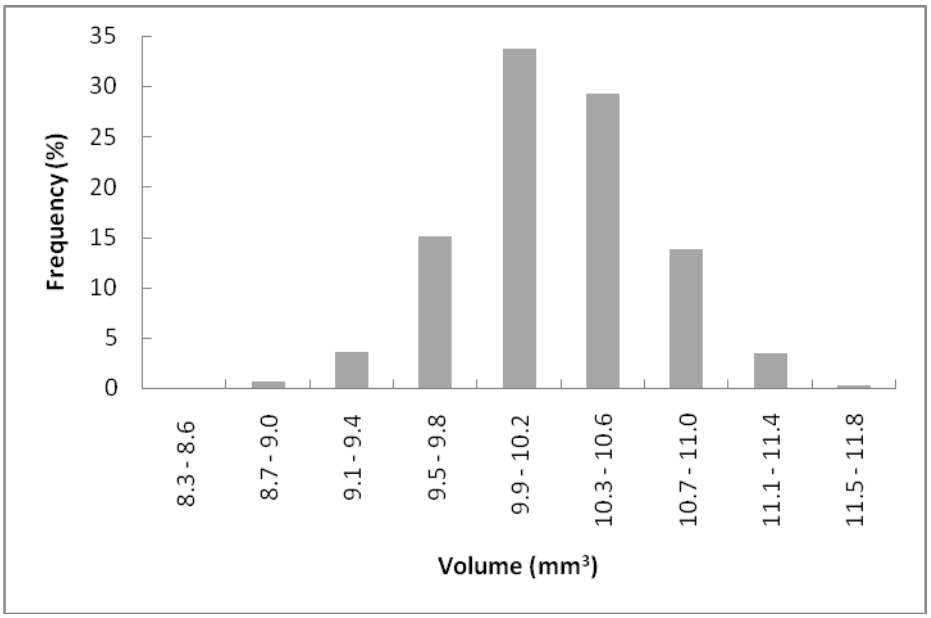


Figure 5.1 Distribution of the mean (A) central, inner and outer macular subfield thicknesses and (B) total macular cube volume (n = 1529)

CHAPTER 6

Macular Measurements in Children

Abstract:

Purpose: To determine the normative values of Cirrus HD-OCT measured macular parameters in an adolescent population and determine the variation of these parameters by gender, ethnicity and ocular parameters.

Methods: Eye examinations were carried out on school students aged 10 to 15 years as part of the Sydney Adolescent Vascular and Eye Study. Macular parameters were measured with a spectral domain optical coherence tomography (OCT) instrument (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA). Visual acuity assessment, cycloplegic autorefraction and optical biometry measurements were also performed.

Results: OCT measurements on 1056 children were included in analysis. Participants had a mean age of 12.5 ± 1.0 years and 51.7% were male. The central subfield had a mean thickness of 255.4 ± 19.0 µm. The average cube thickness was 283.5 ± 12.2 µm, average inner thickness was 321.5 ± 13.5 µm and average outer thickness was 279.8 ± 12.6 µm. Males had thicker macular parameters compared with females in analysis adjusted for age, height, axial length and ethnicity. The differences were greatest in the central macula and least in the outer subfield. Caucasian children had thicker central macula than East Asian children by an average of 11.2µm (95% CI 7.5 – 14.9µm), in data adjusted for age, sex, height and axial length. Axial length was negatively associated with inner and outer subfield macular thickness, and spherical equivalent refraction was positively associated with these parameters.

Conclusions: This study provides normative macular data as measured by Cirrus HD-OCT in children.

Introduction

Optical coherence tomography (OCT) retinal imaging provides detailed qualitative and quantitative measurement of retinal parameters. The current commercial instruments employ spectral domain technology to provide high resolution imaging of retinal structures. This technology has shown great utility in the diagnosis and monitoring of retinal diseases including diabetic macular oedema, age related macular degeneration, macular holes and macular dystrophy.[8-12] OCT is especially useful in younger patients given that it provides detailed information without having to dilate the pupil or having the patient fixate on bright lights.

Cirrus HD-OCT is a spectral domain OCT instrument available for clinical use. Only a few studies have provided normative data from the Cirrus HD-OCT and these studies have been on adult samples.[138,182] Even the current Cirrus HD-OCT internal database is based on measurements of individuals greater than 18 years of age. Clinicians examining macular structure with this instrument in children under the age of 18 years do not have a normative dataset with which to compare their measurements. Given the high resolution of this instrument having comprehensive normative information allows clinicians to better delineate pathologic change from normal variation.

A young adolescent population is also ideal for assessing the associations of retinal thickness with demographic and ocular parameters as this population is largely free of ocular disease which would confound such analysis. The purpose of the current study is to provide normative macular data as measured by Cirrus HD-OCT in a young adolescent population and to determine ocular and demographic factors associated with variation in these parameters.

Specific Methods

Statistical analysis was performed using SAS, Version 9.2 (SAS Institute, Cary NC). For the purposes of this report only scans of the right eye with signal strengths ≥ 8 were used in analysis. The Kolmogorov-Smirnov (K-S) test was used to assess for normality of distributions. The paired t-test was used to compare macular quadrant data. For comparisons of parameters between genders and ethnicity, mixed linear models[150] were employed adjusting for covariates (age, height, axial length and cluster sampling). Mixed linear models were also used to test associations of AL, refraction and height with macular parameters.

Results

Testing was offered to 1618 school children; of these 1068 (66.0%) children had right eye macular OCT scanning. Of these 2 were excluded for signal strength less than 8 and a further 8 were excluded due to visual acuity ≤ 20/40 in the right eye. Another 2 children were excluded due to ocular pathology including Coats' Disease in left eye and ocular albinism leaving 1056 right eye macular scans for analysis. Demographic data for this sample is presented in **Table 6.1**. The mean age of the population was 12.5 ± 1.0 years with a range of 10 to 15 years and 51.7% were male.

The distribution of macular parameters is presented in **Table 6.2**. The central subfield had a mean thickness of 254.4 ± 19.0 μm and a range of 187 to 326 μm. The average cube thickness was 283.5 ± 12.2 μm, average inner thickness was 321.5 ± 13.5 μm and average outer thickness was 279.8 ± 12.6 μm. In the inner subfield the temporal quadrant was the thinnest followed by the inferior, then superior with the nasal quadrant thickest. The same pattern of relative thickness is seen in the outer subfield. All these quadrant differences were

found to be significantly different ($P < 0.001$) using the paired t-test. None of the parameters met the Kolmogorov-Smirnov test criteria for a normal distribution. **Figure 6.1** shows the distributions of the main macular parameters.

The mean macular parameters stratified by gender are seen in **Table 6.3**. Males had thicker macular parameters compared with females in analysis adjusted for age, height, AL and ethnicity. The differences were greatest in the central macula and least in the outer subfield.

The difference in macular parameters between Caucasian and East Asian participants is presented in **Table 6.4**. In data adjusted for age, sex, height and AL significant differences were seen in the central and inner subfields, with Caucasians having a greater macular thickness in these areas, except for the inner superior macula which showed no difference between the two groups. The greatest difference was in the central macula with the mean Caucasian thickness 11.2µm (95% CI 7.5 – 14.9µm) greater than the mean East Asian thickness. In the outer subfield only the superior macular thickness showed a significant difference between ethnicities with East Asians having significantly thicker macula in this region after adjusting for age, sex, height and AL.

In a model adjusting for age, sex, height and ethnicity, AL was not associated with central subfield thickness and was negatively associated with inner and outer subfield thickness (β = -3.0 and -4.9 µm/mm respectively, both $P < 0.0001$). Cube average thickness and volume were also negatively associated with AL (β = -4.2µm/mm and -0.15mm^3/mm respectively, both $P<0.0001$). In the same statistical model, height was positively associated with average cube thickness and cube volume (β = 0.12 µm/cm and 0.0004 mm^3/cm respectively, both P = 0.01). In models adjusting for age, sex, height and ethnicity, spherical equivalent refraction

was positively associated with inner (β = 1.03μm/D, P = 0.002), outer (β = 1.8 μm/D, P<0.0001) and average cube macular thickness (β = 1.5 μm/D, P<0.0001) and cube volume (β = 0.06 mm^3/D, P < 0.0001).

Discussion

In this study we report normative values of macular parameters measured by Cirrus HD-OCT in a very large young adolescent population-based sample. We also report variations in these parameters by gender, ethnicity, AL, refraction and height.

The Cirrus HD-OCT instrument has an in-built database which will provide the user with normal limits for a patient based on their age. However, this in-built database was developed using a sample aged 19 to 84 years of age, and therefore has not been verified for younger populations. Our sample in the current study comprises individuals between 10 and 15 years. **Table 6.5** presents the 5^{th} to 95^{th} percentile limits based on the individuals in the current study and those of the Cirrus HD-OCT database for an individual at 18 years of age. There are only very small differences seen between the two datasets. The largest difference seen is in the central subfield where the lower limit is 214μm in the Cirrus HD-OCT dataset and 225μm based on our data. This 9 μm difference is not likely to present any real clinical significance in the day to day usage of the instrument.

To our knowledge there are no studies presenting normative macular data on childhood samples using Cirrus HD-OCT. The largest published normative study to date on Cirrus HD-OCT was perfomed by Song et al.[182] They examined 198 Korean individuals between the ages of 17 to 83, using the 512 × 128 macular scanning protocol. Their findings for mean macular parameters were central subfield 253.92 ± 24.18 μm, average inner 313.38 ± 19.22

μm, average outer 272.23 ± 14.6μm and total cube volume 9.74 ± 0.71mm^3. Their central subfield value lies between our Caucasian and East Asian value, however their inner and outer subfield values are less than those for both ethnic groups in our sample. These differences are under 10μm in magnitude. The differences could be due to the age differences between our samples or the different scanning protocols.

The macular area demonstrated a thin central macula surrounded by a thickened inner macular ring and then a thinner outer macular region, this pattern has been consistently reported in previous OCT studies.[16,19,60,115,134,135,138,182] The relative thickness of the quadrants that we found (nasal > superior > inferior > temporal) has been consistently reported in studies with spectral domain OCT instruments,[85,117-119,124,126,126,128,133,134,138,182] but not in Stratus OCT studies.[16,60,114-116] The likely reason for this difference is the lower number of scanning points and resolution in the Stratus OCT compared with spectral domain instruments, which would result in a decreased ability to discriminate the different quadrant thicknesses.

In data adjusted for age height, ethnicity and AL we found that males had thicker central, inner and outer macular parameters compared with females. However, the inter-sex difference for the outer macular thickness was small but significant after adjusting for confounding factors. Previous studies utilizing spectral domain technology have reported central and inner macular parameters to be thicker in males compared with females, but not outer macular thickness.[16,60,115,135,138,182] The reason that these studies did not find an inter-sex difference in the outer macula may be related to their smaller sample sizes and the lack of adjustment for confounding factors.

We found that Caucasian children had thicker central macular thickness compared with East Asian children. Inner macular thickness, except for the superior quadrant, was also thicker in Caucasian children compared with East Asian children after adjusting for confounding factors. In a 6 year old cohort examined with the Stratus OCT we previously reported that Caucasian children had thicker central and inner macula than East Asian children.[16] Also, Cirrus HD-OCT macular values reported in studies using East Asian populations[85,182] are generally thinner than those reported in Caucasian populations[126,138]. The ethnic differences found in macular thickness could reflect anatomic variations in foveal pit morphology between these ethnic groups.[138]

In analysis adjusted age, sex, ethnicity and height we found that inner macula, outer macula and average cube thickness as well as total cube volume decreased with increasing AL. Song et al[182] also utilizing Cirrus HD-OCT found that outer macular thickness, but not inner macula thickness, decreased with increasing AL. Also studies with large sample sizes using Stratus OCT have also reported thinning of macular parameters with increasing AL.[16,125,140] It is possible that the retinal tissue needs to spread over larger areas in elongated eyes resulting in decreased thickness. However another explanation is that this finding is an artifact of retinal scanning by OCT, as the scan lengths are not adjusted for AL related magnification, resulting in larger scan areas in eyes with larger AL. A study by Ooto et al[135] is in support of this hypothesis. They found no association between AL and macular thickness in any of the ETDRS subfields after adjusting for scan length magnification. Whatever the actual association of macular thickness and AL, clinicians should be aware that this relationship exists in Cirrus HD-OCT.

The strengths of this study include the large population based sample of school children and uniform examination techniques. The low prevalence of ocular and systemic disease in this age group allows determination of true anatomical relationships in absence of such pathology. A limitation of this study is the low participation rate (66.0%) which has a potential to bias the results.

In conclusion, this study presents Cirrus HD-OCT measured macular parameters for a young adolescent sample. The values presented can be utilized by clinicians examining children below the age range of the Cirrus HD-OCT internal database. Also demonstrated are the associations of macular parameters with gender, ethnicity and AL. An understanding of these normal anatomic associations helps clinicians to better identify pathologic change.

Table 6.1 Characteristics of Participants

Characteristic	**All*** **(n = 1056)**	**White** **(n = 652)**	**East Asian** **(n = 235)**	**P value**
Age, years	12.5 ± 1.0†	12.7 ± 1.0	11.8 ± 0.7	<0.0001
Male *n*, (%),	546 (51.7)	318 (48.8)	120 (51.1)	0.55
SER, D	0.46 ± 1.32	0.81 ± 1.01	-0.61 ± 1.63	<0.0001
AL, mm	23.5 ± 0.9	23.3 ± 0.8	24.0 ± 0.9	<0.0001
Height, cm	155.3 ± 9.2	156.7 ± 9.2	150.8 ± 7.9	<0.0001
Weight, kg	48.1 ± 12.2	49.0 ± 11.9	43.2 ± 10.2	<0.0001

* Consists of 652 white, 235 East Asian, 14 South Asian, 46 Middle Eastern and 109 from other ethnicities.
†Range 10 – 15 years
D = Diopter; SER = Spherical equivalent refraction; AL = Axial length

Table 6.2 Distribution of macular parameters

	Mean (SD)	Median	95% Range	Range	Kurtosis	Skew	K-S
Thickness (µm)							
Central Subfield	254.4 ± 19.0	254.5	218 – 293	187 – 326	0.41	0.17	0.02
Average Cube	283.5 ± 12.2	283	260 – 310	229 – 335	0.82	0.27	<0.01
Average Inner	321.5 ± 13.5	320	296 – 350	280 – 386	0.50	0.27	0.03
Inner Temporal	312.3 ± 13.5	312	285 – 341	271 – 381	0.57	0.24	<0.01
Inner Superior	325.9 ± 13.9	326	299 – 356	281 – 387	0.51	0.27	<0.01
Inner Nasal	326.6 ± 14.4	326	298 – 356	282 – 387	0.31	0.23	<0.01
Inner Inferior	321.4 ± 14.1	321	294 – 350	279 – 388	0.45	0.23	<0.01
Average Outer	279.8 ± 12.6	279	256 – 308	236 – 327	0.49	0.34	<0.01
Outer Temporal	264.2 ± 12.3	264	241 – 291	225 – 318	0.62	0.31	<0.01
Outer Superior	283.4 ± 13.6	283	257 – 314	238 – 328	0.40	0.32	<0.01
Outer Nasal	301.3 ± 14.9	300	274 – 334	251 – 356	0.59	0.37	<0.01
Outer Inferior	270.3 ± 13.5	270	244 – 300	229 – 321	0.35	0.31	<0.01
Volume (mm^3)							
Cube	10.21 ± 0.44	10.20	9.3 – 11.1	8.2 – 12.0	0.84	0.26	<0.01
Total ETDRS	8.14 ± 0.35	8.11	7.5 – 8.9	6.95 – 9.61	0.59	0.35	<0.01

ETDRS = Early Treatment of Diabetic Retinopathy Study (6mm circular grid)
K-S = Kolmogorov-Smirnov (<0.05 not normally distributed)

Table 6.3 Gender-Specific Differences of Macular Parameters

	Difference† Mean (95% CI)	P†
Thickness (µm)		
Central Subfield	7.8 (5.5 – 10.1)	<0.0001
Average Cube	4.3 (2.8 – 5.8)	<0.0001
Average Inner	6.6 (4.9 – 8.3)	<0.0001
Inner Temporal	6.9 (5.2 – 8.6)	<0.0001
Inner Superior	6.3 (4.6 – 8.0)	<0.0001
Inner Nasal	6.5 (4.7 – 8.2)	<0.0001
Inner Inferior	6.7 (5.0 – 8.5)	<0.0001
Average Outer	4.0 (2.5 – 5.6)	<0.0001
Outer Temporal	6.0 (4.5 – 7.5)	<0.0001
Outer Superior	3.4 (1.8 – 5.1)	<0.0001
Outer Nasal	3.6 (1.7 – 5.5)	0.0001
Outer Inferior	3.1 (1.4 – 4.8)	0.0003
Volume (mm^3)		
Cube	0.15 (0.10 – 0.21)	<0.0001
Total ETDRS	0.13 (0.09 – 0.18)	<0.0001

† Boys minus Girls, adjusted for age, height, axial length and ethnicity

Table 6. 4 Ethnic Differences of Macular Parameters

	Difference† Mean (95% CI)	P
Thickness (µm)		
Central Subfield	11.2 (7.5 – 14.9)	<0.0001
Average Cube	0.3 (-1.8 – 2.3)	0.79
Average Inner	2.9 (0.6 – 5.1)	0.01
Inner Temporal	2.7 (0.4 – 4.9)	0.02
Inner Superior	1.9 (-0.5 – 4.2)	0.12
Inner Nasal	2.6 (0.1 – 5.0)	0.04
Inner Inferior	4.4 (2.1 – 6.7)	0.0002
Average Outer	-1.8 (-3.9 – 0.4)	0.11
Outer Temporal	-1.7 (-3.8 – 0.4)	0.11
Outer Superior	-3.6 (-6.1 – -1.2)	0.003
Outer Nasal	-2.2 (-4.8 – 0.4)	0.10
Outer Inferior	0.4 (-1.8 – 2.7)	0.71
Volume (mm^3)		
Cube	0.01 (-0.06 – 0.08)	0.78
Total ETDRS	-0.01 (-0.07 – 0.05)	0.73

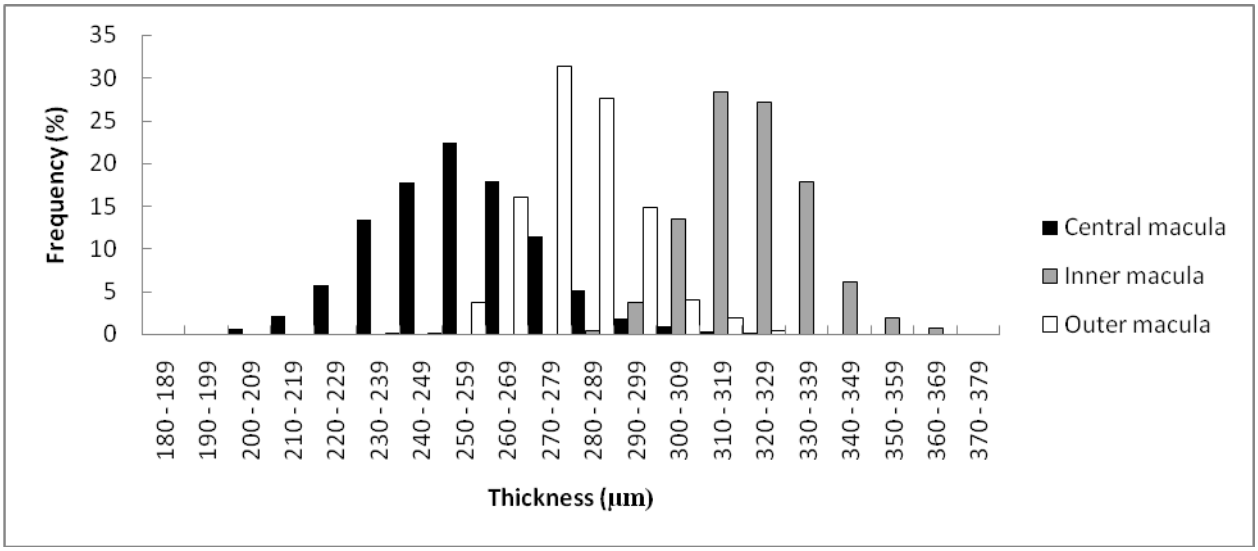
†Caucasian minus East Asian, adjusted for age, sex, height, axial length
ETDRS = Early Treatment of Diabetic Retinopathy Study (6mm circular grid)

Table 6.5 Comparison of Normal limits of Macular Parameters (5^{th} to 95^{th} percentiles)

	Current Study	Cirrus range *
Thickness (µm)		
Central Subfield	225 – 284	214 – 282
Average Cube	265 – 303	263 – 301
Inner Temporal	291 – 334	285 – 333
Inner Superior	304 – 349	302 – 349
Inner Nasal	304 – 350	300 – 350
Inner Inferior	299 – 343	296 – 342
Outer Temporal	245 – 284	242 – 280
Outer Superior	262 – 307	259 – 303
Outer Nasal	278 – 326	280 – 327
Outer Inferior	249 – 293	249 – 289
Cube Volume (mm^3)	9.5 – 10.9	9.5 – 10.8

*Normal range in Cirrus in-built database for an 18 year old individual

A



B

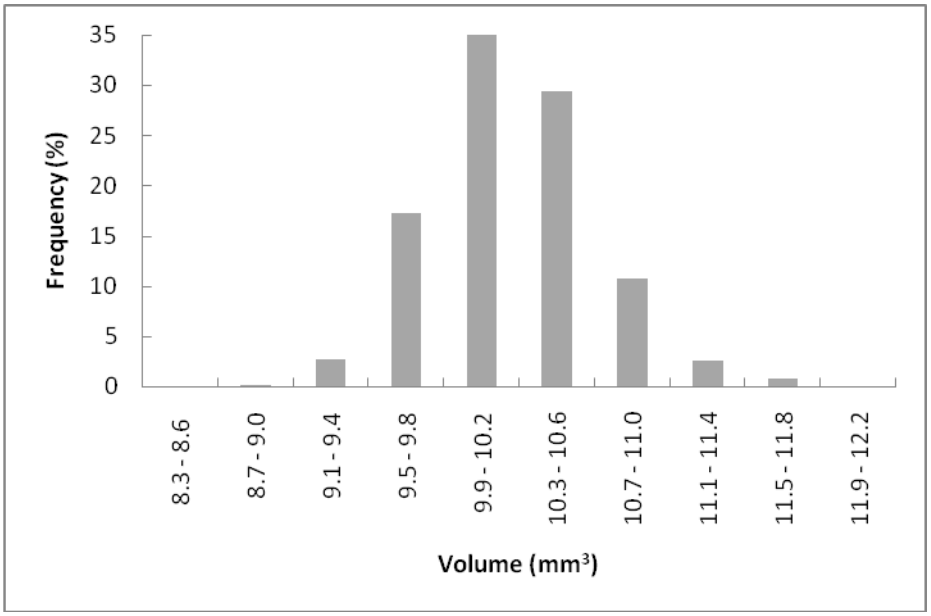


Figure 6.1 Distribution of the mean (A) central, inner and outer macular subfield thicknesses and (B) total macular cube volume (n = 1056)

CHAPTER 7

Ethnic Differences in Macular Thickness

Related publication:

Tariq YM, Li H, Burlutsky G, Mitchell P. Ethnic differences in macular thickness. *Clinical and Experimental Ophthalmology*. 2011;39(9):893-8

Abstract

Purpose: To determine ethnic differences in time-domain (STRATUS) OCT measured macular thickness in 12-year-old children.

Methods: 2367 children from grade 7 (mean age 12.7±0.45 years) recruited as part of the Sydney Myopia Study were examined during 2004-2005. Examination included determination of best corrected logMAR visual acuity (logarithm of minimal angle of resolution) and autorefraction after cycloplegia. Axial length was measured using non-contact interferometry and optical coherence tomography was performed using Stratus OCT. Ethnicity was self reported by participants' parents.

Results: The four largest ethnic groups were Caucasian (n=1224), East Asian (n=291), South Asian (n=107) and Middle Eastern (n=146). The greatest ethnic differences were found at the central macula, which was significantly thicker in Caucasian compared with East Asian, South Asian and Middle Eastern children (mean differences 9.0 µm, 12.1 µm and 6.5 µm respectively, all $p<0.0001$). The average inner macula was significantly thicker in Caucasian than East Asian and South Asian children ($p=0.005$ and $p<0.0001$), respectively. The average outer macula was significantly thicker in Caucasian than Middle Eastern and South Asian children ($p=0.03$ and $p<0.0001$), respectively. South Asian children had thinner inner and outer macula parameters than East Asian children (all $p<0.05$) and thinner inner macula parameters when compared with Middle Eastern children (all $p<0.05$).

Conclusion: Macular parameters were found to vary by ethnicity in 12-year-old children. Caucasian children had the thickest macular parameters and South Asian children had the thinnest. The greatest differences were found in the central macula.

Introduction

Optical coherence tomography (OCT) is a widely used examination technique in the diagnosis and monitoring of retinal pathology.[184] It is especially useful in the quantitative and qualitative evaluation of macular morphology. To utilize the full potential of this technology in determining the presence of pathological change, an understanding of the demographic variables that influence normal variation is required. It was previously shown that ethnicity impacts on macular morphology.[16-19] While previous reports have evaluated differences in macular thickness between Caucasians and African Americans[17-19] or Caucasians and East Asians[16], there have been, to our knowledge, no studies directly comparing other ethnic groups.

In the present study we sought to determine mean differences in macular parameters measured by Stratus OCT between Caucasian, East Asian, South Asian and Middle Eastern individuals. An adolescent population is ideal for this study as it is relatively free from ocular diseases which alter normal macular morphology (e.g., diabetic retinopathy) or conditions affecting the clarity of the ocular media (e.g., cataract).

Specific Methods

The parents of participants completed detailed 193-item questionnaires on demographics, ocular and medical history and birth parameters. Ethnicity was determined based on self-identification by parents by choosing from a list of ethnicities including Caucasian (European), East Asian, Indian/Pakistani/Sri Lankan, African, Melanesian/Polynesian, Middle Eastern, Indigenous Australian, South American and other. A child was considered to

belong to a specific ethnic group if both parents self-identified with a common ethnicity. If the mother and father had different ethnicities the child was classified as having mixed ethnicity, similarly if one or both parents were of mixed ethnicity then the child was classified as having mixed ethnicity. In this paper ethnicity was categorised into Caucasian (European), East Asian, Middle Eastern and South Asian groups. East Asian ethnicity included children from China, Malaysia, Singapore, Indonesia, Philippines, Japan, Korea, Myanmar, Thailand, Laos, Cambodia, and Vietnam. South Asian ethnicity included children from India, Pakistan, Sri Lanka and Nepal. Children of mixed ethnicity and from ethnicities with smaller numbers including Oceanian, African, Indigenous, and South American were excluded from the current analyses.

Statistical analysis was performed using SAS, Version 9.2 (SAS Institute, Cary NC). Only OCT scans of the right eye with signal strength greater than 5 were used. To compare the baseline characteristics of participants (age, gender, visual acuity, axial length, spherical equivalent, height, weight and body mass index) in each ethnic group we used t-tests and chi-square tests. For comparison of macular parameters between ethnic groups mixed linear models[150] were employed adjusting for covariates (age, sex, height and axial length) with the school attended included as a random effect.

Results

The study included 2,367 participants and of these 2,068 (88%) had adequate quality macular scans. The four largest ethnic groups were Caucasian (n=1,224), East Asian (n=291), South Asian (n=107) and Middle Eastern (n=146) children. Characteristics of participants included in this study are presented in **Table 7.1**. The average age of the participants was 12.7 ± 0.45 years, and 52.4% of the group was male. **Table 7.2** presents ethnic differences between

baseline characteristics. The main differences were in visual acuity, axial length, spherical equivalent and height. For example, Caucasian children had better presenting visual acuity (57.4 ± 4.2 vs. 53.0 ± 8.1 letters, P<0.0001), shorter axial length (23.24 ± 0.73 vs. 23.84 ± 1.00mm, P<0.0001), were more hyperopic (0.81 ± 0.79 vs. -0.55 ± 1.69D, P<0.0001), were taller (156.5 ± 8.1 vs. 154.5 ± 7.7cm, P = 0.0001) and weighed more (49.9 ± 12.5 vs. 47.6 ± 11.8kg, P = 0.004) than East Asian children.

Table 7.3 presents macular characteristics in different ethnic groups. **Tables 7.4 and 7.5** present the mean differences between ethnic groups. The central macula and foveal minimum thickness were significantly greater in Caucasian children than children of East Asian, South Asian and Middle Eastern ethnicity (all P<0.0001). The greatest differences were between Caucasian and South Asian children for these central macular parameters, with Caucasian children having a foveal minimum 8.6µm (P<0.0001) thicker than South Asian children and a central macula 12.1µm (P<0.0001) thicker. There were no significant differences for the central macula and the foveal minimum between East Asian, South Asian and Middle Eastern groups, apart from the Middle Eastern children having a 5.6µm (P=0.02) thicker central macula than the South Asian children. Similarly, central macular volume was significantly thicker in Caucasian than in East Asian, South Asian and Middle Eastern children.

The inner macular parameters compared with the foveal minimum and central macular parameters displayed smaller differences between ethnic groups. The greatest differences were seen between Caucasian and East Asian children with the inner macula being 8.1µm thinner in East Asians versus Caucasian children (P<0.0001) (Table 4). South Asian children had a thinner average inner macula compared with both East Asian and Middle Eastern children with a difference of 5.1µm (P = 0.002) and 5.5µm (P = 0.004), respectively (**Table**

7.5). There were no significant differences between the East Asian and Middle Eastern children for inner macular parameters. The ethnic differences seen in the 4 quadrants of the inner macula were similar to the differences in the average inner macula (data not shown).

Caucasian children had an average outer macula 5.6µm (P<0.0001) thicker than South Asian children and 2.7µm (P = 0.03) thicker than Middle Eastern children (Table 4). East Asian children had an average outer macula 5.5µm (P = 0.0002) thicker than South Asian children (Table 5). The Caucasian children had a larger total macular volume than South Asian children (P<0.0001) and Middle Eastern children (P = 0.02). South Asian children had a larger total macular volume than South Asian children (P = 0.0002).

Discussion

In this population based sample of predominantly 12-year-old children there were significant differences between ethnic groups for OCT measured macular parameters. These differences were greatest between Caucasian and South Asian groups. The central macular region had the greatest differences with Caucasian children having a significantly thicker central macula compared with the other three ethnicities.

In a previous report we compared macular parameters between East Asian and Caucasian children at age 6 years.[16] The foveal minimum was 8.2µm thicker, the central macula was 9.3µm thicker and the average inner macula was 2.8µm thicker (all P≤0.0005) in Caucasian children. The mean differences seen in this younger population were remarkably similar to those seen in our 12-year-old group, suggesting that ethnic variability in macular parameters does not change during these childhood years. A study by El Ashry et al[116] found in their adult British population that mean minimum foveal thickness in East Asians was 150.3 ±

4µm compared with 173.4 ± 21µm for Caucasians which is in agreement with our finding of thicker central macular parameters in Caucasians compared with East Asians.

The mean minimal foveal thickness reported by El Ashry et al[116] in their South Asian population (denoted as Indian) was 176.3 ± 16µm, which was very similar to their value for Caucasians (173.4 ± 21µm) and thicker than their value for East Asians (150.3 ± 4µm). The El Ashry findings contrast with our finding of a significantly thinner foveal minmum in South Asian compared with Caucasian children, and that of no significant difference between South Asian and East Asian children. This discrepancy with our results may be due to the adult population with a wide age range (21 to 81 years), and a lack of adjustment for confounding variables and comparatively small sample size (n=100) in the El Ashry study. In another report of macular thickness in a South Asian population, Tewari et al[185] report a mean foveal minimum thickness of 149.2 ± 21µm, similar to our value.

Many studies have documented normative values for macular parameters in Caucasian[80,114,186] and East Asian[66,115,123] populations. However, few studies are available for younger populations. In an American study, El Dairi et al[19] in a Caucasian population aged between 3 to 17 years (n=154), reported a Stratus OCT measured mean central macular thickness of 198 µm (95% CI 160 – 237 µm), which is very similar to our value of 200.3 µm (95% CI 198.4 – 202.2 µm). In an East Asian population aged 11 to 12 years, Luo et al[125] reported a Stratus OCT measured mean minimum foveal thickness of 157.0 µm (95% CI 119.4 – 194.6 µm), which is remarkably similar our East Asians cohort of 156.1 µm (95% CI 153.1 – 159.1 µm). The similar values for central macular parameters found in these studies add weight to our finding of differences in central macular thickness between these ethnic groups.

It is not clear why macular thickness measured by OCT varies by ethnicity. It has been speculated that the differences in melanin in the retinal pigment epithelium (RPE) in different ethnic groups could alter the OCT low-coherence laser light signal [17,187], as melanin scatters and absorbs light. This attenuated signal may result in a decreased thickness measurement in more darkly pigmented individuals. Further research, including histologic studies and studies with higher resolution spectral domain OCT, is needed to determine how ethnicity impacts on retinal thickness and which retinal layers are particularly affected.

Two recent papers have utilized the newer generation spectral domain OCT to examine ethnic differences in macular morphology. Grover et al[134] and Wagner-Schuman et al[188] have both reported a reduction in central macular thickness in African Americans compared with Caucasians, consistent with Stratus OCT reports. Grover et al[134], using the Spectralis OCT (Heidelberg Engineering, Vista, CA), also examined Asian subjects (ethnicity not further specified) and found a thicker central macula (279.5 ± 16.9μm) compared with their Caucasian group (272.7 ± 20.8 μm), a finding that is in contrast with the present study. However, they had a small number of Asian subjects (n=11) which decreases the validity of their findings. Also the use of the Spectralis OCT system by Grover et al may mean comparability with Stratus OCT studies may be invalid due to the different boundary detection definitions used, with the inclusion of the outer segment-RPE-Bruch's membrane complex by Spectralis OCT.[118]

The use of a large population based sample with standardized measurement protocol is a major strength of this study. This predominantly 12 year old sample is also largely free of ocular disease allowing unhindered measurement of true baseline retinal morphology. The

disadvantage of using a childhood sample is the question of whether results are applicable to older age groups. Another limitation is that ethnicity was determined by self report, which could result in a cultural rather than a biological identification of individuals' ethnicity.

In conclusion, we found that macular parameters varied by ethnicity in 12-year-old children. Caucasian children had the thickest macular parameters and South Asian children had the thinnest. The largest differences existed in the central macula which was significantly thicker in Caucasian compared with East Asian, South Asian and Middle Eastern children.

Table 7.1 Baseline characteristics (means ± SD, numbers with proportions) of sample

Age, years	12.7 ± 0.45†
Male, *n (%)*	926 (52.4)
Ethnicity, *n (%)*	
Caucasian	1224 (63.2)
East Asian	291 (16.5)
South Asian	107 (6.1)
Middle Eastern	146 (8.3)
Visual acuity, letters‡	56.4 ± 5.7
Axial length, mm	23.37 ± 0.82
Spherical equivalent, D	0.52 ± 1.17
Height, cm	155.9 ± 8.0
Weight, kg	49.7 ± 12.5
Body mass index, kg/m^2	20.3 ± 20.3

D = Diopters
†Age range 11 – 14 years
‡logMAR presenting visual acuity (total letters read)

Table 7.2 Baseline Characteristics of Participants Stratified by Ethnicity

	Caucasian	East Asian		South Asian		Middle Eastern	
	Mean (95% CI)	Mean (95% CI)	P†	Mean (95% CI)	P‡	Mean (95% CI)	P§
Age, years	12.7 ± 0.44	12.7 ± 0.44	0.24	12.5 ± 0.4	<0.0001	12.7 ± 0.4	0.07
Male, n (%)	649 (53.0)	135 (46.4)	0.04	54 (50.5)	0.61	88 (60.3)	0.10
Visual acuity, letters¶	57.4 ± 4.2	53.0 ± 8.1	<0.0001	54.8 ±7.4	0.0006	55.9 ± 5.9	0.005
Axial length, mm	23.24 ± 0.73	23.84 ± 1.00	<0.0001	23.5 ± 0.90	0.001	23.4 ± 0.67	0.004
Spherical equivalent, D	0.81 ± 0.79	-0.55 ± 1.69	<0.0001	-0.18 ± 1.41	<0.0001	0.76 ± 0.96	0.61
Height, cm	156.5 ± 8.1	154.5 ± 7.7	0.0001	155.0 ± 6.8	0.04	154.2 ± 7.8	0.001
Weight, kg	49.9 ± 12.5	47.6 ± 11.8	0.004	49.5 ± 10.6	0.71	51.9 ± 14.3	0.12
Body mass index, kg/m^2	20.2 ± 4.0	19.8 ± 3.8	0.09	20.5 ± 3.8	0.48	21.6 ± 4.9	0.001

†East Asian vs Caucasian
‡ South Asian vs Caucasian
§Middle Eastern vs Caucasian
¶logMAR presenting visual acuity (total letters read)

Table 7.3 Characteristics of the Macula in Different Ethnic Groups

	Caucasian Mean (95% CI)	East Asian Mean (95% CI)	South Asian Mean (95% CI)	Middle Eastern Mean (95% CI)
Thickness (μm)				
Foveal Minimum	164.1 (162.1 – 166.0)	156.1 (153.1 – 159.1)	155.4 (151.3 – 159.6)	158.4 (154.6 – 162.2)
Central Macula	200.3 (198.4 – 202.2)	191.3 (188.5 – 194.1)	188.2 (184.4 – 192.0)	193.7 (190.2 – 197.2)
Average inner macula	272.9 (271.5 – 274.3)	269.8 (267.7 – 271.9)	264.8 (261.8 – 267.7)	270.3 (267.6 – 272.9)
Average outer macula	239.8 (238.6 – 240.9)	239.7 (237.8 – 241.5)	234.2 (231.5 – 236.8)	237.1 (234.7 – 239.4)
Volume (mm^3)				
Total macula	6.97 (6.94 – 7.00)	6.94 (6.89 – 6.99)	6.79 (6.72 – 6.86)	6.89 (6.82 – 6.96)
Central macula	0.157 (0.156 – 0.158)	0.150 (0.148 – 0.152)	0.148 (0.145 – 0.150)	0.152 (0.149 – 0.154)

Data are from mixed model adjusted for age, gender, height, axial length and cluster-sampling
Central macula, average inner macula and average outer macula are concentric regions with radii of 0.5 mm, 1.5 mm, 3 mm respectively

Table 7.4 Mean Differences in Macular Parameters between Caucasian and Other Ethnic Groups

	Caucasian vs East Asian		Caucasian vs South Asian		Caucasian vs Middle Eastern	
	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
Thickness (μm)						
Foveal Minimum	8.0 (5.0 – 10.9)	<0.0001	8.6 (4.5 – 12.7)	<0.0001	5.7 (1.9 – 9.4)	0.003
Central Macula	9.0 (6.3 – 11.7)	<0.0001	12.1 (8.4 – 15.8)	<0.0001	6.5 (3.1 – 10.0)	0.0002
Average inner macula	3.0 (0.9 – 5.2)	0.005	8.1 (5.2 – 11.0)	<0.0001	2.6 (-0.1 – 5.3)	0.05
Average outer macula	0.1 (-1.8 – 2.0)	0.93	5.6 (2.9 – 8.2)	<0.0001	2.7 (0.2 – 5.1)	0.03
Volume (mm^3)						
Total macula	0.03 (-0.03 – 0.08)	0.30	0.18 (0.11 – 0.25)	<0.0001	0.08 (0.01 – 0.15)	0.02
Central macula	0.007 (0.005 – 0.009)	<0.0001	0.010 (0.007 – 0.012)	<0.0001	0.005 (0.002 – 0.008)	0.0002

Data are from mixed model adjusted for age, gender, height, axial length and cluster-sampling
Central macula, average inner macula and average outer macula are concentric regions with radii of 0.5 mm, 1.5 mm, 3 mm respectively

Table 7.5 Mean Differences in Macular Parameters between East Asian, South Asian and Middle Eastern groups

	East Asian vs South Asian		East Asian vs Middle Eastern		Middle Eastern vs South Asian	
	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
Thickness (μm)						
Foveal Minimum	0.64 (-3.8 – 5.1)	0.77	-2.3 (-6.5 – 1.9)	0.28	3.0 (-2.2 – 8.1)	0.26
Central Macula	3.13 (-0.9 – 7.1)	0.13	-2.4 (-6.3 – 1.4)	0.21	5.6 (0.9 – 10.3)	0.02
Average inner macula	5.1 (1.9 – 8.3)	0.002	-0.4 (-3.4 – 2.6)	0.79	5.5 (1.8 – 9.2)	0.004
Average outer macula	5.5 (2.6 – 8.4)	0.0002	2.6 (-0.1 – 5.3)	0.06	2.9 (-0.4 – 6.3)	0.09
Volume (mm^3)						
Total macula	0.15 (0.07 – 0.23)	0.0002	0.05 (-0.03 – 0.13)	0.19	0.10 (0.01 – 0.19)	0.03
Central macula	0.002 (-0.001 – 0.006)	0.13	-0.002 (-0.005 – 0.001)	0.21	0.004 (0.001 – 0.008)	0.02

Data are from mixed model adjusted for age, gender, height, axial length and cluster-sampling
Central macula, average inner macula and average outer macula are concentric regions with radii of 0.5 mm, 1.5 mm, 3 mm respectively

CHAPTER 8

Ethnic Differences in the Correlation of Retinal Parameters with Axial Length

Related publication:

Tariq YM, Samarawickrama C, Pai A, Burlutsky G, Mitchell P. Impact of Ethnicity on the Correlation of Retinal Parameters with Axial Length. *Investigative Ophthalmology and Visual Science.* 2010;51:4977-4982.

Abstract

Purpose: To examine whether the relationship of axial length (AL) to retinal nerve fibre layer (RNFL) and macular parameters measured by optical coherence tomography (OCT), differs by ethnicity.

Methods: As part of the Sydney Myopia Study, 2353 children from grade 7 (age range 11.1 – 14.4 years) completed detailed ocular examinations during 2004-2005. AL was measured using non-contact interferometry and optical coherence tomography was performed using Stratus OCT.

Results: East Asian children displayed larger AL correlations with average RNFL, inferior RNFL, nasal RNFL, outer macula and macular volume ($r = -0.25, -0.36, -0.31, -0.35$ and -0.31 respectively, $P<0.001$) than Caucasian children ($r = -0.14, -0.20, -0.12, -0.17$ and -0.13 respectively, $P<0.001$). Positive correlations between the temporal RNFL and AL were found only among East Asian and South Asian children ($r = 0.28$, $P<0.001$ and $r = 0.27$, $P = 0.03$ respectively). In Caucasian children, the foveal minimum and central macula were correlated significantly with AL ($r = 0.11$ and $r = 0.13$ respectively, $P\leq0.001$).

Conclusions: Retinal parameters measured by OCT are correlated with AL and the extent of this correlation varies by ethnicity. Ethnicity may therefore need to be considered when interpreting OCT scans on individuals with AL outside the usual range.

Introduction

Optical coherence tomography (OCT) is increasingly being utilized for the diagnosis and monitoring of ocular conditions as it permits quantitative as well as qualitative assessment of retinal parameters. Quantitative measurement of retinal parameters using OCT has shown great potential to delineate pathology from physiology.[51,189,190] Therefore an accurate understanding of normal variation in different populations and ethnicities is important in utilizing the full potential of this technology.

It has now been widely reported that Stratus OCT retinal measurements are correlated with axial length (AL).[14,16,19,20,111,123,125,139,140] In addition, there have been some reports of ethnic differences in retinal parameters measured by Stratus OCT, showing that Caucasians have a thicker central macula and a thinner retinal nerve fibre layer (RNFL) than East Asian or African American subjects.[16-20,63,191] However, there are very few reports on whether the correlations between retinal parameters and AL vary by ethnicity. To our knowledge, only the study by El-Dairi et al.[19] has previously reported on this relationship previously. In their study on 286 healthy children (age range 3 – 17) El-Dairi et al. showed that both retinal nerve fibre layer and macular parameters were associated with AL in eyes from in Caucasian, but not in African American subjects.

Examination of the relationship between AL and retinal parameters is important as it will allow clinicians to consider the context of retinal findings in individuals with AL outside the usual range. The purpose of this report is to explore the effect of AL on RNFL and macular measurements by Stratus OCT in different ethnic groups in a healthy adolescent population.

Specific Methods

Statistical analyses were performed using SAS software (version 9.1.3; SAS Institute, Cary, NC). Only scans that were complete and with signal strength greater than 5 were used in our analyses. To compare various characteristics (age, sex. refractive error, visual acuity, height, weight and axial length) of participants versus non-participants, we used the chi-square test of proportions and the t-test to compare means between groups. Means and standard deviations of retinal parameters and correlation coefficients of AL with retinal parameters were calculated. Partial correlation coefficients with adjustments for age, sex, height and ethnicity were calculated for the whole sample. P_{trend} for retinal parameters with increasing AL were calculated using regression models with medians of quintiles for AL as independent variables. The Bonferroni correction was applied to all correlations.

Results

General and Retinal Characteristics

Of 3144 eligible children, 2353 children were tested, for the others (n = 791), either we did not obtain parental consent for the child to participate in the study or the child was absent from school on days that testing was performed. Those with eye diseases (n = 16) including congenital glaucoma, optic nerve hypoplasia, microphthalmos, congenital nystagmus and cortical blindness due to cerebral palsy, and those with amblyopia (n = 44) were excluded from this report. Of the remaining children there were 2132 (91%) and 2068 (88%) children, respectively, with adequate quality RNFL and macular scans; the characteristics of the included and excluded children are shown in **Table 8.1**. Subjective refraction was performed on 372 of the children. The four largest ethnic groups, Caucasian (n = 1243), East Asian (n = 300), South Asian (n = 109) and Middle Eastern (n = 149), here considered separately to those having ‘European’ Caucasian ethnicity, were utilized for the ethnicity-specific analyses.

East Asian, South Asian and Middle Eastern children all had significantly longer AL than the Caucasian children (P<0.001, <0.001 and 0.002, respectively) (**Table 8.2**). These subgroups also had significant differences in RNFL and macular thickness when compared to the Caucasian group. For example, the East Asian children had significantly thicker temporal and superior RNFL and thinner nasal RNFL than the Caucasian children (all P<0.001).

Correlations

Partial correlation coefficients of the associations between retinal parameters and AL for the whole group, adjusted for age, sex, height and ethnicity, are presented in **Table 8.3**. The average, inferior, nasal and superior RNFL were all negatively correlated with AL, whereas the temporal RNFL had a small positive correlation (r = 0.12) (all P≤0.001). Inner macula, outer macula and macular volume were all negatively correlated with AL (P<0.001). Foveal minimum and central macular thickness were not significantly correlated with AL (P>0.05).

AL correlations with retinal parameters, stratified by ethnicity, are shown in **Table 8.4**. Average, inferior and nasal RNFL were negatively correlated with AL in both Caucasian and East Asian children, with the East Asian children displaying larger correlations for these parameters (r = -0.25, -0.36 and -0.31, respectively, P<0.001). Among both the East Asian and South Asian children, the temporal RNFL was positively correlated with AL (r = 0.28, P<0.001 and r = 0.27, P = 0.03 respectively). In the Caucasian children, there was only a very small positive correlation between AL and the temporal RNFL (r = 0.08, P = 0.004). The superior RNFL was only (weakly) correlated with AL in the Caucasian children (r = -0.08, P = 0.03). We found no significant AL correlations with RNFL parameters in the subgroup of Middle Eastern children.

The foveal minimum and central macular thickness had significant AL correlations in the Caucasian children. ($r = 0.11$, $P = 0.001$ and $r = 0.13$, $P<0.001$, respectively). The inner macula had a negative AL correlation only in the East Asian children ($r = -0.16$, $P = 0.03$), whereas outer macular thickness had negative correlations with AL in all ethnicities. Macular volume showed negative correlations in Caucasian, East Asian and Middle Eastern children (**Table 8.4**).

Discussion

We found significant AL correlations with RNFL and macular parameters in a large adolescent population. The temporal RNFL was positively correlated with AL whereas other RNFL quadrants had a negative correlation with AL. Further, the inner and outer macular thickness and macular volume were negatively correlated with AL. While these overall patterns were seen in the different ethnic subgroups, there were differences in the magnitude of the correlations between groups. We were unable to find significant correlations for most parameters in South Asian and Middle Eastern children, examined separately to 'European' Caucasian and East Asian children.

Retinal Nerve Fibre Layer Thickness

Previous reports have largely indicated a negative AL correlation with the RNFL, as shown in **Table 8.5**. Direct comparison with these earlier studies is difficult because of differences in the measurement protocols and statistical analyses used. However, only two [40,192] of studies failed to show a statistically significant negative AL correlation with the RNFL. One of these studies by Hoh et al[40] used OCT1 technology rather than Stratus OCT and ultrasound

biometry rather than a non-contact optical biometer and the other study by Vernon et al[192] had a very small sample size (n = 31).

An explanation for RNFL thinning with increasing AL is that longer eyes have a larger area over which retinal ganglion cell axons are spread, resulting in a thinner RNFL. A second possible explanation is that this finding represents an artifact of OCT scanning. As OCT is an optical system, the scan circle projected onto the retina in longer eyes, will be larger than the scan circle in shorter eyes.[144,193] As suggested in previous reports,[14,21] this enlarged scan circle could lead to an underestimation of RNFL thickness, as the RNFL thickness decreases with increasing distance from the disc margin.

Few previous studies have examined the relationship of AL to RNFL thickness in different quadrants. The finding that the temporal RNFL is correlated positively with AL[22] and negatively with myopia [104] has recently been reported and is in keeping with our findings. Two previous reports[194,105] failed to find an AL correlation with the temporal RNFL. One of these studies, by Rauscher et al[194], had a small sample size (n=28), and the other, by Leung et al[105], included subjects covering a very wide age range (22 to 60 years), a known confounder for RNFL thickness,[102,195] which could have explained the discrepancy with our findings.

A possible explanation for an AL-related increase in the temporal RNFL thickness was provided by Kim et al[104], who suggested that the retina may be 'dragged' toward the temporal horizon as the AL increases, resulting in thickened RNFL from overlapping of nerve fibre bundles at the temporal sector. This hypothesis is in agreement with our finding of a thicker temporal RNFL in eyes with longer AL.

Macular Thickness

Table 8.6 provides a summary of findings from other studies on the correlation of AL with macular OCT parameters. Both inner and outer macular thickness were found to have negative correlations with AL by some investigators [16,125,140], findings which are in agreement with ours. Wakitani et al[144], using the older generation OCT (Humphrey 2000 OCT), failed to find an AL correlation with inner macular thickness. The different scanning protocol for this system results in scans not directly comparable to Stratus OCT, so we could not compare these findings.

Several authors have proposed that this thinning of the inner and outer macula and overall macular volume reflects the stretching of the retina in eyes with longer AL.[125,139,140] Another proposed hypothesis is that the peripheral retina becomes thinner as a compensatory mechanism to preserve the more essential central macular thickness.[144]

Previous studies have reported a positive AL correlation with central macula and foveal minimum thickness.[111,123,125,139,140] However, in our analysis, we found no positive AL correlations with central macula and foveal minimum thickness in the overall sample. Nevertheless, we did find a significant positive AL correlation in the Caucasian subgroup ($P<0.001$), and a tendency for a positive correlation in the East Asian subgroup. The reason that this correlation did not exist in all ethnic groups remains unclear.

Ethnic Differences

Our findings suggest that the effect of AL on retinal parameters may vary according to ethnicity. The East Asian subgroup displayed the strongest relationship of AL with retinal parameters and reports from East Asian countries generally correspond with our findings,

with differences already discussed. The Caucasian subgroup showed a smaller correlation with AL than the East Asian subgroup in all assessed retinal parameters except foveal minimum and central macular thickness. To our knowledge, this ethnic difference has not been previously reported. One reason may be the differences in AL distribution between the two groups. The East Asian subgroup had a longer mean AL than the Caucasian subgroup (23.89mm versus 23.24mm), so that the AL correlation may have been better demonstrated in the East Asian subgroup due to the inclusion of many individuals with longer AL. It could also be hypothesized that retinal parameters in East Asian eyes are more susceptible to the changes associated with increased AL. From this, we could speculate that the pathological retinal changes associated with high myopia and longer AL may be more prominent in certain ethnicities. Longitudinal analyses, however, would be needed to further explore this relationship.

Although we were able to demonstrate a strong negative correlation of AL with outer macular thickness and macular volume in Middle Eastern children, and a positive correlation of temporal RNFL with AL in South Asian children, we could not demonstrate an AL-link with other retinal parameters for these two ethnic groups. An adult Indian population study reported no significant association of AL with RNFL[79] or macular parameters[185], which is in agreement with the findings for our South Asian subgroup. To our knowledge, no comparable study has previously been carried out in Middle Eastern children.

Strengths of our study include its large sample size, high response rate (74.8%) and standardized examination techniques. The low prevalence of ocular abnormalities in this population allows unhindered analysis of physiological relationships. A possible limitation was the small number of South Asian and Middle Eastern children, due to the less frequent

distribution of these ethnicities in our population, which could have limited our ability to directly compare results between ethnic groups.

In summary, AL impacts on OCT measured retinal parameters in our population. We demonstrated there is overall thinning of RNFL and macular parameters with increases in AL. The strengths of these correlations appear to be more prominent in East Asian children than in Caucasian children. Therefore, ethnicity may be a consideration when interpreting OCT scans on individuals with AL outside the usual range.

Table 8.1 Characteristics of Children with Included and Excluded Scans of Retinal Nerve Fibre Layer and Macula

	Retinal nerve fibre layer		Macula	
	Included n = 2092	Excluded n = 202	Included n = 2031	Excluded n = 263
Age †	12.7 ± 0.4	12.7 ± 0.4	12.7 ± 0.4	12.7 ± 0.4
Boys *n* (%)	1086 (51.9)	77 (38.1) *	1052 (51.8)	111 (42.2) *
Ethnicity *n* (%)				
Caucasian	1263 (60.4)	107 (53.0) *	1224 (60.3)	146 (55.5)
East Asian	300 (14.3)	41 (20.3) *	291 (14.3)	50 (19.0) *
South Asian	109 (5.2)	18 (8.9) *	107 (5.3)	20 (7.6)
Middle Eastern	149 (7.1)	13 (6.4)	146 (7.2)	16 (6.1)
Other ‡	271 (13.0)	23 (11.4)	263 (13.0)	31 (11.8)
SER †	0.51 ± 1.17	0.16 ± 1.63 *	0.52 ± 1.14	0.16 ± 1.66 *
VA (correct letters) †	56.35 ± 5.81	55.55 ± 6.75	56.4 ± 5.6	55.2 ± 7.8 *
AL (mm) †	23.39 ± 0.81	23.41 ± 0.91	23.38 ± 0.81	23.45 ± 0.91
Height (cm) †	156.1 ±7.88	156.6 ± 7.6	156.1 ± 7.9	156.3 ± 7.5
Weight (kg) †	50.31 ± 13.04	49.20 ± 11.86	50.39 ± 13.09	48.90 ± 11.72

SER = spherical equivalent; VA = logMAR visual acuity, AL = axial length
*P < 0.05 included versus excluded children
† Mean ± standard deviation
‡ Other ethnicities included South American, African, Indigenous Australian, Melanesian and Polynesian

Table 8.2 Means of Axial Length and Retinal Parameters by Ethnicity

	All n = 2031	**Ethnicity** (P values versus Caucasian)			
		Caucasian (n=1243)	East Asian (n=300)	South Asian (n=109)	Middle Eastern (n = 149)
Axial length (mm)	23.39	23.24	23.89 (<0.001)	23.60 (<0.001)	23.45 (0.002)
RNFL (µm)					
Average	103.7	103.5	105.7 (0.002)	99.8 (0.01)	101.2 (0.02)
Inferior	128.4	128.5	130.6 (0.07)	123.5 (0.01)	125.0 (0.03)
Nasal	82.0	84.41	73.85 (<0.001)	76.70 (<0.001)	80.17 (0.003)
Superior	129.8	128.3	135.7 (<0.001)	127.1 (0.51)	125.2 (0.04)
Temporal	74.6	73.04	82.53 (<0.001)	71.91 (0.36)	74.44 (0.20)
Macula (µm)					
Foveal minimum	161.4	164.3	157.0 (<0.001)	155.4 (<0.001)	158.5 (0.001)
Central macula	197.3	200.8	191.8 (<0.001)	188.4 (<0.001)	194.1 (<0.001)
Inner macula	272.0	273.8	268.4 (<0.001)	264.2 (<0.001)	270.5 (0.01)
Outer macula	239.5	240.8	237.4 (<0.001)	233.1 (<0.001)	236.5 (<0.001)
Macular volume (mm^3)	6.96	7.00	6.89 (<0.001)	6.77 (<0.001)	6.88 (<0.001)

Data adjusted for height and age
RNFL = Retinal Nerve Fibre Layer

Table 8.3: Partial Correlation Coefficients of Retinal Parameters with Axial Length Adjusted for Age, Sex, Height and Ethnicity

	R	P
Retinal nerve fiber layer		
Average	-0.16	<0.001
Inferior	-0.22	<0.001
Nasal	-0.17	<0.001
Superior	-0.08	0.001
Temporal	0.12	<0.001
Macula		
Foveal minimum	0.05	0.19
Central macula	0.05	0.22
Inner macula	-0.14	<0.001
Outer macula	-0.25	<0.001
Macular volume	-0.22	<0.001

RNFL = retinal nerve fiber layer
r = Partial correlation coefficient.

Table 8.4 Correlation Coefficients (P-value) of Retinal Parameters with Axial Length Stratified for Ethnicity

	Caucasian n=1201		East Asian n=286		South Asian n=106		Middle Eastern n=144	
	r	P	r	P	r	P	r	P
Retinal nerve fibre layer								
Average	-0.14	<0.001	-0.25	<0.001	-0.09	1.0	-0.09	1.0
Inferior	-0.20	<0.001	-0.36	<0.001	-0.21	0.13	-0.15	0.28
Nasal	-0.12	<0.001	-0.31	<0.001	-0.22	0.11	-0.13	0.60
Superior	-0.08	0.03	-0.14	0.06	0.01	1.0	0.07	1.0
Temporal	0.08	0.02	0.28	<0.001	0.27	0.03	0.02	1.0
Macula								
Foveal minimum	0.11	0.001	0.11	0.30	0.01	1.0	0.04	1.0
Central macula	0.13	<0.001	0.15	0.05	0.07	1.0	0.03	1.0
Inner macula	-0.02	1.0	-0.16	0.03	-0.10	1.0	-0.16	0.30
Outer macula	-0.17	<0.001	-0.35	<0.001	-0.20	0.16	-0.30	0.001
Macular volume	-0.13	<0.001	-0.31	<0.001	-0.18	0.30	-0.27	0.01

r = correlation coefficient

Table 8.5 Reports of Correlation between Average Retinal Nerve Fibre Layer and Axial Length

Source	OCT version	Ethnicity	Age (years)	n	Correlation of average RNFL with AL	Correlation coefficient	Regression Coefficient
Huynh et al.[4]	Stratus	Mixed	5-7	1765	Negative*	NR	NR
Budenz et al.[5]	Stratus	Mixed	18 – 85	328	Negative	NR	-2.24 (P<0.0001)
Nagai-Kusuhara et al.[25]	Stratus	Japanese	20 – 63	162	Negative	NR	-1.77 (P = 0.011)
Hoh et al.[21]	OCT 1	Chinese/Malay/Indian	19 – 24	132	No correlation	0.03 (P = 0.75) †	NR
Leung et al.[26]	Stratus	Chinese	22 – 60	115	Negative	-0.31 (P = 0.0001)	NR
Vernon et al.[22]	Stratus	Caucasian (UK)	35 – 60	31	No correlation‡	NR	NR
El-Dairi et al.[6]	Stratus	Caucasian (US) §	3 – 17	154	Negative	NR	-0.27 (P<0.001)
Sony et al.[32]	Stratus	Indian	20 – 70	146	No correlation	NR	NR

*P_{trend}<0.0001

† For 4.5mm scan diameter of RNFL

‡ Tendency for mean RNFL to decrease with increasing AL (P = 0.17)

§ Caucasian subgroup of 286 children. No correlation of AL with RNFL reported for whole group

RNFL = retinal nerve fibre layer; n = number; AL = axial length; NR = not reported

Table 8.6 Reports of Correlation between Macular Parameters and Axial Length

Source	OCT version	Ethnicity	Age (years)	N	Foveal minimum and AL	Central macular thickness and AL	Inner macular thickness and AL	Outer macular thickness and AL
Lam et al.[7]	Stratus	Chinese	N/A *	143	NR	r = 0.374 P<0.001	r = -0.078 P = 0.35	r = -0.471 P<0.001
Luo et al.[9]	Stratus	Chinese	11 – 12	104	β = 0.01 P = 0.02	NR	NR	NR
Huynh et al.[10]	Stratus	Mixed	5 – 7	1543	NR	No association	Negative P<0.0001	Negative P<0.0001
Wong et al.[12]	OCT II	Chinese	13 – 81	117	r = 0.260 P<0.01	β = 5.37 P = 0.001	NR	NR
Wakitani et al.[24]	OCT II	Japanese	12 – 74	203	NR	No association	No association	NR
El Dairi et al.[6]	Stratus	Caucasian	3 – 17	154	No association	NR	No association	β = -0.44 P = 0.003
El Dairi et al.[6]	Stratus	African American	3 – 17	114	No association	NR	No association	No association
Kelty et al.[14]	Stratus	Mixed	22 – 75	83	NR	No association	NR	NR

* Mean age men 40.34 and women 39.01

AL = axial length; n = number; NR = not reported; r = correlation coefficient; β = regression coefficient

CHAPTER 9

Association of Birth Parameters with Stratus OCT Measured Macular and Retinal Nerve Fibre Layer Thickness

Related publication:

Tariq YM, Pai A, Li H, Afsari S, Gole GA, Burlutsky G, Mitchell P. Prematurity is associated with foveal thickening. *Investigative Ophthalmology and Visual Science.* 2011;52:1709-1715

Abstract

Aims: To examine whether birth parameters have associations with macular and retinal nerve fibre layer (RNFL) thickness measurements.

Methods: The Sydney Myopia Study examined secondary school children for ocular conditions, with all eligible Year 7 students from 21 high schools invited to participate. Macular and RNFL measurements were acquired from optical coherence tomography (OCT) scans. Birth variables, including birth weight and gestational duration, were obtained from parental questionnaires and health records. Mixed linear models were used in analyses, after adjusting for age, gender, height, axial length and ethnicity.

Results: 1,756 and 1,698 children had adequate quality scans of RNFL and macula respectively, and had complete examination and questionnaire data. Children with low birth weight (<2500g) had a thinner mean RNFL (98.2μm vs. 103.5μm P<0.0001) and a thicker mean foveal minimum (164.3μm vs. 158.5μm, P = 0.004) compared to children of normal birth weight (2500 – 4000g). With increasing birth weight, average RNFL thickness increased (mixed model coefficient β=2.97μm/kg, P<0.0001) and foveal minimum thickness decreased (β=-2.16μm/kg, P = 0.008). Children born before 32 weeks gestation had significantly thicker mean foveal minimum and central macular thickness (205.5μm vs. 193.4μm, P = 0.001) measurements compared to children born after 37 weeks gestation.

Conclusions: Low birth weight and prematurity are associated with thickening of the fovea and decreased birth weight is associated with decreased RNFL thickness as measured by OCT. These findings suggest that premature birth and low birth weight may impair retinal development and could predispose these children to ocular problems later in life.

Introduction

Prematurity and low birth weight have been associated with many adverse sequelae in later life including high blood pressure[196], metabolic syndrome[197], type 2 diabetes mellitus[198], neurodevelopment disorders[199] and chronic renal insufficiency.[200] Ophthalmic consequences of preterm birth and low birth weight include retinopathy of prematurity (ROP), myopia, strabismus, amblyopia and cortical visual impairment.[24-29] Low birth weight is also a marker of adverse intrauterine development and animal studies have confirmed that placental insufficiency has long term effects on retinal structure.[201] Although a number of studies have described retinal changes in ROP, very few studies have examined the impact of birth parameters on macular and retinal nerve fibre layer (RNFL) thickness.[30-32]

In a brief report we presented the association of birth parameters with the macula and RNFL in 6-year-old children.[202] We found there was increased thickness in the central macula in children born before 37 weeks, and the RNFL and outer macular thickness was increased in higher birth weight children. To ascertain whether these changes persist throughout childhood we aimed to test these associations in the older cohort of the Sydney Myopia Study (SMS). An adolescent population is ideal for this study as these subjects are relatively free of potentially confounding ocular conditions (e.g. diabetes, glaucoma and cataract). In addition, fine retinal development is thought to be ongoing until 4 years of age;[203] therefore, an ideal population to assess the outcome of abnormal development is in later childhood.

Specific Methods

Analyses were performed using SAS, Version 9.2 (SAS Institute, Cary NC). Based on the World Health Organisation definition [146] children less than 2,500g were deemed as low birth weight and for the purposes of this report we created a category of high birth weight for children >4000g. Gestational duration was divided into premature (≤32 weeks), modest prematurity (33 – 36 weeks) and normal (≥37 weeks). Chi square was used to test for heterogeneity of sex and ethnicity between birth weight categories. To test for heterogeneity of baseline characteristics (age, height, weight, body mass index, refractive error and visual acuity) between birth weight categories mixed linear models[150] were used, with school attended as random effect. In order to compare OCT parameters between perinatal categories, mixed linear models were employed, after adjusting for covariates (age, sex, axial length, height and ethnicity) and including school attended as a random effect. Since birth weight and duration of gestation are highly correlated with each other, we did not adjust for these parameters together in the main analyses. However, to assess the relative importance these two parameters in the observed associations with retinal thickness we carried out additional analyses adjusting for birth weight in the gestational duration model and for gestational duration in the birth weight model. A p-value of less than 0.05 was considered significant.

Results

Of 3,144 eligible children, 2,353 children were examined (74.8% response). The remainder (n = 791), did not provide parental consent for the study or were absent from school on days when testing was performed. Children with amblyopia (n = 44) and various eye conditions (n = 16) including congenital glaucoma, optic nerve hypoplasia, microphthalmos, congenital nystagmus and cortical blindness due to cerebral palsy, were excluded from this report. Of

the remaining children (n = 2,293), 1,756 (77%) and 1,698 (74%), respectively, had adequate quality RNFL and macular scans. 1,799 (77%) and 1,631 (71%) children, respectively, provided data for gestational duration and birth weight. Based on questionnaires and examinations no child was noted to have a history of ROP.

Table 9.1 presents various characteristics for participants by birth weight categories. There were significant differences in the gender, ethnicity, height, weight, BMI and axial length between birth weight categories. For example, height, BMI and weight were larger and axial length slightly longer in children with greater birth weight. Caucasian children were over-represented in the >4000g group and East Asian children were under-represented in this group and a larger proportion of South Asian children were in the low birth weight category. **Table 9.2** presents the birth weight by duration of gestation. Children with a longer duration of gestation generally had greater birth weight. There was considerable overlap in the birth weights of the children in the three duration of gestation groups. In the very premature group (≤ 32 weeks) the duration of gestation ranged from 23 to 32 weeks.

Table 9.3 presents the means of retinal parameters in children stratified by birth weight. Children with low birth weight (<2500g) had significantly thinner average, inferior, nasal and superior RNFL compared to those in the normal (2500 – 4000g) birth weight. Foveal minimum and central macular thickness was significantly thicker in the low birth weight compared to the normal birth weight category. Children in the high birth weight category (>4000g) had significantly thicker average and nasal RNFL than children in the normal birth weight range. Inner macular thickness, outer macular thickness and macular volume were

also found to be significantly greater in the high birth weight compared to the normal birth weight category.

After adjusting for gestational duration, the difference in foveal minimum thickness between low birth weight and normal birth weight children was no longer significant (P = 0.49), while all other associations remained significant.

Table 9.4 presents regression coefficients for birth weight, birth length and head circumference with retinal parameters. Greater birth weight and birth length were significantly associated with greater average RNFL thickness, along with the inferior, nasal and superior RNFL, after adjusting for age, gender, height, AL and ethnicity. Larger head circumference was associated only with greater average, inferior and nasal RNFL. For macular parameters, increased birth weight and birth length were found to be associated with reduced foveal minimum thickness. Larger birth weight was associated with thicker inner and outer macula and with larger macular volume.

Figure 9.1 demonstrates the RNFL average thickness, foveal minimal thickness and macular volume by birth weight quintiles. These data are not adjusted for covariates of age, gender, height, AL and ethnicity. Children with larger birth weight tended to have greater average RNFL and macular volume compared to children in lower birth weight quintiles (P-trend < 0.0001 and 0.005 respectively). There was no trend observed between birth weight and foveal minimum thickness (P-trend = 0.72) in this unadjusted analysis.

Table 9.5 presents the means of retinal parameters stratified by gestational duration. Children born before 32 weeks and children born between 33 and 36 weeks had significantly thicker foveal minimum and central macular thickness compared to children born at 37 weeks or later, with the greater difference in the children born before 32 weeks. The temporal RNFL was found to be significantly thinner in the modest prematurity group (32 – 33 weeks) compared to children born after 37 weeks. After adjusting for birth weight the foveal minimum and central macular thickness were still significantly greater in children born before 32 weeks compared to children born after 37 weeks ($P < 0.0001$ and $P = 0.0015$, respectively). The findings for modest prematurity (33 to 36 weeks gestation), however, were no longer significant after adjusting for birth weight.

Discussion

In this population-based study of predominantly 12-year-old children free of confounding ocular conditions, we found that prematurity was associated with thicker foveal and central macular parameters. Decreasing birth weight was associated with thinner average RNFL, outer macular thickness as well as decreased total macular volume and a greater foveal thickness. Decreasing birth length was associated with thinner average RNFL thickness and greater foveal thickness, but not with other macular parameters.

Macular thickness

In our study the significance of a thicker fovea and central macula in low birth weight children became non-significant after adjusting for gestational duration. On the other hand, the association of prematurity of less than 32 weeks and a thicker fovea and central macula

persisted after adjusting for birth weight, suggesting that gestational duration is a stronger factor in this association.

Ecsedy et al,[31] in a study of 10 children (age range 7 to 10 years) born between 26 and 34 weeks gestation, reported a thicker fovea as measured by OCT in the premature group as compared with full term children, findings consistent with those in our study. Similarly, in our previous study on a 6-year old cohort (Sydney Myopia Study) we reported a thickening of the central macula in children born prematurely, but no association with birth weight was observed.[202] In ROP studies, foveal thickening has also been reported. Hammer et al,[30] in an OCT study of 5 subjects (age range 14 to 26 years) born between 26 and 28 weeks gestation with a history of mild ROP, reported a shallower foveal pit with a thickened inner retinal layers compared with controls.

The central retina undergoes maturation later than the peripheral retina and is therefore more susceptible to the effects of the postnatal environment imposed on the infant after premature birth.[24,204] In normal foveal development cone cell nuclei and bipolar cells migrate away from the cone cell outer segments which remain closely arranged at the fovea. This cell migration contributes to the formation of a normal foveal depression.[205] Our finding of a thicker fovea in premature children, may suggest that prematurity and its associated complications may impair cell migration and ultimately lead to abnormal retinal structure. The lack of formation of a normal foveal avascular zone may be another reason for the altered foveal pit formation. In premature or low birth weight children the fovea is traversed by capillaries which may alter the normal elasticity of this area and impair normal foveal pit formation during eye growth,[30,205] and earlier studies have reported that gestational age and birth weight correlate with the size of the avascular zone of the fovea.[206]

RNFL thickness

The finding that larger birth weight is associated with increased RNFL thickness was also reported in our study of 6-year old children.[202] To our knowledge, there are no other studies that have examined this association. Studies on optic disc morphology in low birth weight and premature individuals have shown a spectrum of findings including increased optic disc cupping,[207] and either increased[208] or decreased optic disc area.[209] We previously reported a strong association between greater birth weight and reduced optic cup/disc ratio in this same population.[210] At that time, we speculated that larger birth weight would likely be associated with a greater reserve of ganglion cells; a speculation that is supported by the finding of increased average RNFL thicknesses in larger birth weight children in the current study.

During the course of normal optic nerve development, around 2.85 million nerve fibres develop. In the third trimester 1.85 million supernumerary fibres are eliminated[203]. This process of elimination is therefore susceptible to events occurring in the third trimester. One interesting finding from our study was the lack of RNFL thinning in our sample of premature children, even though these children had a reduced birth weight. In addition to this, the relationship of low birth weight and RNFL thinning was unaffected by adjustment for duration of gestation. Taken together this suggests that premature infants are less likely to have reduced RNFL, regardless of their low birth weight. This could be due to early visual stimulation in these premature children preventing normal third trimester axon elimination. A study on cultured rat cells showed that retinal ganglion cells that receive electrical stimulation produce neurotrophic factors that may then stimulate growth of nearby neurons.[211] It has also been suggested that early visual stimulation in premature infants and the resulting growth promoting electrical signals may interfere with the normal degeneration of retinal ganglion cell axons.[208] This would then lead to these premature children having a thicker RNFL than

expected for their birth weight. It should be noted that our sample only includes low numbers of premature children, with only 20 children born before 32 weeks and 135 children born between 32 and 36 weeks. Studies in larger cohorts of premature children will be needed to determine whether any association exists between prematurity and RNFL thickness.

Another factor to consider when examining the relationship of retinal parameters and birth weight is the reported association of birth weight with retinal vascular caliber. Children with low birth weight have been shown to have narrower arterioles[212] and arteriolar caliber is positively correlated with RNFL thickness and macular (inner/outer) thickness.[213-215] Our current findings, therefore, are consistent with these previously reported relationships. It has been postulated that the development of wider vascular caliber reflects an increased vascular requirement in persons with a thicker RNFL and macula.[214,215] A further consideration, and possibly a confounding factor around this issue, is the effect of a thicker vasculature causing an artifact of increased OCT measurement of retinal parameters.[216] Further investigation including histological studies would be required to determine the interrelationships between retinal structures, retinal vessel caliber and birth weight.

Study Limitations

Strengths of this study include its large population-based sample with high response rate (75.3%), an objective technique of measuring retinal structures, the use of a healthy adolescent sample with little confounding ocular or systemic disease and the use of documented data on birth parameters. A limitation of this study is the relatively low number of children in the low birth weight and premature birth groups, however most associations spanned the continuum of birth weight. Another limitation is the use of Stratus OCT which does not allow adequate resolution to determine changes in specific retinal layers.

In summary, we found that birth parameters have significant associations with both the macular and RNFL thickness of adolescents. Prematurity is associated with thickening of the fovea similar to that reported in ROP. Lower birth weight is associated with a decreased average RNFL, inner and outer macula thickness, and macular volume, but with increased foveal thickness. Further studies should follow preterm and low birth weight children into adulthood to determine whether these changes adversely impact the development of age-related retinal diseases.

Table 9.1: Characteristics of participants (proportions, numbers with proportions, or mean values ± SD), by birth weight categories

	Birth weight (g) <2500 N = 94	2500 to 4000 N = 1366	>4000 N =171	P – value*
Male, %	57.5	50.2	61.4	0.01
Age, years	12.7 ± 0.5	12.7 ± 0.4	12.7 ± 0.5	0.57
Ethnicity, n (%)				0.001
Caucasian	61 (5.7)	876 (82.0)	131 (12.2)	
East Asian	15 (6.5)	211(91.3)	5 (2.2)	
South Asian	7 (9.1)	62 (80.5)	8 (10.4)	
Middle Eastern	5 (7.0)	61 (85.9)	5 (7.0)	
Others	6 (3.3)	156 (84.8)	22 (12.0)	
Height, cm	155.3 ± 9.3	155.9 ± 7.8	158.4 ± 7.6	0.0001
Weight, kg	46.9 ± 10.7	49.5 ± 12.2	54.8 ± 16.3	<0.0001
BMI, kg/m^2	19.3 ± 3.2	20.2 ± 4.0	21.6 ± 5.2	<0.0001
Axial length, mm	23.3 ± 0.8	23.4 ± 0.8	23.6 ± 0.7	0.001
Refractive error, D	0.56 ± 1.03	0.48 ± 1.24	0.65 ± 0.91	0.46
Visual acuity†	56.2 ± 6.2	56.4 ± 5.7	57.7 ± 3.6	0.13

*Test for heterogeneity
† letters correct (logMAR), 55 letters is 20/20 Snellen equivalent
SD = Standard deviation, BMI = Body mass index, D = Diopter

Table 9.2: Birth weight (g) by duration of gestation

Duration of gestation (weeks)	Mean ± SD	Range
≤ 32	1780 ± 461	1200 – 2650
33 – 36	2749 ± 597	1500 – 4880
≥ 37	3420 ± 500	1900 – 6500

SD = Standard deviation

Table 9.3: Retinal parameters, mean (CI), by birth weight categories and comparison with normal birth weight

	Birth weight				
	Low (< 2500g)	P*	Normal (2500 – 4000g)	High (> 4000g)	P*
RNFL	n = 91		n = 1333	n = 167	
RNFL average, µm	98.2 (95.9 – 100.4)	<0.0001	103.5 (102.6 – 104.4)	105.9 (104.1 – 107.7)	0.006
RNFL inferior, µm	119.8 (115.8 – 123.7)	<0.0001	128.7 (127.1 – 130.3)	130.2 (127.0 -133.3)	0.33
RNFL nasal, µm	73.0 (69.6 – 76.5)	0.0003	79.3 (77.8 – 80.8)	83.2 (80.4 – 86.0)	0.003
RNFL superior, µm	126.1 (122.4 – 129.8)	0.02	130.4 (128.9 – 131.9)	133.2 (130.2 – 136.2)	0.05
RNFL temporal, µm	73.8 (71.0 – 76.5)	0.19	75.6 (74.3 – 76.8)	76.8 (74.6 – 79.0)	0.21
Macula	n = 92		n = 1283	n = 162	
Foveal minimum, µm	164.3 (160.0 – 168.6)	0.004	158.5 (156.3 – 160.7)	155.8 (152.2 – 159.4)	0.09
Central macula, µm	197.8 (193.8 – 201.8)	0.02	193.7 (191.5 – 195.8)	192.7 (189.4 – 196.1)	0.51
Inner macula, µm	270.8 (267.7 – 274.0)	0.60	270.0 (268.4 – 271.7)	272.8 (270.1 – 275.5)	0.02
Outer macula, µm	236.5 (233.6 – 239.3)	0.2	238.4 (237.1 – 239.7)	241.1 (238.7 – 243.5)	0.01
Macular volume, mm^3	6.89 (6.81 – 6.96)	0.39	6.92 (6.88 – 6.96)	6.99 (6.93 – 7.06)	0.01

Data adjusted for age, gender, height, axial length, ethnicity and cluster sampling
CI = confidence interval
*P value in comparison to normal birth weight 2500 – 4000g

Table 9.4: Change in retinal characteristics per unit increase in birth parameters

	Birth weight (kg)		Birth length (cm)		Head circumference (cm)	
	β	P value	β	P value	β	P value
RNFL average, μm	2.97	<0.0001	0.28	0.0001	0.44	0.0003
RNFL inferior, μm	4.21	<0.0001	0.37	0.004	0.86	<0.0001
RNFL nasal, μm	4.39	<0.0001	0.35	0.001	0.39	0.03
RNFL superior, μm	2.37	0.001	0.30	0.01	0.33	0.08
RNFL temporal, μm	0.88	0.10	0.09	0.28	0.18	0.21
Foveal minimum, μm	-2.16	0.008	-0.29	0.03	-0.24	0.27
Central macula, μm	-0.98	0.19	-0.16	0.18	-0.18	0.38
Inner macula, μm	1.19	0.05	0.006	0.95	-0.098	0.55
Outer macula, μm	1.73	0.002	0.055	0.54	0.062	0.68
Macular volume, mm^3	0.043	0.005	0.001	0.66	0.0006	0.88

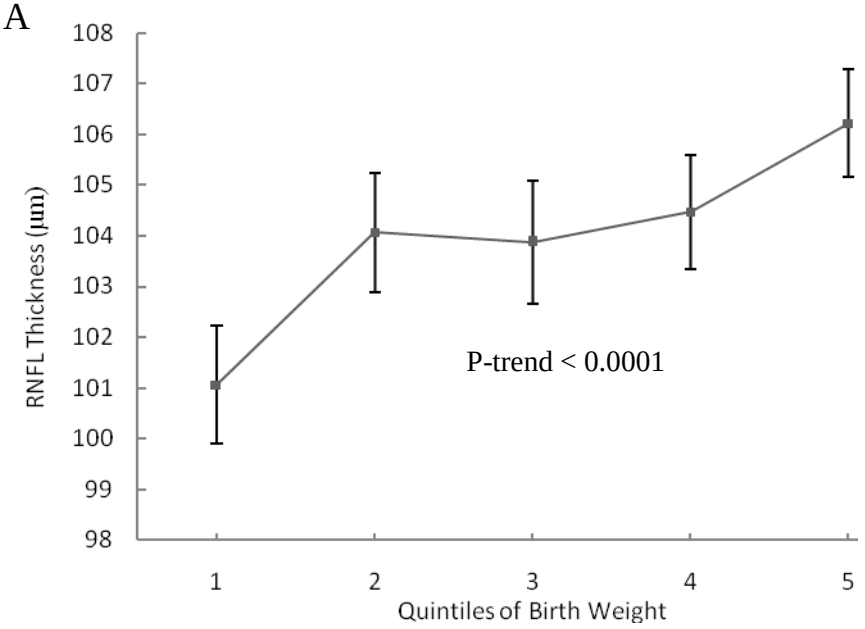
Data adjusted for age, gender, height, axial length, ethnicity and cluster sampling
β = regression coefficient from mixed model

Table 9.5: Mean (CI) of retinal parameters stratified by gestational duration and compared to term birth (≥ 37 weeks)

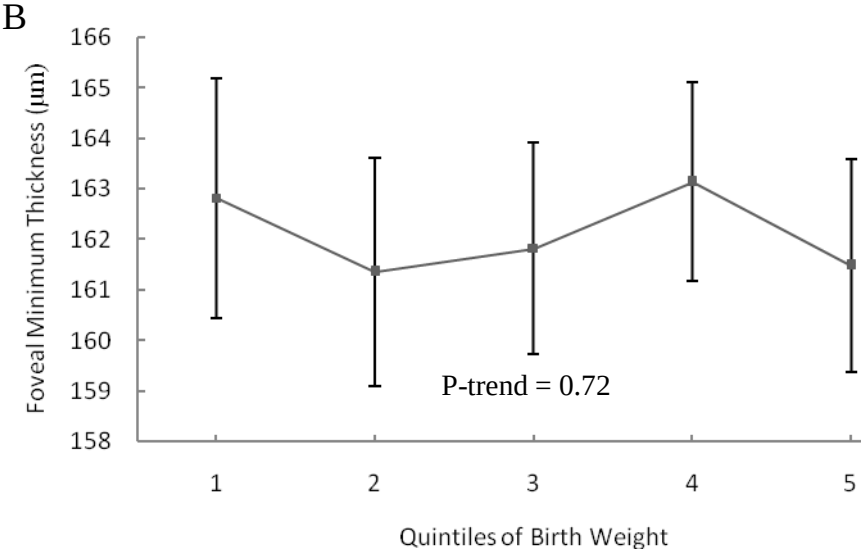
	Gestational duration (weeks)				
	≤ 32	P*	33 - 36	P*	≥ 37
RNFL	n = 19		n = 130		n = 1607
RNFL average, µm	98.9 (94.1 – 103.7)	0.37	102.5 (100.6 – 104.4)	0.37	103.4 (102.5 – 104.2)
RNFL inferior, µm	121.6 (113.3 – 129.9)	0.12	127.0 (123.6 – 130.3)	0.45	128.2 (126.8 – 129.6)
RNFL nasal, µm	73.1 (65.9 – 80.3)	0.07	80.8 (77.9 – 83.8)	0.44	79.7 (78.4 – 81.0)
RNFL superior, µm	126.5 (118.6 – 134.3)	0.37	129.5 (126.3 – 132.7)	0.74	130.0 (128.6 – 131.4)
RNFL temporal, µm	74.7 (69.1 – 80.2)	0.76	72.7 (70.4 – 75.0)	0.01	75.5 (74.4 – 76.6)
Macula	n = 19		n = 126		n = 1553
Foveal minimum, µm	179.1 (170.4 – 187.8)	<0.0001	163.2 (159.3 – 167.0)	0.003	158.0 (155.8 – 160.2)
Central macula, µm	207.9 (199.9 – 215.9)	0.0003	197.0 (193.4 – 200.6)	0.02	193.3 (191.2 – 195.4)
Inner macula, µm	269.6 (263.1 – 276.0)	0.84	270.8 (268.0 – 273.6)	0.65	270.2 (268.7 – 271.7)
Outer macula, µm	235.5 (229.6 – 241.3)	0.30	238.6 (236.1 – 241.1)	1.00	238.6 (237.4 – 239.8)
Macular volume, mm^3	6.86 (6.70 – 7.03)	0.47	6.93 (6.86 – 7.00)	0.83	6.92 (6.89 – 6.96)

Data adjusted for age, gender, height, axial length, ethnicity and cluster sampling
CI = confidence interval
*P value in comparison to ≥ 37 weeks group

A


RNFL Thickness (µm)
108
107
106
105
104
103
102
101
100
99
98
P-trend < 0.0001
1
2
3
4
5
Quintiles of Birth Weight

B


Foveal Minimum Thickness (µm)
166
165
164
163
162
161
160
159
158
P-trend = 0.72
1
2
3
4
5
Quintiles of Birth Weight

C

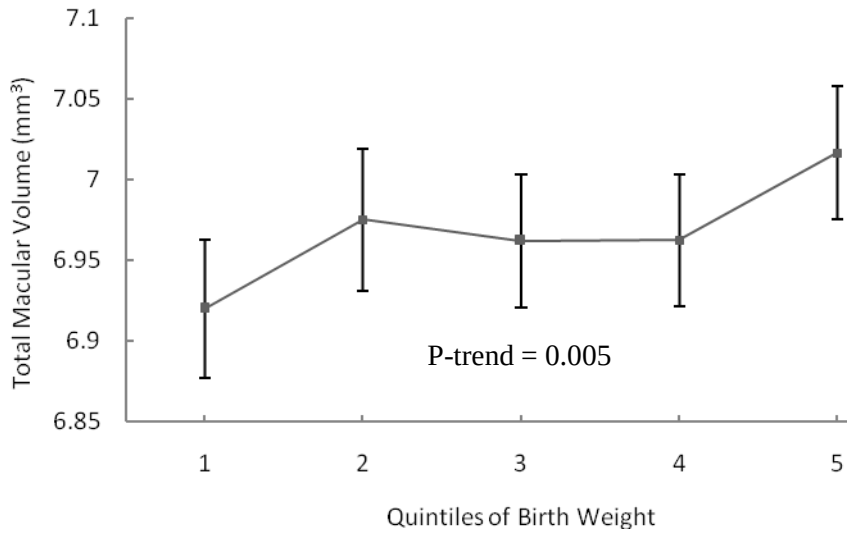

Total Macular Volume (mm³)
7.1
7.05
7
6.95
6.9
6.85
P-trend = 0.005
1
2
3
4
5
Quintiles of Birth Weight

Figure 9.1: Relationship of birth weight to (**A**) average RNFL thickness, (**B**) foveal minimum thickness and (**C**) total macular volume. Error bars representing 95% confidence interval. Birth weight quintiles: 1 = 1058 – 2935g, 2 = 2940 – 3220g, 3 = 3225 – 3510g, 4 = 3515 – 3798g, 5 = 3800 – 6500g

CHAPTER 10

Macular Parameters and Prematurity: a Spectral Domain OCT Study

Related publication

Tariq YM, Burlutsky G, Mitchell P. Macular parameters and prematurity: a spectral domain OCT study. *Journal of AAPOS*. 2012;16(4):382-5

Abstract

Purpose: To investigate the association of premature birth with macular parameters measured by spectral domain (SD-) OCT.

Methods: The Sydney Adolescent Vascular and Eye Study carried out eye examinations in school students across Sydney between 2009 and 2011. Visual acuity, cycloplegic autorefraction and optical biometry measurements were performed. Macular parameters were measured using the Cirrus HD-OCT. Questionnaires previously completed by the participants' parents were used to determine perinatal and medical history. Children with retinal disease or a history of retinopathy of prematurity were excluded from analysis.

Results: Macular measurements from the right eye of 1672 participants (aged 10 – 19 years) were used in the study. The central subfield in those born at ≤32 weeks gestation was significantly thicker than those born after 37 weeks (266.3µm vs. 251.7 µm, P=0.0007). The average cube thickness and average outer thickness were smaller in those born at ≤32 weeks gestation compared to those born at ≥37 weeks (P= 0.03 and 0.02 respectively). Similarly the cube volume was smaller in the ≤32 weeks gestation compared to those born at ≥37 weeks (P = 0.04). No significant differences were found between the 33 – 36 week group and the ≥37 week group.

Conclusion: Gestational age less than 33 weeks is associated with thicker central macular measurements and thinner of the outer macular measurements on SD-OCT.

Introduction

Prematurity has recently been found to be associated with persistent changes in foveal structure.[217-220] These studies have found that, regardless of a history of retinopathy of prematurity (ROP), the foveal thickness is greater in premature individuals compared with term born children. The majority of these studies have used older time domain optical coherence tomography (OCT) to investigate this change in foveal structure. Spectral domain OCT is a newer and higher resolution imaging modality superior to time domain OCT. Hammer et al[30] utilized adaptive optics Fourier/spectral domain OCT and found that in their sample the foveal structure was altered in individuals with a history of ROP. While this was a valuable study, they only included 5 preterm children, and limited their study to those with a history of ROP. The purpose of the current study is to investigate whether there is any change in spectral domain OCT measured macular parameters as a result of preterm birth.

Specific Methods

Statistical analysis was performed using SAS, Version 9.2 (SAS Institute, Cary NC). For the purposes of this report only scans of the right eyes with signal strengths ≥ 8 were used in analysis. The GLM procedure was used to test differences in baseline characteristics between gestational duration categories. The GLM procedure with adjustment for age, sex, height, axial length and ethnicity was also used to test differences in macular parameters for the 3 gestational duration categories.

Results

The number of participants with complete perinatal data and macular thickness measurements were 1672. One child was excluded due to a history of ROP. Baseline characteristics of this sample stratified by duration of gestation is presented in **Table 10.1**. The age range of the

sample was 10 to 19 years. The mean age of the ≤32 weeks gestation group (16.6 ± 1.8 years) was significantly larger than the ≥37 weeks group (15.3 ± 2.4 years, P = 0.02). The ≤32 weeks group had a worse mean visual acuity (54.3 ± 4.8 letters) than the ≥37 weeks group (57.4 ± 4.1 letters, P = 0.002).

In **Table 10.2** macular parameters for the three groups is presented. The central subfield was 266.3μm (95% confidence interval 257.9μm – 274.7μm) in those born at ≤32 weeks gestation which was significantly greater than those born after 37 weeks (251.7 μm, 250.3 – 253.1 μm, P=0.0007). The average cube thickness and average outer thickness were smaller in those born at ≤32 weeks gestation compared to those born at ≥37 weeks (P= 0.03 and 0.02 respectively). Similarly the cube volume was smaller in the ≤32 weeks gestation compared to those born at ≥37 weeks (P = 0.04).

Discussion

In this study we found that there is increased thickness of the central macula and thinning of the outer macular region in individuals born before 32 weeks in comparison with those born at term. These changes are not seen in modest degrees of prematurity (33 to 36 weeks).

Studies using time domain OCT have previously found similar central macular thickening in premature individuals. Two studies using Stratus OCT (Carl Zeiss, Meditec, Dublin CA) found greater central retinal thickness in children (aged between 5 and 16 years) with ROP compared to children born at term. [31,217] We previously used Stratus OCT to examine macular thickness by gestational duration in the 12 year old children.[219] We found that the thickening of the fovea and central macula was greater in children born before 37 weeks compared to those born after 37 weeks. These results, taken together with the results of the

current report, suggest that retinal changes are associated with prematurity, and that these changes persist into late adolescence.

In the current study we did not find a significant increase in central macular thickness in the modest prematurity group (33 – 36 weeks gestation) compared with term born children, whereas in our previous study, using Stratus OCT in a 12 year old cohort, we found that modestly premature groups had increased central macular thickness compared with term born children.[219] The current study includes older children and therefore retinal thickness changes associated with changes in AL which occur in adolescence may have impacted on this association. Longitudinal analysis, however, is required to determine whether this is the case.

It has been speculated that the increased thickness in the foveal region in preterm individuals occurs secondary to altered foveal pit formation. The normal foveal depression is formed when the ganglion cells and inner nuclear layers migrate peripherally and the cone outer segments migrate centrally.[205,221] This process may be susceptible to the adverse effects of premature birth. Also it has been found that the foveal avascular zone does not adequately develop in premature children, which may interfere with normal cell migration.[206,222]

Our finding of a smaller average cube and outer macula in the preterm children has, to our knowledge, not previously been reported. The magnitude of the mean difference in outer macular thickness between these groups is small (6.8µm). It is possible that this outer macular thinning is also secondary to the impaired cell migration which is thought to contribute to the foveal thickening. Further studies using spectral domain OCT in larger cohorts are needed to verify this finding.

Strengths of this study include its large population based sample with standardized examination techniques. The use of the OCT technology allows quantitative an objective assessment of macular parameters. A limitation of this study is the small size of the premature cohort. Another limitation of this study is the lack of medical records from the neonatal period providing ROP status in this cohort. As we relied on the history obtained from parents and the retinal examination findings at ages 6 and 12 years, there is the potential that mild degrees of ROP could have been missed.

In conclusion, we found using spectral domain OCT there is thickening of the central macula and thinning of the outer macula in children born before 33 weeks gestation. This finding highlights the alteration of normal retinal development in premature individuals.

Table 10.1 Baseline characteristics

	Duration of Gestation (weeks)				
	≤32		32 to 36		≥37
	n = 18	P*	n = 130	P*	n = 1557
Male, n (%)	11 (61.1)	0.38	71 (54.6)	0.39	791 (50.8)
Age (years)†	16.6 ± 1.8	0.02	15.2 ± 2.4	0.72	15.3 ± 2.4
Height (cm)	167.8 ± 13.1	0.17	163.4 ± 10.5	0.51	164.1 ± 11.7
Weight (kg)	58.6 ± 13.9	0.96	57.8 ± 15.7	0.51	58.8 ± 16.2
BMI (kg/m^2)	20.6 ± 3.4	0.36	21.3 ± 3.9	0.59	21.6 ± 4.4
Visual Acuity‡ (letters)	54.3 ± 4.8	0.002	57.1 ± 4.2	0.47	57.4 ± 4.1
Axial length (mm)	23.8 ± 1.0	0.20	23.7 ± 0.9	0.15	23.5 ± 0.9
SER (D)	-0.16 ± 1.70	0.15	0.39 ± 1.2	0.49	0.30 ± 1.4

*P value versus gestational age ≥ 37 weeks
† range = 10.9 to 19.0 years
‡ best corrected visual acuity
SER = spherical equivalent refraction

Table 10.2 Mean (CI) of macular parameters stratified by gestational duration and compared to term birth (≥ 37 weeks)

	Duration of gestation (weeks)				
	≤ 32		33 - 36		≥ 37
Thickness (µm)		P*		P*	
Central Subfield	266.3 (257.9 – 274.7)	0.0007	252.3 (249.0 – 255.6)	0.74	251.7 (250.3 – 253.1)
Average Cube	276.8 (271.3 – 282.3)	0.03	282.4 (280.3 – 284.6)	0.76	282.8 (281.9 – 283.7)
Average Inner	315.6 (309.4 – 321.8)	0.11	320.7 (318.3 – 323.2)	0.99	320.7 (319.7 – 321.7)
Average Outer	272.2 (266.5 – 277.9)	0.02	278.5 (276.2 – 280.7)	0.66	279.0 (278.0 – 279.9)
Volume (mm^3)					
Cube	9.97 (9.77 – 10.17)	0.04	10.17 (10.09 – 10.25)	0.85	10.18 (10.14 – 10.21)
Total ETDRS	7.95 (7.80 – 8.11)	0.04	8.10 (8.05 – 8.17)	0.75	8.12 (8.09 – 8.14)

Data adjusted for age, gender, axial length, height and ethnicity
CI = confidence interval
*P value in comparison to ≥ 37 weeks group

CHAPTER 11

Retinal Thickness in Children from Diabetic Pregnancies

Related publication:

Tariq YM, Samarawickrama C, Li H, Huynh SC, Burlutsky G, Mitchell P. Retinal Thickness in Offspring of Diabetic Pregnancies. *American Journal of Ophthalmology*. 2010;150(6):883-887

Abstract

Purpose: To examine macular and peripapillary retinal nerve fibre layer (RNFL) thickness in children from diabetic pregnancies.

Methods: As part of the Sydney Myopia Study, 2367 children from grade 7 (age range 11.1 – 14.4 years) completed detailed ocular examinations during 2004-2005. Examination included determination of best corrected visual acuity (logarithm of minimal angle of resolution) and autorefraction after cycloplegia. Axial length was measured using non-contact interferometry and optical coherence tomography was performed using Stratus OCT through dilated pupils. Participants and parents completed comprehensive questionnaires including questions on birth and medical history.

Results: 1741 and 1687 children had adequate quality scans of macula and RNFL respectively, and had complete examination and questionnaire data. Of these there were 57 children (3.3%) who were from diabetic pregnancies. Children from diabetic pregnancies had significantly thinner inner (264.9μm vs. 270.2 μm, P = 0.007) and outer (231.9μm vs. 238.6μm, P = 0.0001) macular thickness and macular volume (6.75mm3 vs. 6.92mm3, P = 0.0003) compared with the children from non diabetic pregnancies. Central macular thickness, foveal minimum thickness and RNFL parameters showed no significant differences between the two groups.

Conclusion: Diabetes during pregnancy is associated with changes in retinal morphology in children. There is thinning of pericentral macular parameters measured by Stratus OCT in children of diabetic pregnancies. This may be a marker of adverse neurological development in utero in these children, or may reflect the impact on the retina of adverse glucose metabolism.

Introduction:

Maternal diabetes occurs in 2 to 8% of pregnancies in Australia[223] and 4 to 14% of pregnancies in the United States.[224] The effects of maternal diabetes on the fetus are numerous [33-36]. Increased serum glucose concentrations in the mother are transferred to the fetus via the placenta. In response, the fetus, increases insulin secretion to compensate. This has a secondary effect of causing excessive growth and a large-for-gestational-age fetus.[33] These larger fetuses are more prone to shoulder dystocia and neonatal asphyxia during vaginal delivery.[34] Post-delivery complications include hypoglycemia, infant respiratory distress syndrome, cardiomyopathy and polycythemia.[35] During adolescence, children of diabetic pregnancies are more likely to be obese, and to develop metabolic syndrome or type 2 diabetes.[36] Maternal type 1 diabetes has been associated with the development of superior segmental optic nerve hypoplasia in offspring.[225] However we are unaware of any studies which have systematically tested for changes in retinal structure in children whose mothers have had diabetes during pregnancy.

Time-domain optical coherence tomography (OCT) allows imaging of total retinal and nerve fibre layer thickness with a resolution up to 8μm.[226] It is increasingly used in the diagnosis and monitoring of retinal diseases including age-related macular degeneration [178], diabetic retinopathy[227] and glaucoma.[228] The purpose of this study was to determine whether diabetes during pregnancy affects the OCT-measured retinal structure in offspring, by comparing with children born of non-diabetic pregnancy.

Specific Methods:

A 193-item questionnaire was completed by parents. The questionnaire also specifically asked whether the mother has diabetes or had developed diabetes during pregnancy and whether her child had been diagnosed with diabetes.

Statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC). Only OCT scans of the right eye, that were complete and with signal strength greater than 5 were used in our analyses. Means and 95% confidence intervals of baseline characteristics (age, height, weight, body mass index [BMI], birth weight, AL, spherical equivalent refraction, and visual acuity) were calculated and t-tests were used to compare differences in means between gestational diabetes and non-diabetic pregnancy groups. The chi-square test of proportions was used to compare frequencies of sex and ethnicity between groups. Mixed linear models were utilized to compare OCT parameters (adjusted for age, sex, height, axial length and ethnicity) between groups with the school attended as the random effect.

Results:

During 2004-2005, 2367 high school children were tested, of whom 1741 and 1687 had adequate quality OCT scans of RNFL and macula respectively, as well as having complete questionnaire and examination data.

Table 11.1 presents the characteristics of the non-diabetic and diabetic pregnancy groups. There were 57 individuals in the diabetic pregnancy group (3.3%), with a mean age of 12.7 years, of whom 62.1% were boys. AL was larger in the diabetic pregnancy group (23.6mm) compared to the non diabetic pregnancy group (23.4mm), with borderline significance (P =

0.05). None of the children in the diabetic pregnancy group none had a diagnosis of diabetes. Two children in the non-diabetic pregnancy group had a diagnosis of diabetes.

Table 11.2 presents RNFL data for the two groups. Though all measured parameters were thinner in the diabetic pregnancy group, these differences were not statistically significant.

Table 11.3 presents macular parameters for the two groups. There were no significant differences in central macular and foveal minimum thickness. However, in the diabetic pregnancy group the mean inner macular thickness, outer macular thickness and macular volume were significantly thinner than in the non-diabetic pregnancy group (264.9μm, 231.9μm and 6.75mm^3 respectively versus 270.2μm, 238.6μm and 6.92mm^3 respectively, all $P < 0.05$).

Discussion

In this population-based study of adolescents, we report a modest but significant difference in retinal parameters between children of diabetic compared with non-diabetic pregnancy. The differences were seen in the pericentral retinal regions scanned using the macular protocol of the Stratus OCT, with children from diabetic pregnancies having a thinner inner and outer macular region than children from non-diabetic pregnancies. The degree of thinning observed was only 5 to 10μm and is therefore not likely to be clinically significant. However this finding may have implications for the pathophysiology of diabetic retinopathy or diabetic macular edema[229-232] and the impact of maternal diabetes on the developing neurological system of the fetus.[233-239]

We are unaware of any previous studies examining retinal structure in offspring of diabetic pregnancies to compare our findings with (PubMed search used). However, studies have shown retinal thinning in early diabetes before the onset of frank retinopathy. Bronson-Castain et al[229] performed Stratus OCT macular scans on 15 adolescents with type 2 diabetes (without retinopathy) and found a 10μm thinner central retina compared to with a control group. Oshitari et al[230] also reported significantly thinner central retinal thickness in adults (mean age 61.6 years) with diabetes but no retinopathy, than in controls. In a study of patients with type 1 diabetes and minimal diabetic retinopathy van Dijk et al[231] described thinning of the pericentral retina compared with age-matched controls. This pattern of retinal thinning is quite similar to the pattern we have described in the children from diabetic pregnancy, in support of our findings.

In their type 1 diabetic subjects van Dijk et al[231] localised the thinning to the ganglion cell/inner plexiform layer and the inner nuclear layer of the pericentral retina. Evidence from animal studies suggests that diabetes may induce apoptosis in the ganglion cell layer.[232] However the literature is conflicting, Verma et al[240] utilizing spectral domain OCT demonstrated photoreceptor layer thinning in the fovea of patients with diabetes but no retinopathy, which could suggest that the pathological process affects this layer preferentially. As time domain OCT does not provide adequate resolution to discriminate between such layers we cannot determine which particular retinal layers were involved in our subjects. Further, studies utilizing multifocal electroretinography indicate that functional neuro-retinal deficits may also occur in diabetes.[229,231,241-243]

We speculate that children of diabetic pregnancies may also develop the same pattern of retinal changes observed in diabetes before the onset of retinopathy. One possible

explanation could be that the offspring of diabetic pregnancies may be already experiencing some degree of hyperglycemia and insulin resistance, due to their predisposition to develop diabetes in the future,[36] which is triggering these changes in retinal structure.

Another possible cause for these retinal changes could be the *in utero* environment. There are many neuro-developmental abnormalities associated with maternal diabetes including impairments in motor functioning, language development, attention span, activity level and learning ability.[233,244,245] Diabetic pregnancy may compromise neurological development by a number of mechanisms. The high insulin levels produced by the fetus in response to hyperglycemia results in tissue overgrowth and an increased metabolic rate resulting in a relative hypoxia which can lead to neurological damage.[234] Increased hematopoesis also occurs secondary to hypoxia. This results in decreased iron availability which can adversely affect the development of neurological tissues.[235] Another potential mechanism is an increase in levels of neurotoxic inflammatory cytokines such as TNFα which are associated with gestational diabetes.[236,237] Maternal hyperglycemia also causes excessive production of free radicals which are transferred to the fetus,[238] and directly exert a cytotoxic effect on various organ systems including the developing fetal neurological system.[239] The retina, as a neurological tissue, may be susceptible to the damage induced by these various insults and the observed retinal thinning could simply be a marker of this. If this finding is validated in further studies, the measurement of OCT parameters could be a valuable proxy marker for effects on central nervous system development *in utero*, both in clinical and research settings.

Strengths of this study include its large population based sample, which allowed comparison of children from diabetic versus non-diabetic pregnancy with a standardized examination protocol for all children. A weakness of this study is the reliance on questionnaire data to

determine diabetes status of both mother and child. This could have resulted in missing cases, although in Australia universal screening for gestational diabetes is recommended.[246] Moses and Colagiuri[247] have estimated that in the period between 1991 to 1994, up to 50% of women in New South Wales were probably not tested for gestational diabetes. Such missed cases of gestational diabetes would be likely to have shifted the results towards the null. Another weakness is the relatively small number of individuals (n = 57) in the diabetic pregnancy group. These analyses will need to be reproduced and validated in larger cohorts, preferably using more advanced spectral domain OCT technology to better define the specific morphological changes.

In summary, this study has compared OCT-derived retinal parameters in children from diabetic and non-diabetic pregnancies. We found that children from diabetic pregnancies had thinner inner and outer macular thickness, plus a smaller total macular volume, compared with offspring of non-diabetic pregnancies. There were no differences in RNFL thickness between the groups. The degree and pattern of retinal thinning seen in these children is similar to the retinal thinning seen in individuals with diabetes before the onset of retinopathy. These findings may suggest that maternal diabetes impacts on the development of the retina. Further studies should be performed utilizing the higher resolution spectral domain OCT to determine the changes in particular retinal layers in the offspring of women with diabetes in pregnancy.

Table 11.1: Characteristics of diabetic and non-diabetic pregnancy groups

	Non-Diabetic Pregnancy N = 1684	**Diabetic Pregnancy N = 57**	**P Value**
Sociodemographic factors			
Age, mean years (CI)	12.7 (12.7 – 12.7)	12.7 (12.6 – 12.8)	0.60
Boys, n (%)	873 (51.6)	36 (62.1)	0.11
Ethnicity, n (%)			
Caucasian	1052 (62.2)	29 (50.0)	0.06
East Asian	250 (14.8)	13 (22.4)	0.11
South Asian	84 (5.0)	3 (5.2)	0.94
Middle Eastern	101 (6.0)	3 (5.2)	0.80
Others	205 (12.1)	10 (17.2)	0.24
Anthropometry, mean (CI)			
Height (cm)	156.0 (155.6 – 156.3)	156.6 (154.5 – 158.8)	0.52
Weight (kg)	50.0 (49.4 – 50.6)	52.6 (48.8 – 56.3)	0.15
BMI (kg/m^2)	20.4 (20.2 – 20.6)	21.2 (20.0 – 22.4)	0.14
Birth weight (g)	3381 (3323 – 3437)	3411 (3277 – 3545)	0.68
Ocular parameters, mean (CI)			
Visual acuity[a]	56.4 (56.2 – 56.7)	55.7 (53.9 – 57.6)	0.47
Axial length (mm)	23.4 (23.3 – 23.4)	23.6 (23.4 – 23.8)	0.05
SER (Diopters)	0.51 (0.46 – 0.57)	0.15 (-0.29 – 0.58)	0.10

CI = 95% confidence interval; BMI = body mass index; SER = spherical equivalent refraction
[a]logMAR visual acuity (letters correct)

Table 11.2: Retinal nerve fibre layer thickness in children of diabetic and non-diabetic

RNFL (µm)	**Non-Diabetic Pregnancy N = 1684**		**Diabetic Pregnancy N = 57**		**P**
	Mean	95% CI	Mean	95% CI	
Average	103.2	102.4 – 104.1	101.8	99.0 – 104.6	0.32
Inferior	128.2	126.8 – 129.6	124.6	119.6 – 129.5	0.15
Nasal	79.5	78.2 – 80.8	78.3	74.0 – 82.6	0.58
Superior	130.1	128.7 – 131.4	129.6	124.9 – 134.2	0.83
Temporal	75.1	74.1 – 76.2	74.8	71.4 – 78.1	0.83

pregnancies
Data adjusted for age, sex, height, axial length and ethnicity
RNFL = retinal nerve fibre layer; CI = confidence interval

Table 11.3: Macular thickness and volume in children of diabetic and non-diabetic

Macula (µm)	**Non Diabetic Pregnancy N = 1630**		**Diabetic Pregnancy N = 57**		**P**
	Mean	95% CI	Mean	95% CI	
Foveal Minimum	157.9	155.7 – 160.2	159.4	153.9 – 164.9	0.57
Central	193.2	191.1 – 195.3	194.0	188.9 – 199.0	0.76
Inner	270.2	268.6 – 271.7	264.9	261.0 – 268.9	0.007
Outer	238.6	237.4 – 239.8	231.9	228.4 – 235.4	0.0001
Volume (mm^3)	6.92	6.89 – 6.96	6.75	6.65 – 6.85	0.0003

pregnancies
Data adjusted for age, sex, height, axial length and ethnicity
CI = confidence interval

CHAPTER 12

Conclusions, Implications and Future Directions

The development and implementation of OCT technology in ocular imaging in recent times has re-invigorated research into retinal structure and changed the landscape of ophthalmology practice. However, the application of this technology has been disproportionately limited to adults. This is highlighted by the fact that the Cirrus HD-OCT normative database was developed using individuals between 19 and 84 years old, and therefore the software will not provide age specific data for those under 18 years of age. This is unfortunate as OCT is particularly useful in younger populations in whom tolerance to standard fundoscopy techniques may be limited. Because OCT imaging provides such detailed imaging, one of its greatest potential uses will be in pre-emptive diagnosis of disease that alter retinal structure (e.g. glaucoma[147,148]), which further highlights the need to develop normative data for younger populations. A secondary benefit of studying OCT measured retinal structure in younger populations is that it allows the measurement of true retinal morphology relatively unhindered by media opacity (e.g. cataract) or confounding ocular and systemic diseases which are more prevalent in older populations. Therefore study of OCT findings in younger populations will yield important findings.

The purpose of this thesis was to develop spectral domain OCT normative data in two sample population groups. One is a young adult population, study of which would allow a verification of current normative data and allow measurement of baseline retinal morphology. The other is a young adolescent population, in whom normative OCT data was not previously available. Also the variation of retinal parameters in relation to gender, ethnicity, anthropometric, ocular and perinatal variables was also studied. Identification of these associations has the potential to help clinicians to delineate normal variation from pathologic change. However, the degree of difference of OCT measurements between gender and ethnic groups, while statistically significant for some parameters, is too small to have direct clinical

relevance when using OCT for the determination of, for example, glaucomatous RNFL change or macular oedema related to diabetic retinopathy. However these differences do indicate an underlying structural disparity between such groups, the relevance of which is as yet uncertain. These novel associations also highlight areas of possible future research.

This thesis provided results for a young adult and adolescent population using the Cirrus HD-OCT. It contains normative data that can be referred to by clinicians when examining populations within this age group. Our normal range was similar to the Cirrus HD-OCT in-built normal range, and therefore clinicians can now use this in-built normal range with confidence in younger populations.

This thesis also provided side-by-side comparison of spectral domain OCT measured retinal parameters in Caucasian and East Asian populations. We showed that the RNFL topography and macular thickness varies between these two ethnic groups. To our knowledge this type of direct comparison has not been previously carried out with Cirrus HD-OCT. These findings would suggest that manufacturers should consider ethnicities when developing normative databases for OCT instruments, as normative databases would vary depending on the ethnic composition of the sample used.

The association of AL and SER with macular and RNFL parameters in both Stratus OCT and Cirrus HD-OCT was investigated in this thesis. The finding that these ocular characteristics may impact on retinal thickness will need to be considered by clinicians when examining patients with abnormal AL or SER. The correlation of AL with macular and RNFL parameters was found to vary by ethnic groups and also by retinal location. These novel

findings indicate that more research is needed into how retinal morphology may be altered between eyes of different AL. Also further study of the ocular magnification effect on OCT scanning protocols needs to be undertaken. The Cirrus HD-OCT does not perform automatic correction of scan size for differences in AL, therefore clinicians need to be aware of the associations of retinal parameters with AL.

Another finding in this thesis was the association between perinatal factors with retinal morphology in adolescents. Prematurity, even in the absence of ROP, was associated with thicker foveal and central macular parameters. Also birth weight was found to be associated with RNFL and outer macular parameters. The findings presented for these associations within this thesis are unique as we studied a population-based, rather than clinic-based, sample and were able to show that these associations exist even with modest degrees of prematurity and low birth weight, a finding that may indicate the sensitivity of retinal tissue to even minor insults in the newborn period. These findings indicate that further investigation into possible pathophysiological mechanisms underlying such associations is now needed. Clinicians working with premature neonates should be aware that retinal structure is microscopically altered and that further study is need to determine whether visual maturation is hindered secondary to this.

The association of maternal diabetes during pregnancy and macular thickness was another finding in this thesis. In the older SMS cohort, we discovered that the outer macula was thinner in 12 year olds born to mothers who were diabetic during pregnancy. Although this finding requires further verification from additional studies in larger cohorts, it does coincide with emerging evidence in the literature on how maternal diabetes impacts on neurological

development in utero. This finding also indicates the potential of OCT retinal scanning as a biomarker of neurological health and development. With the emerging epidemic of diabetes and diabetes related illnesses, more research into how parental diabetes impacts on offspring is needed. Further research into this area is needed before any clinical implications can be derived from the associations we have discovered between diabetic pregnancy and retinal structure.

The strengths of this thesis are the use of a large population based cohort in both SMS and SAVES, with standardized examination technique across studies. The comprehensive examinations and questionnaires, not only allowed determination of associations with retinal parameters but also allowed for adjustment of confounding covariates. A limitation of our study design was that causality cannot be determined, and our finding of various associations needs confirmation by other study designs. Another limitation was that the Stratus OCT measurements obtained in SMS could not be compared with the Cirrus HD-OCT data obtained in SAVES, because retinal thickness measurements from these instruments are not interchangeable. The rapid development of OCT technology in recent times has meant that no large longitudinal analysis of retinal changes in a normal population has been carried out. Therefore further studies are now needed to better elucidate how retinal parameters may change over time and how this change is associated with changes in ocular and demographic variables. Another limitation of the current thesis is that the normative data presented is limited to the Cirrus HD-OCT and therefore will no longer be relevant when this instrument is superseded by newer technology, although this instrument will most likely continue to be used for quite some time. Also the association of retinal structures with demographic, ocular and perinatal factors which are presented in this thesis should continue to be applicable with newer OCT or other retinal imaging technology.

Newer OCT systems are now in development which will allow more detailed imaging of retinal structures. Swept-Source OCT (SS-OCT) uses a photodetector instead of a spectrometer, and the narrow bandwidth and longer wavelength of these systems means that there is less signal drop off with depth allowing imaging of the outer retina, retinal pigment epithelium and choroid. The disadvantage of this system is the lower axial resolution due to the longer wavelength. Adaptive optics OCT is another system currently under investigation. It allows greater transverse resolution in comparison to spectral domain OCT by using a wider diameter OCT beam while correcting for aberrations with the application of wavefront sensing and deformable mirrors. The greater resolution of adaptive optics OCT allows visualisation of the RNFL axon bundles and cone photoreceptor mosaics. Issues with adaptive optics OCT include the inability to focus on different retinal depths simultaneously and also the reduced field of view. Although further work is needed before these systems are ready for commercial use they have the potential to increase our understanding of the normal retina and changes which occur as a result of disease as well as enhance the diagnostic capability of clinicians.

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School: _____

Study ID No. _____ _____ _____ _____

Name _____

Class _____

DOB: ☐☐ ☐☐ ☐☐☐☐ **Female:** ☐ **Male:** ☐

Date of examination: ☐☐ ☐☐ ☐☐☐☐

The Sydney Adolescent and Vascular Eye Study (SAVES)

Examination Booklet

1.1 Vertometry

1.11 Current glasses:

unifocal	☐	no glasses	☐
bifocal.	☐	glasses not brought	☐
multifocal	☐	missing	☐

1.12 Normal use of glasses:

Distance only ☐ Near work only ☐

All the time ☐ Don't wear ☐

If not worn, why not?

_____

1.12 Attach printout here

1.13 Contact lenses worn ☐

1.14 OBSERVATIONS

_____

1.15 For Reporting:

Normal ☐

Other:

EXAMINATION CHECK LIST

Test	Normal	Abnormal	Not Completed
Vision Has Glasses ☐ Subjective refraction Required ☐ Not required ☐	☐	☐	☐
Cover Test/ Eye Motility	☐	☐	☐
Slit Lamp	☐	☐	☐
Fundus Photography	☐	☐	☐
IOP	☐	☐	☐
Pachymetry	☐	☐	☐

Test	Completed	Not Completed
Questionnaires		
Ankle-Brachial Index		
Blood Pressure		
Anthropometry		
Non Cycl. Auto Refraction		
Abberometry		
IOL Master		
Video Keratometry		
OCT		

Autorefraction	☐ ≥ +3.00 D (Hyperopic)	☐ Anisometropia ≥ 1D
(Spherical Equivalent)	☐ +2.00 - < +3.00D (Mild	☐ Astigmatism ≥ 1D
	☐ > +0.50D - < +2.00 (Normal)	
	☐ < -0.50 - +0.50D (Mild myope)	
	☐ ≥ -0.50D (Myopic)	

STATION 1 Examiner: ☐☐

1.2 VISUAL ACUITY

Visual Acuity should be measured at 2.44m with and without glasses. If the 6/60 line cannot be read move chart to 1.22m. If again the top line cannot be read proceed with CFs, HMS and LP at 38cm.

WITHOUT GLASSES

1.21 LogMAR Distance VA performed at 2.44m ☐

1.22 If VA ≤ 6/7.5 OR one line difference (5 letters) between eyes, check with pinhole at 2.44 m

If VA is normal with glasses pinhole is not required without glasses

RIGHT EYE				
Snel. Eq	Log MAR	LogMAR letters	No. correct (…/5)	With Pinhole
6/60	1.0	H V Z D S	5	5
6/48	0.9	N C V K D	10	10
6/36	0.8	C Z S H N	15	15
6/30	0.7	O N V S R	20	20
6/24	0.6	K D N R O	25	25
6/19	0.5	Z K C S V	30	30
6/15	0.4	D V O H C	35	35
6/12	0.3	O H V C K	40	40
6/9.5	0.2	H Z C K O	45	45
6/7.5	0.1	N C K H D	50	50
6/6	0.0	Z H C S R	55	55
6/4.8	-0.1	S Z R D N	60	60
6/3.8	-0.2	H C D R O	65	65
6/3.0	-0.3	R D O S N	70	70
TOTAL LETTERS READ				

LEFT EYE				
Snel. Eq	Log MAR	LogMAR letters	No. correct (…/5)	With Pinhole
6/60	1.0	N C K Z O	5	5
6/48	0.9	R H S D K	10	10
6/36	0.8	D O V H R	15	15
6/30	0.7	C Z R H S	20	20
6/24	0.6	O N H R C	25	25
6/19	0.5	D K S N V	30	30
6/15	0.4	Z S O K N	35	35
6/12	0.3	C K D N R	40	40
6/9.5	0.2	S R Z K D	45	45
6/7.5	0.1	H Z O V C	50	50
6/6	0.0	N V D O K	55	55
6/4.8	-0.1	V H C N O	60	60
6/3.8	-0.2	S V H C Z	65	65
6/3.0	-0.3	O Z D V K	70	70
TOTAL LETTERS READ				

1.23 If VA <6/60, measure VA at 1.22m ☐

RIGHT EYE			
Snel. Eq	Log MAR score	LogMAR letters	No. correct (…/5)
6/120	1.3	H V Z D S (6/60 line)	
6/96	1.2	N C V K D (6/48 line)	
6/72	1.1	C Z S H N (6/36 line)	
TOTAL LETTERS READ			

LEFT EYE			
Snel. Eq	Log MAR score	LogMAR letters	No. correct (…/5)
6/120	1.3	H V Z D S (6/60 line)	
6/96	1.2	N C V K D (6/48 line)	
6/72	1.1	C Z S H N (6/36 line)	
TOTAL LETTERS READ			

1.24 If VA <3/60, measure VA at 38 cm

RIGHT EYE		
CF ☐	HM ☐	
PL+P ☐	PL ☐	NPL ☐

LEFT EYE		
CF ☐	HM ☐	
PL+P ☐	PL ☐	NPL ☐

W I T H G L A S S E S

1.25 LogMAR Distance VA performed at 2.44m ☐

1.26 If VA ≤ 6/7.5 OR one line difference (5 letters) between eyes, check with pinhole at 2.44 m

If VA is normal with glasses pinhole is not required without glasses

R I G H T E Y E

Snel. Eq	Log MAR	LogMAR letters	No. correct (…/5)	With Pinhole
6/60	1.0	H V Z D S	5	5
6/48	0.9	N C V K D	10	10
6/36	0.8	C Z S H N	15	15
6/30	0.7	O N V S R	20	20
6/24	0.6	K D N R O	25	25
6/19	0.5	Z K C S V	30	30
6/15	0.4	D V O H C	35	35
6/12	0.3	O H V C K	40	40
6/9.5	0.2	H Z C K O	45	45
6/7.5	0.1	N C K H D	50	50
6/6	0.0	Z H C S R	55	55
6/4.8	-0.1	S Z R D N	60	60
6/3.8	-0.2	H C D R O	65	65
6/3.0	-0.3	R D O S N	70	70
TOTAL LETTERS READ				

L E F T E Y E

Snel. Eq	Log MAR	LogMAR letters	No. correct (…/5)	With Pinhole
6/60	1.0	N C K Z O	5	5
6/48	0.9	R H S D K	10	10
6/36	0.8	D O V H R	15	15
6/30	0.7	C Z R H S	20	20
6/24	0.6	O N H R C	25	25
6/19	0.5	D K S N V	30	30
6/15	0.4	Z S O K N	35	35
6/12	0.3	C K D N R	40	40
6/9.5	0.2	S R Z K D	45	45
6/7.5	0.1	H Z O V C	50	50
6/6	0.0	N V D O K	55	55
6/4.8	-0.1	V H C N O	60	60
6/3.8	-0.2	S V H C Z	65	65
6/3.0	-0.3	O Z D V K	70	70
TOTAL LETTERS READ				

1.27 If VA <6/60, measure VA at 1.22m ☐

R I G H T E Y E

Snel. Eq	Log MAR score	LogMAR letters	No. correct (…/5)
6/120	1.3	H V Z D S (6/60 line)	
6/96	1.2	N C V K D (6/48 line)	
6/72	1.1	C Z S H N (6/36 line)	
TOTAL LETTERS READ			

L E F T E Y E

Snel. Eq	Log MAR score	LogMAR letters	No. correct (…/5)
6/120	1.3	H V Z D S (6/60 line)	
6/96	1.2	N C V K D (6/48 line)	
6/72	1.1	C Z S H N (6/36 line)	
TOTAL LETTERS READ			

1.28 If VA <3/60, measure VA at 38 cm

R I G H T E Y E

CF ☐	HM ☐	
PL+P ☐	PL ☐	NPL ☐

L E F T E Y E

CF ☐	HM ☐	
PL+P ☐	PL ☐	NPL ☐

CF – to perform, hold up different numbers of fingers 4-5 times asking the person to count how many fingers they see. At 38cms CF is approximately equivalent to 6/60

HM – to perform, move the hand in different directions, up, down and horizontally at a distance of 38cms, ask the subject in which direction is the hand moving.

LP – switch a small bright fixation torch on and off, held in different locations at 38cms from the subject. Light perception with projection (LP + P) indicates that they can locate the source of the light.

If VA in any eye is ≤6/7.5 you MUST do dry autorefraction and subjective refraction.

1.3 BEST CORRECTED VISUAL ACUITY

1.31 RIGHT EYE

Best corrected VA should be measured at 2.44m

WITH best correction ☐			
Snel. Eq	LogMAR letters	No. correct	LogMAR score
6/60	H V Z D S	5	1.0
6/48	N C V K D	10	0.9
6/36	C Z S H N	15	0.8
6/30	O N V S R	20	0.7
6/24	K D N R O	25	0.6
6/19	Z K C S V	30	0.5
6/15	D V O H C	35	0.4
6/12	O H V C K	40	0.3
6/9.5	H Z C K O	45	0.2
6/7.5	N C K H D	50	0.1
6/6	Z H C S R	55	0.0
6/4.8	S Z R D N	60	-0.1
6/3.8	H C D R O	65	-0.2
6/3.0	R D O S N	70	-0.3
TOTAL LETTERS READ			
Sphere			
Cylinder			
Axis			

Attach
non-cycloplegic
autorefraction
printout here

(DO NOT PUT STICKY TAPE OVER THE PRINT)

1.32 LEFT EYE

WITH best correction ☐			
Snel. Eq	LogMAR letters	No. correct	LogMAR score
6/60	H V Z D S	5	1.0
6/48	N C V K D	10	0.9
6/36	C Z S H N	15	0.8
6/30	O N V S R	20	0.7
6/24	K D N R O	25	0.6
6/19	Z K C S V	30	0.5
6/15	D V O H C	35	0.4
6/12	O H V C K	40	0.3
6/9.5	H Z C K O	45	0.2
6/7.5	N C K H D	50	0.1
6/6	Z H C S R	55	0.0
6/4.8	S Z R D N	60	-0.1
6/3.8	H C D R O	65	-0.2
6/3.0	R D O S N	70	-0.3
TOTAL LETTERS READ			
Sphere			
Cylinder			
Axis			

1.4 STEREOACUITY

1.41 TNO ***Tick all plates seen***

Only plates V to VII required. If not seen return to plate I to determine if there is any BSV present.

Plate I	☐	Plate II	☐	Plate III	☐
Plate IV	☐	No BSV Demonstrated			☐
Plate V 480"	☐	Plate VI 120"	☐	Plate VII 30"	☐
240"	☐	60"	☐	15"	☐

Perform four-dioptre test if TNO is negative i.e. No BSV demonstrated.

1.42 $4^{\Delta D}$**: RE** Positive ☐ Negative ☐ **LE** Positive ☐ Negative ☐

1.5 COVER TEST

1.51 <u>Near</u> (perform at 33 cm)

WITHOUT Glasses

Esophoria ☐	Esotropia ☐	Right eye ☐	Intermittent ☐	mf ☐
Exophoria ☐	Exotropia ☐	Left eye ☐	Constant ☐	nmf ☐
Orthophoria ☐	Vertical component ☐	Alternating ☐		

WITH Glasses 

Esophoria ☐	Esotropia ☐	Right eye ☐	Intermittent ☐	mf ☐
Exophoria ☐	Exotropia ☐	Left eye ☐	Constant ☐	nmf ☐
Orthophoria ☐	Vertical component ☐	Alternating ☐		

1.52 <u>Distance</u> (perform at 6 m)

WITHOUT Glasses

Esophoria ☐	Esotropia ☐	Right eye ☐	Intermittent ☐	mf ☐
Exophoria ☐	Exotropia ☐	Left eye ☐	Constant ☐	nmf ☐
Orthophoria ☐	Vertical component ☐	Alternating ☐		

WITH Glasses 

Esophoria ☐	Esotropia ☐	Right eye ☐	Intermittent ☐	mf ☐
Exophoria ☐	Exotropia ☐	Left eye ☐	Constant ☐	nmf ☐
Orthophoria ☐	Vertical component ☐	Alternating ☐		

1.6 PRISM BAR COVER TEST

1.61 Near (perform at 33 cm)

WITHOUT Glasses

Horizontal _____ △ BI ☐ BO ☐ Vertical _____ △ BU ☐ BD ☐

WITH Glasses 

Horizontal _____ △ BI ☐ BO ☐ Vertical _____ △ BU ☐ BD ☐

1.62 Distance (perform at 6 m)

WITHOUT Glasses

Horizontal _____ △ BI ☐ BO ☐ Vertical _____ △ BU ☐ BD ☐

WITH Glasses 

Horizontal _____ △ BI ☐ BO ☐ Vertical _____ △ BU ☐ BD ☐

Measure convergence and accommodation only if symptoms of aesthenopia are present or you suspect a reduction in these functions

1.7 CONVERGENCE 1.8 ACCOMMODATION

☐ ≤ 6 cm (*tick*) Other _____ cm ☐ 20 D (*tick*) Other _____ D

1.9 OCULAR DOMINANCE

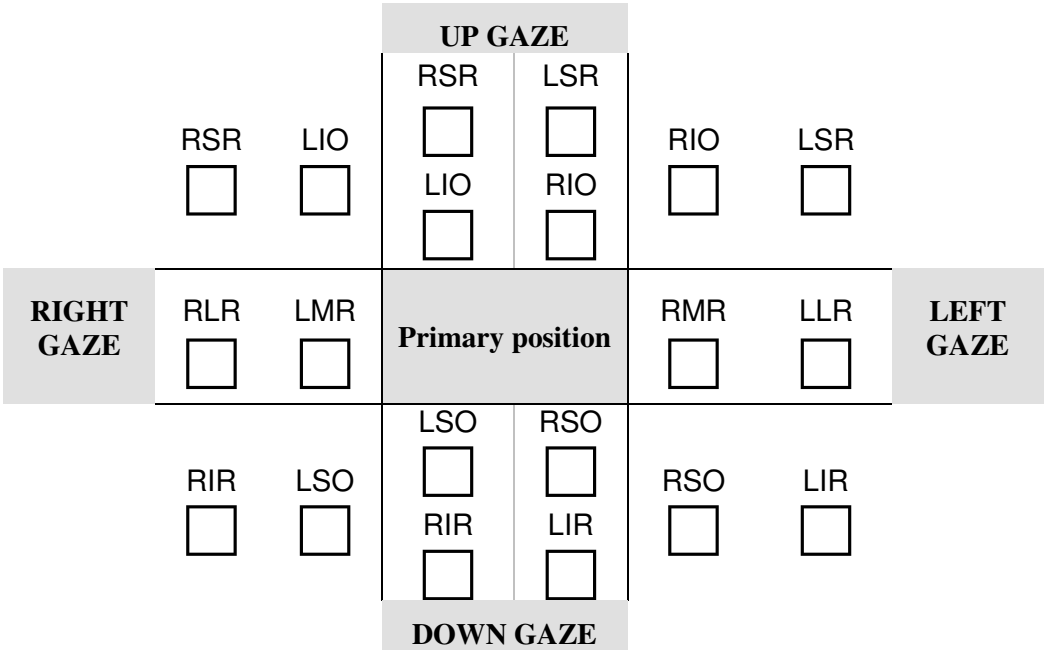
1st Attempt:	RE dominant	☐	LE dominant	☐	Uncertain	☐
2nd Attempt	RE dominant	☐	LE dominant	☐	Uncertain	☐
3rd Attempt	RE dominant	☐	LE dominant	☐	Uncertain	☐

1.10 HANDEDNESS ☐ Right handed ☐ Left handed ☐ Ambidextrous

1.11 OCULAR MOVEMENTS

NAD ☐ Abnormality detected (see below) ☐

Identify abnormality (Indicate if overaction (**+ sign**) or underaction (**– sign**) in the boxes)



V pattern ☐

Exo ☐ Eso ☐

A pattern ☐

Exo ☐ Eso ☐

☐ **Significant** (> 15Δ or tropia in position of gaze)

STATION 2

First Instillation of :

Amethocaine **Time** ☐☐ : ☐☐

2 minutes later

Cyclopentolate 1% **Time** ☐☐ : ☐☐

Tropicamide **Time** ☐☐ : ☐☐

Phenylephrine **Time** ☐☐ : ☐☐

5 minutes later

Second Instillation of :

Cyclopentolate 1% **Time** ☐☐ : ☐☐

Tropicamide **Time** ☐☐ : ☐☐

Phenylephrine **Time** ☐☐ : ☐☐

Height:_____(cms)

Waist Circumference:_____ (cms)

Weight _____(kgs)

Autorefraction

20-25 minutes after 2nd cycl. drop

Attach Autorefraction printout

Attach TANITA printout

STATION 3

Blood Pressure Measurements

Seated Blood Pressure: Right Arm unless otherwise specified:
***(Omron 780 Small, middle and large cuffs)**

1) Blood Pressure: _____ /_____ Performed manually ☐
Pulse: _____BPM Not able to be performed ☐

2) Blood Pressure: _____ /_____ Performed manually ☐
Pulse: _____BPM Not able to be performed ☐

3) Blood Pressure: _____ /_____ Performed manually ☐
Pulse: _____BPM Not able to be performed ☐

Lying Blood Pressure: Right Ankle unless otherwise specified:
***(Omron 780 Small, middle and large cuffs)**

4) Blood Pressure: _____ /_____ Performed manually ☐
Pulse: _____BPM Not able to be performed ☐

5) Blood Pressure: _____ /_____ Performed manually ☐
Pulse: _____BPM Not able to be performed ☐

6) Blood Pressure: _____ /_____ Performed manually ☐
Pulse: _____BPM Not able to be performed ☐

STATION 4

Slit lamp examination

	Eye condition NAD ☐	RE	LE	
Eyelids, lacrimal system	Hordeolum or deep inflammation of the eye lid (abscess, furuncle, stye)	☐	☐	
	Chalazion	☐	☐	
	Blepharitis (excl: blepharoconjunctivitis)	☐	☐	
	Ptosis	☐	☐	
	Epiphora	☐	☐	
	Entropion and Trichiasis	☐	☐	
Conjunctiva and external eye	Mucopurulent conjunctivitis	☐	☐	
	Pterygium	☐	☐	
	Pingueculum	☐	☐	
	Conjunctival degenerations and deposits (concretions, pigmentation, xerosis NOS)	☐	☐	
	Conjunctival scars	☐	☐	
Corneal disease	Corneal ulcer	☐	☐	
	Superficial keratitis	☐	☐	
	Corneal scars or opacities	☐	☐	
	Heredity corneal dystrophies	☐	☐	
	Keratoconus	☐	☐	
Iris and ciliary body	Anterior uveitis	☐	☐	
	Pupillary membrane	☐	☐	
	Iris Stranding	☐	☐	
Lens	Opacity	☐	☐	

Comments:

STATION 5

Aberrometry

Post-dilated

☐ Performed: ☐ Not performed Reason:_____

(Printout)

Video Keratometry

Post-dilated

☐ Performed: ☐ Not performed Reason:_____

(Printout)

IOL Master

☐ Performed: ☐ Not performed Reason:_____

(Printout)

STATION 6

OCT

Cirrus ☐ **Stratus** ☐

Right Eye

☐ Performed: ☐ Not performed Reason:_____

Left Eye

☐ Performed: ☐ Not performed Reason:_____

STATION 7

Retinal Photography

☐ Disc ☐ Colour ☐ Red free

☐ Macula ☐ Colour ☐ Red free

	RE	LE
NAD	☐	☐
Abnormality Detected	☐	☐

Description _____

_____

Unable to take photographs:

Reason	RE	LE
(1) Unable to keep still	☐	☐
(2) Refusal	☐	☐
(3) Failure to dilate	☐	☐

Objective Retinoscopy-*(optional)*

Right Eye:

☐ Emmetrope ☐ Myope ☐ Hypermetrope ☐ Astigmatism

SPH:_____ CYL:_____ AXIS:_____

Left Eye:

☐ Emmetrope ☐ Myope ☐ Hypermetrope ☐ Astigmatism

SPH:_____ CYL:_____ AXIS:_____

Indirect Ophthalmoscope- *(optional)*

Right eye only ☐ Left eye only ☐ Both eyes ☐

	RIGHT			LEFT		
Macula:	Normal ☐	Abnormal ☐		Macula:	Normal ☐	Abnormal ☐
Disc:	Normal ☐	Abnormal ☐		Disc:	Normal ☐	Abnormal ☐
Media:	Normal ☐	Abnormal ☐		Media:	Normal ☐	Abnormal ☐
Periphery:	Normal ☐	Abnormal ☐		Periphery:	Normal ☐	Abnormal ☐

Describe: _____

_____

STATION 8

Intraocular Pressure

Right Eye

☐ Performed: ☐ Not performed Reason:_____

Left Eye

☐ Performed: ☐ Not performed Reason:_____

Pachymetry

Right Eye

☐ Performed: ☐ Not performed Reason:_____

Left Eye

☐ Performed: ☐ Not performed Reason:_____

School: _____

Study ID No. _____ _____ _____ _____

Name _____

Class _____

The Sydney Adolescent Vascular and Eye Study (SAVES)

Parent Questionnaires

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THE SYDNEY ADOLESCENT AND VASCULAR EYE STUDY QUESTIONNAIRE

The purpose of this study

The National Health and Medical Research Council has funded the Sydney Adolescent and Vascular Eye Study to look at the frequency of myopia and factors contributing to its development. We will also look at the frequency of other problems affecting children's eyes such as strabismus (turned eye) and amblyopia (lazy eye or poor vision in one eye). It will also assess the relationship between changes in the small blood vessels at the back of the eye (in the retina), signs like blood pressure and parental history of vascular problems.

You and your child are invited to participate in this large study that will involve children from all over Sydney.

This questionnaire will give us important information relating to you, your child and your family. Please take as much time as necessary to complete it. All of the answers you provide will be regarded as strictly confidential. If you feel any questions are unreasonably intrusive, just leave these out.

In a few weeks we will provide your child with a complete eye test, and a report will be sent to you.

Common questions and answers

What is myopia?
People with myopia, or short-sightedness, are usually not able to see objects in the distance clearly, so that they may find it hard to read signs, play ball games or see the classroom board.

What occurs in the eye?
The eye normally focuses light on the back of the eye (retina) so that you can see objects clearly. However, in a myopic eye, which is too long, the light is focused in front of the retina, so that objects are blurred.

When and why myopia occurs?
Myopia usually develops during a child's school years. The exact cause is unknown. It can occur in some families (genetic) or in association with some diseases. Recent evidence also suggests that some environmental factors may play a part.

Why is myopia a problem?
While vision problems can usually be corrected with glasses, myopia can lead to other eye diseases as a person gets older. In addition, there is evidence that the number of people with myopia is increasing worldwide.

Guidelines

- Where possible we would like one parent or guardian to take responsibility for completing the questionnaire in consultation with other family members/caregivers.
- Please attempt to answer every question. In some circumstances you will be directed to skip questions because they don't apply to you.
- If you have difficulty with a question, please give the best response you can and make a comment in the margin.
- We understand that some children will not be living with both, or even one of their biological parents, and we ask you to please note this in completing the relevant parts of the questionnaire.
- The majority of questions in this questionnaire are standard questions derived from the Australian Bureau of Statistics (ABS) National Census, the NSW Child Health Survey and other international eye studies.
- Please feel free to ask our staff for assistance. They can be contacted on the telephone numbers below.

Please note: While it would greatly assist the examiners if the questionnaire was completed prior to your child's examination, it will be possible to collect it from you later.

Statement of confidentiality

Information that would permit the identification of any person completing this questionnaire will be regarded as strictly confidential. All information provided will be used only for the Sydney Adolescent and Vascular Eye Study and will not be disclosed or released for any other purpose without your consent.

You may correct any personal information provided at any time by contacting:

Administration
Centre for Vision Research
Westmead Hospital
Telephone: 9845 9077
Fax: 9845 8345

Rochelle Jeffery
Project Coordinator,
University of Sydney.
Telephone: 9787 9400
Mobile: 0423 825 309
Fax: 9787 9411
Email: Rochelle_everill@wmi.usyd.edu.au

Professor Paul Mitchell
Project principal investigator,
Department of Ophthalmology,
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Westmead Hospital.
Telephone: 9845 8316
Fax: 9845 8345
Email: **paul_mitchell@wmi.usyd.edu.au**

ABOUT YOUR CHILD

Personal Information

1. Your child's name: _____ _____
(First name) *(Family name)*

2. Your child's address: _____

3. Suburb _____ Postcode ☐☐☐☐

4. How long has your child lived in the above suburb? ☐☐ / ☐☐
(years) *(months)*

5. Since your child was born, where else has he/she lived?

	Location	Length of time at location	From age- to age
1			
2			
3			
4			
5			
6			

6. Gender (please tick): ☐ Female ☐ Male

7. Date of birth: ☐☐ ☐☐ ☐☐☐☐
(day) *(month)* *(year)*

8. In which country was your child born: _____

Parent's name: _____

Telephone (day): _____

Telephone (night): _____

Mobile: _____

Email: _____

9. Could you please provide us with the details of three people we could contact to obtain your address if you were to move?

☐ No **(go to question 13)**

☐ Yes (please fill in details below)

10. **Contact 1**

Name _____Telephone _____

Address _____

Relationship _____

11. **Contact 2**

Name _____Telephone _____

Address_____

Relationship _____

12. **Contact 3**

Name _____Telephone _____

Address_____

Relationship _____

General Practitioner (GP)

13. When did your child last visit his/her GP? _____weeks/months ago *(please circle)*

14. On average, how many times per year does your child visit the GP? _____per year

15. Please tick the box if you do not want a report outlining the results of the examination to also be sent to your nominated GP.

☐ I don't want a report to be sent to my child's GP.

If you prefer not to answer questions about your child's GP, go to Q18.

16. Who is your child's GP? _____

17. What is the address of his/her surgery?_____

_____

Vision and Hearing Questions

The following questions are important because certain hearing and eye conditions can affect your child's schooling.

Hearing Questions

18. Has your child ever had his/her hearing tested?
    - ☐ No **(go to question 26)**
    - ☐ Unsure **(go to question 26)**
    - ☐ Yes

19. If yes, what age? _____ Who performed the test? _____
    Date Performed? _____

20. Did you receive a written report?
    - ☐ No
    - ☐ Unsure
    - ☐ Yes

21. Were there any abnormalities found with your child's hearing?
    - ☐ No
    - ☐ Unsure
    - ☐ Yes

22. Did your child visit a local doctor or a hearing specialist for further testing?
    - ☐ No
    - ☐ Unsure
    - ☐ Yes

23. Were you told what was wrong with your child's hearing?
    - ☐ No **(go to question 26)**
    - ☐ Unsure **(go to question 26)**
    - ☐ Yes

    If yes, the problem was? _____

24. How many months/years ago was the problem reported? ☐☐ / ☐☐
    (years) *(months)*

25. Which ear was involved?
    - ☐ Right ear
    - ☐ Both ears
    - ☐ Left ear
    - ☐ Unsure

26. Has any treatment been started?
    - ☐ No
    - ☐ Unsure **(go to question 26)**
    - ☐ Yes

    If yes, what treatment was given? _____

Vision Questions

27. Did your child participate in the Sydney Myopia Study?

☐ No ☐ Unsure

☐ Yes

28. Has your child ever had his/her vision tested? Or since participating in the Sydney Myopia Study has your child had his/her vision testing elsewhere?

☐ No **(go to question 33)** ☐ Unsure **(go to question 33)**

☐ Yes

29. If yes, what age? _____Who performed the test? _____

30. Did you receive a written report?

☐ No ☐ Unsure

☐ Yes

31. Were there any abnormalities found with your child's eyes?

☐ No **(go to question 33)** ☐ Unsure

☐ Yes

If yes, the problem was: _____

32. Did your child visit a local doctor or eye practitioner for further testing of the problem?

☐ No ☐ Unsure

☐ Yes

33. Was this examination part of treatment and visits that were ongoing before participating in the Sydney Myopia Study?

☐ Yes

☐ No ☐ Unsure

34. If no or unsure, did you decide that your child should have the eye test because:

☐ the report I received from the Sydney Myopia Study suggested they should

☐ another person suggested they should have an eye test

☐ my child reported vision problems

☐ my child had symptoms related to their eyes (eg. headaches)

☐ other, please specify_____

☐ Unsure

35. Were you told what was wrong with your child's eyes?

☐ No **(go to question 33)** ☐ Unsure **(go to question 33)**

☐ Yes

36. How many months ago was the problem reported? ☐☐ / ☐☐
(*years*) (*months*)

37. Does your child have any of the following sight problems?

☐ Totally blind in both eyes
☐ Partially blind in both eyes
☐ Totally blind in 1 eye only
☐ Partially blind in 1 eye only
☐ Glaucoma
☐ Trachoma
☐ Cataract
☐ Don't know
☐ Other _____

38. Which eye was involved?

☐ Right eye
☐ Both eyes
☐ Left eye
☐ Unsure

39. Is your child colour blind?

☐ No
☐ Unsure
☐ Yes

40. Does your child have any other sight problems?

☐ No
☐ Unsure
☐ Yes

If yes, please describe: _____

The following section asks you about any visits your child may have had to an eye practitioner. An eye practitioner includes:
- **Ophthalmologist (eye specialist)**
- **Optometrist**
- **Orthoptist (eye therapist)**

41. How long ago did your child last see an **eye practitioner?**

☐ Never **(go to question 41)**
☐ 2 to less than 5 years
☐ Less than 1 year
☐ 5 years or more
☐ 1 to less than 2 years
☐ Don't know **(go to question 41)**

42. Does your child attend regular eye examinations?

☐ No **(go to question 41)**
☐ Unsure **(go to question 41)**
☐ Yes

43. Which eye practitioner(s) has your child seen (currently or in the past)? **(Specialists will not be contacted directly)**

☐ **Ophthalmologist (Eye Specialist)** ___/___/____*(date last seen)*

Name:_____ Suburb: _____

☐ **Optometrist** ___/___/___ *(date last seen)*

Name:_____ Suburb: _____

☐ **Orthoptist (Eye Therapist)** ___/___/___ *(date last seen)*

Name:_____ Suburb: _____

☐ **Unsure** ___/___/___ *(date last seen)*

Name:_____ Suburb: _____

44. How often is the eye practitioner seen? (refer to the eye practitioner that the child sees most often)

☐ More than once in 6 months ☐ Once a year

☐ Every 6 months ☐ Less than once a year

Any other comments? _____

_____

45. Does your child **currently** wear glasses or contact lenses to correct, or partially correct, his/her eyesight?

☐ No **(go to question 44)**

☐ Glasses

☐ Contact lenses

46. How often are the glasses or contact lenses worn?

☐ All the time

☐ Most of the time

☐ Sometimes

☐ Hardly ever

☐ Only when eyes feel tired

47. Why were the glasses/contact lenses prescribed? *(You may tick more than one box)*

☐ Astigmatism

☐ Short-sightedness / Myopia

☐ Long-sightedness / Hyperopia

☐ Don't know

☐ Other (please describe) _____

48. Has your child worn glasses or contact lenses **in the past**, but no longer needs to wear them?

☐ No (**go to question 48)** ☐ Unsure **(go to question 48)**

☐ Yes

If yes, please state the date and age when first prescribed _____

Date stopped: ☐☐ / ☐☐☐☐
(month) *(year)*

Reason stopped _____

_____

49. How often did your child wear their glasses / contact lenses?

☐ All the time

☐ Most of the time

☐ Sometimes

☐ Hardly ever

☐ Only when eyes feel tired

50. Do you have your child's old glasses?

☐ No **(go to question 48)**

☐ Yes (could the child please bring the glasses with them to the examination)

51. Do you have a **copy** of your child's last prescription?

☐ No

☐ Yes

Please attach a copy of the prescription below. Please do not provide originals.

_____

_____

_____

(Attach prescription here)

52. Has your child had one or more of the following treatments for myopia (short-sightedness)?

- ☐ Bifocals
- ☐ Progressive lenses (multifocal)
- ☐ Atropine eye drops
- ☐ Orthokeratology
- ☐ None of the above
- ☐ Don't know

53. Has an eye practitioner ever noted your child to have a lazy or weak eye (amblyopia)?

- ☐ No **(go to question 52)**
- ☐ Unsure **(go to question 52)**
- ☐ Yes

54. How old was your child when he/she was diagnosed with amblyopia? ☐☐

years *months*

55. Which eye was affected?

- ☐ Right eye
- ☐ Both eyes
- ☐ Left eye

56. Has your child ever worn an eye patch?

- ☐ No **(go to question 54)**
- ☐ Yes

If yes, for how long: _____

57. On which eye was the patch worn?

- ☐ Right eye
- ☐ Left eye
- ☐ Both eyes, alternately

58. Have you ever been told by an eye practitioner that your child has strabismus (turned eye or squint)?

- ☐ No **(go to question 56)**
- ☐ Unsure **(go to question 56)**
- ☐ Yes

59. Has your child received treatment for this condition?

- ☐ No
- ☐ Unsure
- ☐ Yes (please describe) _____

60. Has your child ever had eye surgery?

- ☐ No **(go to question 58)**
- ☐ Yes (If yes, what was it for?)
  - ☐ *Strabismus (turned eye or squint)*

☐ *Other (please describe)* _____

61. When was the eye surgery performed? ☐☐ / ☐☐☐☐
(month) *(year)*

How old was your child? _____

On which eye was the surgery performed?

☐ Right eye ☐ Both eyes, alternately

☐ Left eye ☐ Unsure

62. Has your child ever sustained any serious injury to the eyes or area around the eyes?

☐ No **(go to question 60)** ☐ Unsure **(go to question 60)**

☐ Yes

If yes, explain the injury (please describe) _____

_____

63. Was your child's vision affected by the injury?

☐ No ☐ Unsure

☐ Yes

64. Is your child **currently** using any eye drops/ointments?

☐ No ☐ Unsure

☐ Yes

Please list all eye drops/ointments **currently** used.

	Name of eye drop/ointment	Times per day	Date started month/year	Reason for using
1.				
2.				
3.				

65. Has your child ever used eye drops/ointment in the **past?**

☐ No ☐ Unsure

☐ Yes

Please list all eye drops/ointments **previously** used.

	Name of eye drop/ointment	Times per day	Duration of usage	Age at time of usage	Reason for using
1.					
2.					
3.					

66. Has your child ever complained of any eye problems in the past?

☐ No ☐ Unsure

☐ Yes

67. Has anyone, other than a health practitioner ever noted a problem with your child's eyesight?

☐ No **(go to question 65)** ☐ Unsure **(go to question 65)**

☐ Yes

68. What was thought to be wrong with his/her eyes?

☐ Eyes not looking in same direction (squint or turned eye)

☐ Colour blind

☐ Amblyopia (weak or lazy eye)

☐ Cannot see blackboard

☐ Something else (please describe) _____

☐ Don't know

69. Do you think your child might need to wear glasses?

☐ No ☐ Unsure

☐ Yes (please give the reason) _____

70. Have you noticed your child to have a squint (turned eye)?

☐ No **(go to question 70)** ☐ Unsure **(go to question 70)**

☐ Yes

71. How old was your child when you first noticed this?

☐☐ ☐☐

years *months*

72. Which eye was affected?

☐ Right eye ☐ Left eye

73. Has a doctor checked this?

☐ No

☐ Yes

If yes, how many year(s)/month(s) were there between the first time you noticed this and the time your child was seen by the doctor? ☐☐ ☐☐

years *months*

Questions on General Health

The following questions are relating to your child's past and current health.
A chronic illness or disability is a condition that has been detected in the past and is ongoing, requiring treatment.

74. Has your child ever been diagnosed with a chronic illness or disability?

☐ No **(go to question 75)** ☐ Unsure **(go to question 75)**

☐ Yes

75. What was the nature of the illness or disability?_____

_____

76. Does your child still have this condition?

☐ No ☐ Unsure

☐ Yes

77. Does your child receive treatment for this condition?

☐ No **(go to question 75)** ☐ Unsure **(go to question 75)**

☐ Yes

78. Please tick the treatment(s) given:

☐ Medicine prescribed ☐ Surgery ☐ Given injections

☐ Physiotherapy ☐ Speech therapy ☐ Dental treatment

☐ Naturopathy ☐ Chiropractic treatment

☐ Homeopathic treatment

☐ Counselling / guidance

☐ Other (please describe)_____

The following questions refer to a condition that has been detected for the 1st time in the last 2 weeks. For example: the flu.

79. Has your child visited a doctor in the last 2 weeks?

☐ No **(go to question 82)** ☐ Unsure **(go to question 82)**

☐ Yes

If yes, please state the reason(s)

_____

80. Was any treatment given?

☐ No **(go to question 82)** ☐ Unsure **(go to question 82)**

☐ Yes

81. What treatment(s) were given:

☐ Medicine prescribed ☐ Surgery performed or recommended

☐ Referred to another practitioner (specify)_____

☐ Other (specify)_____

82. Has your child had a second reason to visit a doctor during the last 2 weeks?

☐ No **(go to question 82)** ☐ Unsure **(go to question 82)**

☐ Yes

83. What was the illness or injury that caused your child's second visit to the doctor?

_____

84. Was any treatment given?

☐ No **(go to question 82)** ☐ Unsure **(go to question 82)**

☐ Yes

85. Please tick the treatment(s) given:

☐ Medicine prescribed ☐ Surgery performed or recommended

☐ Referred to another practitioner/ doctor

☐ Other (please describe)_____

The following questions refer to an illness that was severe enough to require your child's admission into hospital or day surgery. For example: appendicitis.

86. Has your child had any periods of prolonged absence from school due to ill health? **(More than 2 weeks)**

☐ No ☐ Unsure

☐ Yes

If yes, how many days? _____

87. Has your child had a major illness in the past that has required admission to hospital or day surgery?

☐ No **(go to question 91)** ☐ Unsure **(go to question 91)**

☐ Yes

88. Please describe the reason for your child's admission? _____

_____

89. At what age did this occur? _____

90. Did your child have surgery?

☐ No **(go to question 91)** ☐ Unsure (**go to question 91)**

☐ Yes

91. Please name or describe the **surgical procedure** _____

92. What was the name of the hospital and in which suburb was it located?_____

_____

93. Has your child had more than one admission to hospital or day surgery?

☐ No **(go to question 91)** ☐ Unsure **(go to question 91)**

☐ Yes

The following questions relate to medications that your child is currently using:
Please note that vitamins, inhaled medicines, skin lotions, eye-drops, laxatives, homeopathic and herbal remedies should also be included.

94. Has your child taken any medication(s) in the **last 2 weeks**?

☐ No **(go to question 92)** ☐ Unsure **(go to question 92)**

☐ Yes *(If yes, please list all the medications in the table below)*

	Medication name	Method of intake (ie. oral, injected)	Number of times per day	Date started	Reason for taking
1					
2					
3					
4					

Medications used for a period of at least 3 months

33. In the **past** has there been any *prescribed* or *non-prescribed* medication(s) that your child has taken every day (or nearly every day) for a period of at least 3 months?

☐ No (go to question 93) ☐ Unsure (go to question 93)

☐ Yes *(If yes, please list all the medications in the table below)*

Please list all ***prescribed*** medications taken for a period of at least 3 months.

	Medication name	Method of intake (ie oral, injected)	How many times a day	Duration in weeks	Reason for taking	Age at time
1						
2						
3						
4						
5						

Please list all ***over the counter*** medications *(medications not requiring a doctors prescription for purchase)*, taken for a period of at least 3 months.

	Medication name	Method of intake (ie oral, injected)	How many times a day	Duration in weeks	Reason for taking	Age at time
1						
2						
3						
4						
5						

We would like to ask you about common medical conditions. Certain conditions have been shown to be associated with myopia.

95. Has your child ever been told by a doctor or nurse that he/she has asthma?

☐ No **(go to question 95)** ☐ Unsure **(go to question 95)**

☐ Yes

96. Does your child still have asthma?

☐ No ☐ Unsure

☐ Yes

97. Do you (parent – mother or father) smoke?

☐ No

☐ Yes **(please complete question 96)**

98. Do other people living in your home smoke inside the house?

☐ No

☐ Yes

If you answered ***Yes*** to *questions 95 or 96,* please complete the table below.

Cigarettes/day	Mother	Father	Other
1-10/ day			
11-20/ day			
21-40/day			
41+/day			

99. Was there any delay in your child's early development?

☐ No ☐ Unsure

☐ Yes (Please tick below)

Delayed development in:

☐ Sitting

☐ Walking

☐ Talking

☐ Other (please describe) _____

100. Has your child had any learning difficulties at school?

☐ No ☐ Unsure

☐ Yes

If yes, please describe_____

101. Have you ever been told that your child has Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD)?

☐ No **(go to question 102)** ☐ Unsure **(go to question 102)**

☐ Yes

102. What age was your child when you were first told that he/she had Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD)

☐☐ ☐☐ ☐ Don't Know

years *months*

103. Is your child receiving treatment for this disorder?

☐ No ☐ Unsure

☐ Yes

104. Has your child ever been diagnosed with any of the following?

☐ Epilepsy ☐ Meningitis

☐ Diabetes ☐ Down Syndrome

☐ Stickler Syndrome ☐ Marfan Syndrome

☐ Toxoplasmosis ☐ Congenital heart disease

☐ Other (please describe) _____

*The following questions apply only to **FEMALE STUDENTS**. The start of puberty has been associated with the onset of myopia and can have an effect on eye development. We would like to ask you the following questions so that we can study these effects further. If they do not apply to your child, please skip to question 105.*

105. Has you daughter had a period in the past 12 months?

☐ Yes ☐ Don't know

☐ No

106. How old was she when her periods (or menstrual cycles) started?

☐ Her periods haven't started yet

☐ I'm not sure when her periods started

☐ Her periods started at age ☐☐ / ☐☐

(years) *(months)*

104. In the past **ONE month**, how much of a **problem** has your child had with…

PHYSICAL FUNCTIONING (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Doing chores around the house	0	1	2	3	4

EMOTIONAL FUNCTIONING (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other children	0	1	2	3	4
2. Other children not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4

SCHOOL FUNCTIONING (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school work	0	1	2	3	4

ABOUT YOUR FAMILY

This section will ask about your child's biological (natural) parents and family members to identify genetic associations. People with particular ethnic backgrounds seem to develop myopia more than others. We realise that some parent(s) may not be the biological parent(s) and in some cases not have the knowledge to complete some sections. If this is the case, please tick unsure. Where possible it is preferable that the biological parent completes this section.

Biological Parents

107. Please tick the box that applies to your child:

☐ Both parents are the biological parents

☐ Current father is the biological father and current mother is not the biological mother

☐ Current mother is the biological mother and current father is not the biological father

☐ Current father is the biological father and no mother present (single father)

☐ Current mother is the biological mother and no father present (single mother)

☐ Both parents are **not the** biological parents

☐ Other (please describe) _____

108. Which language(s) is most commonly spoken at home? _____

109. Please tick all medical conditions the child's **BIOLOGICAL MOTHER** may have had or currently has:

Height: ……. Weight: ……...

Has a doctor advised you that you have any of the following conditions……..

(a) angina?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107b)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Was the diagnosis confirmed with an ECG? ☐Yes ☐No ☐Unsure		
(iii)	Name & address of Dr. who made diagnosis? ……. …….		
(iv)	How often do you take anginine tablets or sprays? …… times per……		

(b) heart attack?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107c)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Was the diagnosis confirmed with an ECG? ☐Yes ☐No ☐Unsure Was the diagnosis confirmed with a blood test? ☐Yes ☐No ☐Unsure		
(iii)	Name & address of Dr. who made diagnosis? ……. …….		
(iv)	Were you admitted to hospital? ☐Yes ☐No ☐Unsure For how long? …….. days		
(v)	Treatment for your heart attack? ☐Bypass……years ago at…….hospital ☐Angioplasty……years ago at ……hospital ☐Pacemaker ……years ago at……hospital ☐Valve replacement ……years ago at……hospital ☐Other: specify……..		

(c) stroke?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107d)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Was the diagnosis confirmed with a CT Scan? ☐Yes ☐No ☐Unsure		
(iii)	Name & address of Dr. who made diagnosis? ……. …….		
(iv)	Were you admitted to hospital? ☐Yes ☐No ☐Unsure		
(v)	For how long? …… days		

(vi)	How did the stroke affect you? ☐Mild ☐Moderate ☐Severe Part of body affected: **Arm** ☐Right ☐Left **Leg** ☐Right ☐Left **Speech** ☐ **Other** ……..	
(vii)	How well have you recovered from the stroke?..…% (100% is full recovery) How long did it take? …..……months Treatment for your stroke? ☐ Aspirin, clopidogrel, persantin ☐ Anticoagulation (heparin, clexane and warfarin) ☐ Don't know	

(d) mini <u>stroke or TIA?</u>	Yes ☐ **(go to (i))**	No☐ **(continue on to 107e)**	Unsure☐
(Stroke-like episodes with weakness in your face, fingers, hands, arms which last for short periods of time transient loss of vision in one eye)			
(i)	When was the first attack? …… years ago?		
(ii)	Did you ever have surgery to the brain or neck to correct or prevent a stroke? ☐Yes ☐No ☐Unsure		
(iii)	How many years ago was the surgery ……..		

(e) High Blood Pressure?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107f)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	For how many years has it been treated with medications?……years		

(f) High Cholesterol?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107g)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Are you taking tablets? Gemfibrozil (lopid, ausgem) ☐ Fluvastatin (lescol, vastin) ☐ Simvastatin (lipex, zocor) ☐ Other _____☐ No ☐ **Unsure** ☐ (Colestipol, Atorvastatin, Cerivastatin, Pravastatin, Probucol, Cholestyramine, Nicotinic Acid)		

(g) Diabetes? High sugar in blood or urine	Yes ☐ **(go to (i))**	No☐	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	In what year did you begin and finish each type of treatment?		

	Started	Finished	Current	Yes	No	Unsure
Diet Alone						
Tablets						
Insulin						
No Treatment						

110. Please tick all medical conditions the child's **BIOLOGICAL FATHER** may have had or currently has:

Height: ……. Weight: ……...

Has a doctor advised you that you have any of the following conditions……..

(a) angina?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107b)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Was the diagnosis confirmed with an ECG? ☐Yes ☐No ☐Unsure		
(iii)	Name & address of Dr. who made diagnosis? ……. …….		
(iv)	How often do you take anginine tablets or sprays? …… times per……		

(b) heart attack?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107c)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Was the diagnosis confirmed with an ECG? ☐Yes ☐No ☐Unsure Was the diagnosis confirmed with a blood test? ☐Yes ☐No ☐Unsure		
(iii)	Name & address of Dr. who made diagnosis? ……. …….		
(iv)	Were you admitted to hospital? ☐Yes ☐No ☐Unsure For how long? …….. days		
(v)	Treatment for your heart attack? ☐Bypass……years ago at…….hospital ☐Angioplasty……years ago at ……hospital ☐Pacemaker …….years ago at……hospital ☐Valve replacement ……years ago at……hospital ☐Other: specify……..		

(c) stroke?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107d)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Was the diagnosis confirmed with a CT Scan? ☐Yes ☐No ☐Unsure		
(iii)	Name & address of Dr. who made diagnosis? ……. …….		
(iv)	Were you admitted to hospital? ☐Yes ☐No ☐Unsure		
(v)	For how long? …… days		

(vi)	How did the stroke affect you? ☐Mild ☐Moderate ☐Severe Part of body affected: **Arm** ☐Right ☐Left **Leg** ☐Right ☐Left **Speech** ☐ **Other** ……..	
(vii)	How well have you recovered from the stroke?..…% (100% is full recovery) How long did it take? …..……months Treatment for your stroke? ☐ Aspirin, clopidogrel, persantin ☐ Anticoagulation (heparin, clexane and warfarin) ☐ Don't know	

(d) mini <u>stroke or TIA?</u>	Yes ☐ **(go to (i))**	No☐ **(continue on to 107e)**	Unsure☐
(Stroke-like episodes with weakness in your face, fingers, hands, arms which last for short periods of time transient loss of vision in one eye)			
(i)	When was the first attack? …… years ago?		
(ii)	Did you ever have surgery to the brain or neck to correct or prevent a stroke? ☐Yes ☐No ☐Unsure		
(iii)	How many years ago was the surgery ……..		

(e) High Blood Pressure?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107f)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	For how many years has it been treated with medications?……years		

(f) High Cholesterol?	Yes ☐ **(go to (i))**	No☐ **(continue on to 107g)**	Unsure☐
(i)	When was it first diagnosed? …….years ago		
(ii)	Are you taking tablets? Gemfibrozil (lopid, ausgem) ☐ Fluvastatin (lescol, vastin) ☐ Simvastatin (lipex, zocor) ☐ Other _____☐ No ☐ **Unsure** ☐ (Colestipol, Atorvastatin, Cerivastatin, Pravastatin, Probucol, Cholestyramine, Nicotinic Acid)		

(g) Diabetes? High sugar in blood or urine			Yes ☐ **(go to (i))**	No☐		Unsure☐
(i)			When was it first diagnosed? …….years ago			
(ii)			In what year did you begin and finish each type of treatment?			
	Started	Finished	Current	Yes	No	Unsure
Diet Alone						
Tablets						
Insulin						
No Treatment						

111. Please state whether anyone in your child's **biological mother's family** has had a cataract operation or any other eye condition?

	Cataract Operation *(Age when surgery performed)*	**Other Eye Condition** *(Please describe)*
☐ Mother	_____ *years*	_____
☐ Mother's father	_____ *years*	_____
☐ Mother's mother	_____ *years*	_____
☐ Mother's brothers	_____ *years*	_____
☐ Mother's sisters	_____ *years*	_____
☐ Unsure		

112. Please state whether anyone in your child's **biological father's family** has had a cataract operation or any other eye condition?

	Cataract Operation *(Age when surgery performed)*	**Other Eye Condition** *(Please describe)*
☐ Father	_____ *years*	_____
☐ Father's father	_____ *years*	_____
☐ Father's mother	_____ *years*	_____
☐ Father's brothers	_____ *years*	_____
☐ Father's sisters	_____ *years*	_____
☐ Unsure		

113. Please indicate the total number of children in the household

☐ Males ☐ Females

114. Please list the full name, sex, year and place of birth for **ALL** brothers and sisters <u>including</u> biological and non-biological.

Christian name initial	Family name initial	Gender	Year of birth	Birthplace Town/country	Same mother	Same father
		☐Male ☐Female			☐Yes ☐No	☐Yes ☐No
		☐Male ☐Female			☐Yes ☐No	☐Yes ☐No
		☐Male ☐Female			☐Yes ☐No	☐Yes ☐No
		☐Male ☐Female			☐Yes ☐No	☐Yes ☐No
		☐Male ☐Female			☐Yes ☐No	☐Yes ☐No
		☐Male ☐Female			☐Yes ☐No	☐Yes ☐No

115. Do any children living in your household have any known eye problems?
Please list:

Name	Eye Problem

116. This table refers to all children **except** your child involved in the study.

Children	**Does the child wear glasses or contact lenses?**	**At what age did the child start wearing glasses**	**What does the child wear glasses and/or contact lens primarily for?**	**Does the child have astigmatism?**
1. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
2. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
3. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
4. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
5. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
6. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
7. First name: _____	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know

We would like to know whether other family members including the parents have eye conditions requiring correction with glasses, contact lenses.

117. Please fill out the tables with reference to your child's ***biological*** family members.

Family members	Do they wear glasses or contact lenses?	At what age did they start wearing glasses?	What do they wear glasses or contact lens primarily for?	Do they have astigmatism?
1. Father	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know
2. Mother	☐ Yes ☐ No ☐ Don't know		☐ Seeing clearly in distance (e.g. television, movies) ☐ Reading, working at a computer, or other close work ☐ Equally important for distance and close work.	☐ Yes ☐ No ☐ Don't know

Children with parents who are myopic are more likely to develop myopia. We are therefore keen to know the strength of any glasses (or contact lenses) worn by either parent.

118.

Parent 1:

☐ I do not wear glasses/contact lenses

☐ I have enclosed a copy of my glasses/ contact lens prescription.

☐ I give permission for the Sydney Myopia Study to contact my optometrist/ eye specialist to obtain a copy of my glasses/contact lenses prescription.

Eye specialist's/ Optometrist's name:
Address:
Telephone:

PARENT'S NAME:_____

SIGNATURE:_____ DATE:_____

Parent 2:

☐ I do not wear glasses/contact lenses

☐ I have enclosed a copy of my glasses/ contact lens prescription.

☐ I give permission for the Sydney Myopia Study to contact my optometrist/ eye specialist to obtain a copy of my glasses/contact lenses prescription.

Eye specialist's/ Optometrist's name:
Address:
Telephone:

PARENT'S NAME:_____

SIGNATURE:_____DATE:_____

119. Has anyone in your family had refractive/ laser correction eye surgery?

☐ No **(go to question 163)**

☐ Yes

120. If yes, what is his or her relation to the child (e.g., father, sister) _____

121. Refractive surgery (laser surgery/ LASIK) was done at the age of _____ years old and for correction of:

☐ Myopia ☐ Presbyopia

☐ Hyperopia ☐ Don't know

☐ Astigmatism

The questions in this section refer to the <u>current</u> parents caring for the child (which in some cases may not be the biological parents).

Current parents

122. Parents' occupation(s):

Mother's Occupation: _____

Current Occupation:_____

Father's Occupation:_____

Current Occupation _____

123. How would you describe the mother's employment status?

- ☐ Employed full time (includes self employment)
- ☐ Employed part time (includes self employment)
- ☐ Unemployed
- ☐ Home duties
- ☐ Student and working
- ☐ Student and not working
- ☐ Retired
- ☐ Unable to work due to health problems
- ☐ Pension
- ☐ Other _____

124. How would you describe the father's employment status?

- ☐ Employed full time (includes self employment)
- ☐ Employed part time (includes self employment)
- ☐ Unemployed
- ☐ Home duties
- ☐ Student and working
- ☐ Student and not working
- ☐ Retired
- ☐ Unable to work due to health problems
- ☐ Pension
- ☐ Other _____

125. What is the highest level of education completed by the mother?

- ☐ Never attended school
- ☐ Some primary school completed
- ☐ Some high school completed
- ☐ Completed School Certificate – Intermediate -Year 10 - 4th Form
- ☐ Completed HSC - Year 12 – Leaving - 6th Form
- ☐ TAFE Certificate or Diploma, including trade certificate
- ☐ University, CAE or some other tertiary institute degree
- ☐ Higher degree including a Masters or PhD
- ☐ Other _____

126. What is the highest level of education completed by the father?

- ☐ Never attended school
- ☐ Some primary school completed
- ☐ Some high school completed
- ☐ Completed School Certificate – Intermediate -Year 10 - 4th Form
- ☐ Completed HSC - Year 12 – Leaving - 6th Form
- ☐ TAFE Certificate or Diploma, including trade certificate
- ☐ University, CAE or some other tertiary institute degree
- ☐ Higher degree including a Masters or PhD
- ☐ Other _____

127. What type of place does the family live in?

- ☐ Own house
- ☐ Own flat/unit
- ☐ Rented house
- ☐ Other (please describe) _____
- ☐ With relatives
- ☐ Don't know
- ☐ Rented flat

The date when the questionnaire was completed: ☐☐ / ☐☐ / ☐☐
(Day) *(Month)* *(Year)*

Name of person filling out the questionnaire:

Name_____ Relationship to child_____

Please give us any final comments, and thank you again for your time:

Thank you for completing this questionnaire.
We look forward to seeing your child at the examination.

School: _____

Study ID No. _____ _____ _____ _____

Name _____

Class _____

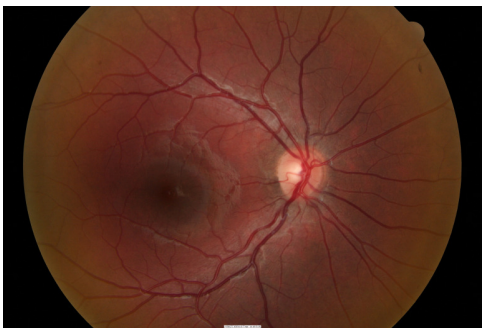
Student Withdrawal (please tick if you wish to withdraw) _____

The Sydney Adolescent Vascular and Eye Study (SAVES)

Student Questionnaires

THE SYDNEY ADOLESCENT VASCULAR EYE STUDY (SAVES) QUESTIONNAIRE FOR STUDENTS

What is the purpose of this study?
There are two components to this follow-up exam from the Sydney Myopia Study (SMS) 5 years ago. The first is a **Long-term Eye Study** that is looking at changes in your vision over the past 5 years. Worldwide, there has been an increase in the frequency of short sightedness (myopia). We still do not understand all the reasons behind this, but this study aims to discover some of the risk factors for myopia. The second is a **Long-term Vascular Study** looking at the origins of heart and vessel disease occurring in adult life. Recent studies have shown that narrowing of small blood vessels at the back of the eye (see below) predicts the development of high blood pressure and vascular problems. We want to explore this in your eyes.



What we found in the initial SMS examinations:
Key findings included 'less myopia with increasing time spent outdoors' and no harm from reading. Our overall frequency of myopia was low.

What now?
This questionnaire will give us important information about you, your health and lifestyle. We would like to know how you spend your weekdays, weekends and holidays. You might think that some of the questions we ask are not relevant to short-sightedness to the eye. But in fact, lots of recent studies have linked eye diseases to lifestyle and a person's living environment.

Please fill out the questionnaire as best you can and bring it back on the day in the sealed envelope. **All answers will be strictly confidential. We will ensure that they are kept private and we will not discuss them with your teachers, parents or friends**. If you find some questions difficult, we are happy to explain them to you on the day of your examination.

We are confident that you will enjoy the experience of being part of this very important project and that you will learn many interesting facts about your eyes. **At any stage if you do not wish to participate. Please do not hesitate to contact any of the study staff and advice of your withdrawal. They will immediately remove your information and update relevant student listings for testing.**

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CONTACT DETAILS FOR STUDENT

1) Name: _____ _____
(first name) *(family name)*
2) Home phone: _____
3) Mobile: _____
4) Email: _____

QUESTIONS ABOUT YOUR VISION

Tell us whether or not you currently wear contact lenses or glasses and how often. Think about whether you have any difficulty seeing at near and far distances and whether you sometimes get headaches when reading or looking into the distance.

5) Do you **currently** wear *glasses* or *contact lenses*?
- ☐ No **(go to question 8)**
- ☐ Glasses (could you please bring them to the eye examination)
- ☐ Contact lenses

6) How often do you wear *glasses* or *contact lenses*?
- ☐ All the time
- ☐ Most of the time
- ☐ Sometimes
- ☐ Hardly ever
- ☐ Only when my eyes feel tired

7) If you wear contact lenses, do you have your old glasses?
☐ No ☐ Yes (could you please bring them to the eye examination)

8) Have you ever experienced any of the following?
- ☐ Blurred vision when looking in the distance
- ☐ Double vision
- ☐ Sore eyes (How often?) _____
- ☐ Other (Please describe) _____
- ☐ None of the above

9) Do you get headaches when reading or doing close work?

☐ No ☐ Don't know ☐ Yes

If yes, how often?_____*times per week*. And at what time of the day? _____

How long do the headaches usually last? ☐☐ / ☐☐

(hours) (minutes)

10) How many books or magazines do you finish reading in a week?

☐☐ books or magazines <u>per week</u>

11) Where do you do **most** of your reading or close work?

☐ At a quiet location at home (e.g. bedroom, study)

☐ At another location at home (e.g. lounge room)

☐ In the library

☐ Other (please describe) _____

12) What type of lighting is **normally used** when you read or do close work? (*you may tick more than one box*)

☐ Desk lamp

☐ Ceiling or room light

☐ Natural light (e.g. sunlight through a window, skylight)

☐ Other (please describe) _____

13) For how long do you **continuously** read or do close work before taking a break of 5 minutes or longer?

☐ 0-15 minutes

☐ 16-30 minutes

☐ 31-45 minutes

☐ 46-60 minutes

☐ More than 60 minutes

14) How often do you borrow books from a library?

☐ Never

☐ Less than once a week

☐ Around once a week

☐ More than once a week

15) Do you have access to any of the following? (*you may tick more than one box*)

- ☐ Your own mobile phone
- ☐ Access to a computer at home
- ☐ Access to the Internet at home
- ☐ Personal organiser
- ☐ Video Game System (X-Box, PlayStation, etc…)
- ☐ Digital Camera
- ☐ DVD Player

16) Do you use a mobile phone either to make calls or play games?

☐ No ☐ Yes

17) How long does it take you to get to school?

☐☐
Minutes

18) How far away is your school from home?

☐☐
Kilometers

19) If you are driven to school in a car, train or bus, what do you usually do during the journey?

- ☐ Read a book/study
- ☐ Talk to other people in the vehicle
- ☐ Play hand held games
- ☐ Sleep
- ☐ Look outside the window
- ☐ Other (please describe) _____

ACTIVITY QUESTIONS

20) Please tick the number of **hours per day** that you spend doing the following activities outside of school.

	ON A SCHOOL WEEKDAY				ON A SCHOOL WEEKEND			
	Not at all	**Less than 1 hour**	**1-2 hours**	**3 or more hours**	**Not at all**	**Less than 1 hour**	**1-2 hours**	**3 or more hours**
a) Out of doors (*in your backyard, walking, riding a bike/scooter)*	☐	☐	☐	☐	☐	☐	☐	☐
b) Outdoor leisure activities (*BBQs, picnic, beach, bushwalk*)	☐	☐	☐	☐	☐	☐	☐	☐
c) Watching T.V/ videos /DVDs	☐	☐	☐	☐	☐	☐	☐	☐
d) Playing video games (eg. *Playstation, Wii)*	☐	☐	☐	☐	☐	☐	☐	☐
e) Drawing, painting and/or writing	☐	☐	☐	☐	☐	☐	☐	☐
f) Hobbies and crafts	☐	☐	☐	☐	☐	☐	☐	☐
g) Cooking, making or constructing things	☐	☐	☐	☐	☐	☐	☐	☐
h) School homework	☐	☐	☐	☐	☐	☐	☐	☐
i) Reading books for pleasure	☐	☐	☐	☐	☐	☐	☐	☐
j) Playing musical instruments	☐	☐	☐	☐	☐	☐	☐	☐
k) Using a computer or playing computer games	☐	☐	☐	☐	☐	☐	☐	☐
l) Playing ***hand-held*** computer games (e.g. *Gameboy*)	☐	☐	☐	☐	☐	☐	☐	☐
m) Playing with and caring for pets	☐	☐	☐	☐	☐	☐	☐	☐
n) Going shopping	☐	☐	☐	☐	☐	☐	☐	☐
o) Playing board games	☐	☐	☐	☐	☐	☐	☐	☐

21) Please tick the activities you do ***during the last school term*** and the number of ***hours per week*** *you* spend doing the activity. Include activities done **at school** and **at home**.

DURING THE 7 DAYS OF THE WEEK

	YES	**Number of hours per week spent in this activity**	**Where is this done?**		
			Outdoors	In a hall or gym	In a classroom or smaller
a) Dancing, gymnastics martial arts	☐	_____hrs per week	☐	☐	☐
b) Athletics	☐	_____hrs per week	☐	☐	☐
c) Swimming	☐	_____hrs per week	☐	☐	☐
d) Football, soccer, rugby, league, AFL	☐	_____hrs per week	☐	☐	☐
e) Netball, basketball	☐	_____hrs per week	☐	☐	☐
f) Tennis, squash or racquet sports	☐	_____hrs per week	☐	☐	☐
g) Cricket, golf	☐	_____hrs per week	☐	☐	☐
h) Skating, rollerblading	☐	_____hrs per week	☐	☐	☐
i) Baseball/ softball	☐	_____hrs per week	☐	☐	☐
j) Bushwalking, rock climbing	☐	_____hrs per week	☐	☐	☐
k) Attending a youth group/club	☐	_____hrs per week	☐	☐	☐
l) Attending a religious centre	☐	_____hrs per week	☐	☐	☐
m) Other, please describe below: _____	☐	_____hrs per week	☐	☐	☐

SLEEP QUESTIONS

22) What time do you usually go to sleep at night on a school weekday? ☐☐.☐☐

23) What time do you usually go to sleep at night on a weekend? ☐☐.☐☐

24) What time do you usually wake up in the morning on a school week day? ☐☐.☐☐

25) What time do you usually wake up in the morning on a weekend? ☐☐.☐☐

QUESTIONS ABOUT YOUR LIVING ENVIRONMENT

Think about where you currently live and how you could best describe the building or buildings and there surrounds before answering these questions.

26) Please tick the box that best describes your home:

☐ Separate house
- ☐ *One storey*
- ☐ *Two or more stories*

☐ Semi-detached, row or terrace house with:
- ☐ *One storey*
- ☐ *Two or more stories*

☐ Flat attached to a house

☐ Other flat/unit/apartment:
- ☐ *In a 1 or 2 storey block*
- ☐ *In a 3 storey block*
- ☐ *In a 4 or more storey block*

☐ Caravan/cabin in a caravan park, houseboat in a marina,

☐ Caravan not in a caravan park/houseboat not in a marina, etc.

☐ Improvised home/campers out

☐ House or flat attached to a shop, office, etc.

27) Do you live in ***another home*** for at least 2 days?

☐ No **(go to question 30)** ☐ Yes **(go to next question)**

28) If yes, please tick the box that best describes the home you live in regularly for at least 2 days per week:

☐ Separate house
- ☐ *One storey*
- ☐ *Two or more stories*

☐ Semi-detached, row or terrace house with:
- ☐ *One storey*
- ☐ *Two or more stories*

☐ Flat attached to a house

☐ Other flat/unit/apartment:
- ☐ *In a 1 or 2 storey block*
- ☐ *In a 3 storey block*
- ☐ *In a 4 or more storey block*

☐ Caravan/cabin in a caravan park, houseboat in a marina,

☐ Caravan not in a caravan park/houseboat not in a marina, etc.

☐ Improvised home/campers out

☐ House or flat attached to a shop, office, etc

29) From the front door of your home how many other **homes** can you see?

☐ Less than 5 ☐ Don't know

☐ 5-10

☐ Greater than 10

30) From the front door of your home how many **shops or offices** can you see?

☐ None ☐ Don't know

☐ Less than 5

☐ Greater than 5

31) From the front door of your home how many **high-rise buildings** can you see?

☐ None ☐ Don't know

☐ Less than 5

☐ Greater than 5

32) Is it possible to get a view of the horizon from the ground floor of your home?

☐ No ☐ Don't know ☐ Yes

QUESTIONS ABOUT YOUR EATING HABITS

*Think about the kinds of foods you **usually** eat. How many times a **day** do you eat these foods? Please tick only one answer for each question.*

33) How many serves of vegetables, including potato, do you USUALLY eat each day? (A 'serve' is a half-cup if cooked vegetables or 1 cup of salad vegetables) This includes all fresh, dried, frozen and tinned vegetables.

☐ I don't eat vegetables

☐ 1 serve or less

☐ 2 serves

☐ 3 serves

☐ 4 serves or more

34) How many serves of fruit do you USUALLY eat each day, where a serve is 1 medium piece or 2 small pieces of fruit, a cup of diced pieces? This includes all fresh, dried, frozen and tinned fruit.

☐ I don't eat fruit

☐ 1 serve or less

☐ 2 serves

☐ 3 serves

☐ 4 serves or more

35) How much milk (in total) do you USUALLY drink each day? (include all types of milk, including flavoured milk and milk on cereal)

☐ I don't drink milk

☐ Less than 250mL

☐ 250-500mL (300 ml is a small carton)

☐ 501 –750mL

☐ 750mL or more

36) What type of milk do you USUALLY drink? Choose one type of milk only.

☐ I don't drink milk

☐ Whole milk (full cream)

☐ Low or reduced fat milk (1 or 2% fat)

☐ Evaporated Milk

☐ Skim (non fat) milk

☐ Other type milk (i.e. soy, rice, goat)

☐ Not sure

37) How often do you eat bread? (bread rolls, flat breads, crumpets, bagels, English or bread type muffins)

☐ Never or rarely

☐ About 1-3 times a day

☐ About 3-5 times a day

☐ 6 or more times a day

38) How often do you add butter or margarine to your bread or rolls?

☐ Never

☐ Not very often

☐ Sometimes

☐ Almost always

☐ Always

*Now think about what you **usually** ate over the **past 4 weeks**. Tick only one answer for each question.*

39) How often do you drink 100% fruit juices such as orange and apple?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

40) How often do you consume cheese or yoghurt?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a day
- ☐ About 4-6 times a day
- ☐ Everyday

41) How often do you eat breakfast cereal? (ready-made, home-made or cooked)

- ☐ Never or rarely
- ☐ Less than twice a week
- ☐ About 2-6 times a week
- ☐ Everyday

42) How often do you eat pasta, rice, and/or noodles?

- ☐ Never or rarely
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

43) How often do you eat red meat such as beef, mince, lamb or liver?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

44) How often do you USUALLY eat chicken or fish?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

45) How often do you eat baked beans, three bean mix, lentils, split peas or dried beans?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

46) How often do you eat meat products such as sausages, frankfurters, Belgium, devon, salami, meat pies, bacon or ham?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

47) How often do you USUALLY eat eggs?

- ☐ Never or rarely
- ☐ Less than twice a week
- ☐ About 2-6 times a week
- ☐ Everyday

48) How often do you eat chips, wedges, fried potatoes or crisps?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

49) How often do you have meals or snacks such as burgers, pizza, chicken or chips from place like McDonalds, Hungry Jacks, Pizza Hut, Red Rooster or local take-away food places?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

50) How often do you USUALLY eat potato crisps or other salty snacks (i.e. Twisties, Corn chips)?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

51) How often do you USUALLY eat sweets (i.e. chocolates and lollies)?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Everyday

52) How often do you drink soft drinks or sports drinks like soda, cordial, Coke, Lemonade, Gatorade?

- ☐ Never or rarely
- ☐ Less than once a week
- ☐ About 1-3 times a week
- ☐ About 4-6 times a week
- ☐ Once a day
- ☐ 2-3 times a day

53) Are you allergic to or intolerant of any foods (e.g. milk, nuts, etc)?

- ☐ No
- ☐ Unsure
- ☐ Yes

Please specify: _____

QUESTIONS ABOUT YOUR HEALTH

The following questions are about smoking.

54) Have you ever tried or experimented with cigarette smoking, even one or two puffs?

- ☐ No
- ☐ Yes

55) How old were you when you first tried a cigarette?

- ☐ I have never smoked cigarettes
- ☐ 7 years old or younger
- ☐ 8 or 9 years old
- ☐ 10 or 11 years old
- ☐ 12 or 13 years old
- ☐ 14 or 15 years old

56) During the past 30 days (one month), on how many days did you smoke cigarettes?

- ☐ 0 days
- ☐ 1 or 2 days
- ☐ 3 to 5 days
- ☐ 6 to 9 days
- ☐ 10 to 19 days
- ☐ 20 to 29 days
- ☐ All 30 days

57) During the past 30 days (one month), on the days you smoked, how many cigarettes did you usually smoke?

- ☐ I did not smoke cigarettes during the past 30 days (one month)
- ☐ Less than 1 cigarette per day
- ☐ 1 cigarette per day
- ☐ 2 to 5 cigarettes per day
- ☐ 6 to 10 cigarettes per day
- ☐ 11 to 20 cigarettes per day
- ☐ More than 20 cigarettes per day

Thank you for completing the questionnaire.
We look forward to seeing you at the examination.