Peripapillary choroidal thickness in childhood

Scott A. Read a Email: sa.read@qut.edu.au
David Alonso-Caneiro a Email: d.alonso-caneiro@qut.edu.au
Stephen J. Vincent a Email: sj.vincent@qut.edu.au
Michael J. Collins a Email: m.collins@qut.edu.au

a Contact Lens and Visual Optics Laboratory, School of Optometry and Vision Science, Queensland University of Technology, Brisbane, Queensland, Australia

Corresponding author:
Dr Scott A Read
Contact Lens and Visual Optics Laboratory
School of Optometry and Vision Science
Queensland University of Technology
Room D517, O Block, Victoria Park Road, Kelvin Grove 4059
Brisbane, Queensland, Australia
Phone: 617 3138 5714, Fax: 617 3138 5665
Email: sa.read@qut.edu.au

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Abstract

Changes in the thickness of the \textit{in vivo} peripapillary choroid have been documented in a range of ocular conditions in adults; however, choroidal thickness in the peripapillary region of children has not been examined in detail. This study therefore aimed to investigate the thickness of the peripapillary choroid and the overlying retinal nerve fibre layer (RNFL) in a population of normal children with a range of refractive errors. Ninety-three children (37 myopes and 56 non-myopes) aged between 11 and 16 years, had measurements of peripapillary choroidal and RNFL thickness derived from enhanced depth imaging optical coherence tomography images (EDI-OCT, Heidelberg Spectralis). The average thickness was determined in a series of five 0.25 mm width concentric annuli (each divided into 8 equal sized 45° sectors) centred on the optic nerve head boundary, accounting for individual ocular magnification factors and the disc-fovea angle. Significant variations in peripapillary choroidal thickness were found to occur with both annulus location \((p<0.001)\) and sector position \((p<0.001)\) in this population of children. The innermost annulus (closest to the edge of the optic disc) exhibited the thinnest choroid (mean 77 ± 16 µm) and the outermost annulus, the thickest choroid (191 ± 52 µm). The choroid was thinnest inferior to the optic nerve head (139 ± 38 µm) and was thickest in the superior temporal sector (157 ± 40 µm). Significant differences in the distribution of choroidal thickness were also associated with myopia, with myopic children having significantly thinner choroids in the inner and outer annuli of the nasal and temporal sectors respectively \((p<0.001)\). RNFL thickness also varied significantly with annulus location and sector \((p<0.001)\), and showed differences in thickness distribution associated with refractive error. This study establishes the normal variations in the thickness of the peripapillary choroid with radial distance and azimuthal angle from the optic nerve head boundary. A significant thinning of the peripapillary choroid associated with myopia in childhood was also observed in both nasal and temporal regions. The changes in peripapillary RNFL and choroidal thickness associated with refractive error are consistent with a redistribution of these tissues occurring with myopic axial elongation in childhood.

\textbf{Keywords:} Choroid; Retinal Nerve Fibre Layer; Optical Coherence Tomography; Refractive Error; Childhood
1. Introduction

The choroid provides nutrients and oxygen to the outer retina and the pre-laminar optic nerve, and is also involved in a range of additional ocular physiological roles including regulation of ocular temperature and IOP, and the absorption of stray light (Nickla and Wallman, 2010). There is also evidence from a number of animal studies that the choroid plays an important role in the regulation of eye growth through the secretion of growth factors and that alterations in choroidal thickness are known to accompany the development of myopic and hyperopic refractive errors (Nickla and Wallman, 2010; Summers, 2013). When myopia development is induced experimentally in young animals (either through form deprivation or exposure to hyperopic defocus), a rapid thinning of the choroid is typically observed, followed by increases in axial eye growth, whereas when hyperopia is induced experimentally (through exposure to myopic defocus), a rapid choroidal thickening, followed by a slowing of axial eye growth is observed (Nickla and Wallman, 2010).

Advances in ocular imaging technology, such as the development of enhanced depth imaging (Spaide et al., 2008) and long wavelength (Unterhuber et al., 2005) optical coherence tomography (OCT), mean that the structure of the choroid can now be imaged and measured reliably invivo. Studies utilizing these OCT imaging methods, have substantially improved our understanding of the structure of the normal invivo human choroid. Topographical variations have been documented in the thickness of the normal adult choroid across the posterior pole (Margolis and Spaide, 2009; Esmaeelpour et al., 2010; Hirata et al., 2011; Ikuno et al., 2010; Ouyang et al., 2011; Chen et al., 2012), along with changes in choroidal thickness associated with age.
(Margolis and Spaide, 2009; Esmaeelpour et al., 2010) and refractive error (Esmaeelpour et al., 2010; Hirata et al., 2011; Li et al., 2011; Chen et al., 2012). In adults, myopic eyes and longer axial lengths are typically associated with thinner choroids, while on the other hand hyperopic eyes and shorter axial lengths are associated with thicker choroids (Esmaeelpour et al., 2010; Hirata et al., 2011; Li et al., 2011; Chen et al., 2012). A range of ocular pathological conditions including central serous chorioretinopathy (Imamura et al., 2011), age related macular degeneration (Manjunath et al., 2011), diabetic retinopathy (Esmaeelpour et al., 2011), glaucoma (Roberts et al., 2012) and inherited retinal diseases (Yeoh et al., 2010; Dhoot et al., 2013) have also been shown to be associated with changes in choroidal thickness.

A number of recent studies have examined macular choroidal thickness in pediatric populations, documenting the normal thickness profile of the choroid in children (Mapelli et al., 2013; Read et al., 2013a; Read et al., 2013b; Ruiz-Moreno et al., 2013), and demonstrating variations in choroidal thickness with age (Mapelli et al., 2013; Read et al., 2013a) and refractive error (Read et al., 2013b; Li et al., 2014) in childhood. These studies demonstrate that choroidal thinning in the foveal region occurs with increasing myopia and a longer axial length in childhood (Read et al., 2013b; Li et al., 2014).

The majority of previous studies examining *in vivo* choroidal thickness have concentrated upon measures of choroidal thickness in the macula region, with fewer studies examining the choroid in other locations such as the peripapillary region.
However, a small number of studies have examined peripapillary choroidal thickness in normal adults (Ho et al., 2011; Tanabe et al., 2012; Huang et al., 2013), and have also reported significant reductions in the thickness of the peripapillary choroid associated with high myopia (Lee et al., 2014), diabetic retinopathy (Vujosevic et al., 2012), normal tension glaucoma (Park et al., 2014) and in patients with sclerotic glaucomatous optic disc damage (Roberts et al., 2012).

The thickness of the peripapillary retinal nerve fibre layer (RNFL), has been well characterised in normal children with high resolution OCT imaging (Tsai et al., 2012; Tariq et al., 2012; Turk et al., 2012; Barrio-Barrio et al., 2013; Yanni et al., 2013) and shown to be significantly influenced by refractive error, with myopic children reported to exhibit a thinner RNFL, in all quadrants around the optic nerve, except the temporal quadrant (Tsai et al., 2012). However, to date there have been no reports of the peripapillary choroidal thickness in children. Given the paucity of knowledge regarding the normal choroidal thickness in the region surrounding the optic nerve head in children, our current study aimed to characterise the thickness of the peripapillary choroid (and the overlying RNFL) in a population of children with no eye disease and a range of refractive errors.

2. Material and methods

This cross-sectional study examined peripapillary choroidal and RNFL thickness in a population of 93 children aged between 11 and 16 years of age (mean ± SD age 13.6 ± 1.4 years). Approval from the Queensland University of Technology human
research ethics committee was obtained before commencement of the study, and all parents provided written informed consent, and children written assent prior to participation. All children were treated in accordance with the tenets of the Declaration of Helsinki.

All children enrolled in the study underwent an ophthalmic examination to determine their visual acuity and refractive status, and to ensure normal eye health and binocular vision. All children exhibited best corrected visual acuity of logMAR 0.00 or better in each eye, no history or evidence of significant ocular disease, and no (non-cycloplegic) hyperopic refractive errors greater than +1.25 DS. Children were classified based upon their non-cycloplegic subjective spherical equivalent refractive error (SER) of their right eye as either myopic (SER of -0.75 DS or more, n = 37, mean SER -2.72 ± 1.6 D, range: -0.75 to -8.13) or non-myopic (SER between +1.00 to -0.50 DS, n = 56, mean SER +0.23 ± 0.28 D, range: +0.75 to -0.38). The myopic and non-myopic children were well matched for age (mean age 13.5 ± 1.5 years in the myopes and 13.6 ± 1.3 years in the non-myopes) and gender (51% of the myopic children and 50% of the non-myopic children were female).

Chorio-retinal OCT images of the peripapillary region of each child’s right eye were captured using the Heidelberg Spectralis OCT instrument (Heidelberg Engineering, Heidelberg, Germany). This is a spectral domain OCT that uses a super luminescent diode of central wavelength 870 nm, a scanning speed of 40,000 A-scans per second and provides cross-sectional chorio-retinal images with digital axial resolution of 3.9 µm. This instrument has been shown to provide measures of
choroidal (Rahman et al., 2010) and RNFL thickness (Langenegger et al., 2011) with excellent repeatability. For each child, a volumetric scanning protocol was used, imaging a 15° by 15° region surrounding the optic nerve head. The volume scan consisted of 37 horizontal cross-sectional OCT images (with each image separated by ~120 µm) (Figure 1). To improve the visualisation of the choroid in the OCT images, the instrument’s enhanced depth imaging (EDI) mode was used in combination with automatic real-time eye tracking and frame averaging (each OCT image was the average of 20 B-Scans, each with 768 A-Scans). All volume scans had a mean Quality Index (QI) of >15 dB (Turk et al., 2012), with the average QI from all subjects being 24.5 ± 2.8 dB. At the same imaging session, each child also had foveal OCT images collected (a 6-line star scan centred on the fovea), in order to determine the position of foveal centre, relative to the centre of the optic nerve head in the peripapillary scans.

To reduce the potential confounding influence of diurnal variations in choroidal thickness (Chakraborty et al., 2012; Tan et al., 2012), all OCT measurements were carried out between 2pm and 5pm. In addition to OCT imaging, a range of additional axial ocular biometric dimensions (including: central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT) and axial length (AXL)) were also measured using the Lenstar LS900 optical biometer (Buckhurst et al., 2009).
2.1 Data analysis

Following image acquisition, all OCT images were analysed using custom written software. Initially, each subject’s individual ocular biometry information was used to adjust the transverse scale of their OCT images, in order to account for ocular magnification, using a previously described method (Read et al., 2013b). Figure 2 provides an overview of the image analysis procedures performed on each subject’s OCT data. Each of the OCT images were analysed using an algorithm (Alonso-Caneiro et al., 2014; Read et al., 2014) to automatically delineate the position of the inner limiting membrane (ILM), the outer boundary of the retinal nerve fibre layer (RNFL), the outer boundary of the retinal pigment epithelium/Bruch’s membrane complex (RPE) and the inner boundary of the chorio-scleral interface (CSI) (Figure 1c). An experienced observer, masked to the demographics and refractive status of the subjects tested, then checked the integrity of the automated segmentation of each of the 4 boundaries of interest and manually corrected any segmentation errors. In the OCT images intersecting the optic nerve head, the observer also manually marked the position of the edge of the optic nerve, defined as the point of termination of Bruch’s membrane (i.e. the position of Bruch’s membrane opening (BMO)) (Figure 1b). Although some subjects (n = 17, 14 myopes, 3 non-myopes) exhibited evidence of peripapillary scleral crescents in their enface scanning laser ophthalmoscope (SLO) fundus images, the position of BMO could be detected for all subjects. Comparison of the automated segmentation with the final manually corrected segmentation results revealed only small differences in the mean position of each of the boundaries of interest, suggesting that in the majority of cases, only minor manual corrections were required (mean ± SD difference between the automated and manually corrected boundary positions were: -0.4 ± 1.9 pixels, -2.6 ±
7.0 pixels, -1.6 ± 5 pixels, 1.0 ± 4.5 pixels for the ILM, RNFL, RPE and CSI respectively).

The segmentation information in each of the peripapillary volume scans was then used to derive peripapillary choroidal and RNFL thickness maps, over the 15° by 15° region surrounding the centre of the optic nerve head. A bilinear interpolation method was used to resample the original thickness data from the volume scan into the same resolution grid as the enface SLO fundus image (51 pixels per degree), to facilitate the remainder of the analysis. The thickness maps were each rotated around the centre of the optic nerve to account for each individual subject’s disc-fovea angle (i.e. the angle between horizontal and the line joining the centre of the optic nerve head and the centre of the fovea). The centre of the optic nerve head was determined based upon the centroid of the circle that best fit the locations of the BMO coordinates in the peripapillary OCT scans, and the foveal centre was determined based upon the position of the deepest foveal pit in the foveal OCT images for each individual subject. The overlapping enface foveal SLO image and peripapillary SLO image were then combined into a single enface image containing both the fovea and the optic nerve head, based upon common features in the two images (e.g. retinal blood vessels) using an automated image processing procedure based upon an invariant feature based approach, similar to that described by Brown and Lowe (2007). This image provided the relative coordinates of the position of the optic nerve head centre and foveal centre, allowing the disc-fovea angle to be calculated for each subject (Figure 2b).
The average thickness within a series of 5 concentric annuli (of 0.25 mm width) surrounding the edge of the optic nerve was then extracted from each subject’s individual rotated and resampled thickness maps. Each annulus of thickness data were further divided into 8 equal 45° sized sectors in order to extract the average temporal, superior temporal, superior, superior nasal, nasal, inferior nasal, inferior and inferior temporal thickness within each of the annuli (Figure 2d).

Repeated measures analysis of variance (ANOVA) was then used to examine the variations in the thickness of the peripapillary choroid and RNFL. These analyses included two within-subject factors (annulus location from optic nerve head centre, and angular sector position) and two between-subject factors (gender and refractive error group). Age was also included as a covariate in the ANOVA. Any significant main effects in the ANOVA were further examined using Bonferroni corrected pairwise comparisons. Stepwise multiple regression analysis with backward elimination was also used to examine the association between choroidal and RNFL thickness (in each of the considered annuli and sectors) with the ocular biometry measures. Given that ocular biometric measures (particularly axial length) provide a structural correlate of refractive error, this analysis provided an assessment of the relationship between refractive error and choroidal and RNFL thickness, where refractive error was considered as a continuous variable (rather than stratified into groups). Additionally, correlation analysis was used to examine any association between choroidal and RNFL thickness.
3. Results

In this population of 93 children, the mean ± SD diameter of BMO was 1.49 ± 0.18 mm. The myopic children exhibited a significantly larger BMO diameter (1.55 ± 0.17 mm) compared to the non-myopic children (1.45 ± 0.17 mm) (independent sample t-test, p<0.001). The average disc-fovea angle was -5.8 ± 3.6°, indicating that the fovea was located on average 5.8° inferior to the disc. The disc-fovea angle was not significantly different between the myopic (-5.6 ± 3.6°) and non-myopic children (-6.0 ± 3.6°) (p>0.05).

3.1 Peripapillary choroidal thickness

Repeated measures ANOVA revealed that choroidal thickness varied significantly with annulus location, and sector, and there was also a significant annulus by sector interaction (all p<0.001) (Figure 3). For all children considered together, the choroid was found to be thinnest in the innermost annulus (mean thickness 77 ± 16 µm), and increased significantly in thickness with increasing distance from the edge of the optic nerve, being thickest at the outermost annulus (191 ± 52 µm) (Figure 3a). In terms of sectors, the inferior (139 ± 38 µm) and nasal (141 ± 37 µm) sectors exhibited the thinnest choroids which were significantly different to the superior (155 ± 41 µm), superior temporal (157 ± 40 µm) and temporal (152 ± 45 µm) sectors that exhibited the thickest choroids (Figure 3b). Although the thickness in all sectors was seen to gradually increase from the innermost to the outermost annulus, the magnitude of change in thickness with increasing distance from the edge of the optic nerve head varied depending upon the sector, with the greatest magnitude of increase in thickness from inner to outer annulus seen in the nasal sector (mean
increase in thickness of 137 ± 43 µm), and the smallest magnitude increase observed in the inferior sector (mean increase of 77 ± 44 µm) (Figure 3c).

The mean peripapillary choroidal thickness (across all annuli and sectors) was found to be 139 ± 32 µm in the myopic children, and 152 ± 39 µm in the non-myopic children. Although the overall difference in choroidal thickness between the refractive groups was not statistically significant (p>0.05), significant refractive group by annulus (p = 0.014) and refractive group by annulus by sector (p<0.001) interactions were observed, indicating differences in the distribution of choroidal thickness around the optic nerve head associated with refractive error (Figure 4). The difference in choroidal thickness associated with refractive error was seen to increase with increasing distance from the optic nerve head, with the myopic children (178 ± 41 µm) having significantly thinner choroids in the outermost annulus compared to the non-myopic children (200 ± 56 µm) (p<0.05) (Figure 4a). Significantly thinner choroids were also observed in the myopic children compared to the non-myopic children within the three innermost annuli in the nasal sector, the innermost annulus of the inferior nasal sector, and in the three outermost annuli of the temporal sector, the two outermost annuli of the superior temporal sector, and the outermost annulus of the inferior temporal sector (each p<0.05, Figure 4d). There were no significant effects of gender or age observed for the peripapillary choroidal thickness data (both p>0.05).
3.2 Peripapillary RNFL thickness

Significant variations in RNFL thickness were also observed with annulus location and sector, along with a significant sector by annulus interaction (all p<0.001) (Figure 5). For all children considered together, the RNFL thickness reduced significantly from the innermost annulus (249 ± 41 µm) to the outermost annulus (103 ± 8 µm) (Figure 5a). The thickest RNFL was observed in the inferior (210 ± 37 µm) and superior sectors (194 ± 27 µm) and the thinnest in the nasal (124 ± 31 µm) and temporal sectors (87 ± 11 µm) (Figure 5b). The changes in RNFL thickness with annulus location also varied with sector, with the greatest magnitude of decrease in RNFL thickness with distance from the edge of the optic nerve head observed in the inferior sector (mean decrease in RNFL thickness from the innermost to the outermost annulus of 221 ± 66 µm) and the smallest magnitude decrease seen in the temporal sector (mean decrease of 52 ± 19 µm) (Figure 5c).

There were no significant differences in the overall RNFL thickness between the myopic (156 ± 19 µm) and non-myopic children (158 ± 16 µm) (p<0.05). However, significant refractive group by sector (p<0.001), and refractive group by sector by region (p<0.05) interactions were observed (Figure 6). The myopic children were found to have a significantly thinner RNFL in the nasal sector (mean difference -15 µm), and a significantly thicker RNFL in the temporal (mean difference +6 µm), superior temporal (mean difference +15 µm) and inferior temporal (mean difference +13 µm) sectors compared to the non-myopic children (Figure 6c). No significant effects of age or gender were observed in the RNFL thickness data (both p>0.05).
3.3 Associations with ocular biometry

The results from the multiple regression analysis examining the relationship between ocular biometry and peripapillary choroidal and RNFL thickness are illustrated in Tables 1 and 2. The biometric variable that generally exhibited the strongest association with choroidal thickness was axial length, with significant negative associations between axial length and choroidal thickness observed in the outer annuli (Table 1) and in the nasal sector (Table 2). For RNFL thickness, the strongest associations were also observed with axial length, with a significant negative association between RNFL thickness and axial length observed in the nasal sector, and a significant positive association between RNFL thickness and axial length in the temporal and superior temporal sectors (Table 2).

We also examined the association between the choroidal thickness and RNFL thickness in this population of subjects, which revealed a significant positive correlation between the mean (i.e. averaged across all sectors and regions) RNFL thickness and choroidal thickness \((r = 0.336, p = 0.001)\). When considered in terms of sectors, a significant positive association between RNFL thickness and choroidal thickness was observed in the nasal \((r = 0.302, p = 0.003)\), superior nasal \((r = 0.296, p = 0.004)\), superior \((r = 0.286, p = 0.005)\), inferior \((r = 0.207, p = 0.046)\) and inferior nasal \((r = 0.410, p <0.001)\) sectors, but not in the other considered sectors (all \(p>0.05\)).
4. Discussion

To our knowledge, this study provides the first examination of peripapillary choroidal thickness in a pediatric population. We have shown that significant variations occur in the thickness of the peripapillary choroid as a function of the radial distance and azimuthal angle from the optic nerve. The choroid was found to increase in thickness with increasing distance from the edge of the optic nerve head, and was observed to be thinnest in inferior and nasal sectors, and thickest in superior and temporal sectors. Significant differences in the distribution of peripapillary choroidal thickness were also found between myopic and non-myopic children, with myopic children seen to have thinner choroids, particularly in the temporal and nasal sectors.

Given that the choroidal tissue terminates at the edge of the optic nerve, the tapering of choroidal thickness in the region approaching the edge of the optic nerve head observed in our results is consistent with the anatomical features of the optic nerve region. A thinner choroid inferiorly, has also been a consistent finding in previous studies of peripapillary choroidal thickness in adults (Ho et al., 2011; Ouyang et al. 2011, Hirooka et al., 2012; Tanabe et al., 2012; Vujosevic et al., 2012; Huang et al., 2013; Lee et al., 2014), and it has been suggested that this inferior thinning may be related to the location of the embryological inferior fetal fissure, influencing the thickness of the choroid in this region (Ikuno et al., 2010; Ouyang et al., 2011). Our finding that a thinner choroid in the inferior region is also a feature of the peripapillary choroid in children, tends to support a mechanism underlying this thinning occurring relatively early in ocular development.
In our previous work examining pediatric macular choroidal thickness, we found the choroid in regions nasal to the fovea (equivalent to the region temporal to the optic nerve head in the current study), were thinner compared to regions temporal to the fovea (Read et al., 2013a; Read et al., 2013b). In our current study, the temporal sector of the peripapillary choroid was found to be thicker than the nasal sector, and this may reflect the greater metabolic demands of the outer retina in the region temporal to the optic nerve head (i.e. the foveal region). These observed asymmetries suggest that the choroidal thickness in the nasal regions beyond the optic nerve towards the periphery is likely to be thinner than an equivalent temporal region closer to the fovea, although further research utilising wide field imaging techniques is required to confirm this assumption.

Although peripapillary choroidal thickness has not been previously examined in pediatric subjects, the distribution of choroidal thickness seen in our pediatric subjects with normal ocular health is similar to that observed in studies of normal adults. Previous studies of normal adults with a range of different ages and refractive errors have also reported that choroidal thickness increases with increasing distance from the optic nerve head (Ho et al., 2011; Ouyang et al., 2011; Lee et al., 2014). The peripapillary choroid has also typically been found to be thinnest inferiorly to the optic nerve and thicker in superior regions (Ho et al., 2011; Hirooka et al., 2012; Tanabe et al., 2012; Vujosevic et al., 2012; Huang et al., 2013, Lee et al., 2014). Previous studies of peripapillary choroidal thickness in adults have used a variety of different instruments, scanning protocols and analysis approaches, which limits the direct comparison between these studies and our current work. However, the majority of studies of normal adults have analysed peripapillary
choroidal thickness in a circular region approximately 3.5 mm from the centre of the optic nerve head (roughly equivalent to the location of our outermost annulus) and report mean choroidal thickness values ranging from 149 µm to 198 µm (Hirooka et al., 2012; Roberts et al., 2012; Vujosevic et al., 2012; Huang et al., 2013), which is comparable with our mean thickness of 191 ± 52 µm in the outermost annulus in our population of children.

Our current findings add to the understanding of the spatial distribution of choroidal thickness across the posterior eye associated with refractive error in childhood. Although the myopic children, on average, exhibited a thinner choroid than non-myopic children, these differences only reached statistical significance in some of the considered annuli and sectors, indicating that the choroidal thinning associated with myopia is not uniform across the peripapillary region. The difference in choroidal thickness associated with refractive error tended to increase with increasing distance from the optic nerve head, and was also more prominent in nasal and temporal sectors. Our findings of a thinner peripapillary choroid in the temporal sectors is consistent with recent reports of macular choroidal thickness in children that have also found a thinner subfoveal choroid associated with myopia and longer axial lengths (Read et al., 2013b; Li et al., 2014). We have recently reported upon the distribution of macular choroidal thickness in myopic and non-myopic children, and found that the magnitude of choroidal thinning associated with myopia was greatest closest to the fovea (Read et al., 2013b), which is in line with our current finding of a greater magnitude of choroidal thinning in myopic subjects with increasing distance from the temporal edge of the optic nerve.
Although the exact cause of the choroidal thinning associated with myopia in childhood is not known, our findings suggest that the forces and/or signals associated with myopic eye growth in childhood are not uniform across the posterior eye. Previous studies have documented that a range of changes in the optic disc shape, such as optic disc tilting and β parapapillary atrophy (where choroidal vessels and sclera are visible in the region bordering the optic disc in fundus photographs) appear to accompany myopia and its progression in childhood (Samarawickrama et al., 2011; Kim et al., 2012; Guo et al., 2014). It has been proposed that these optic disc changes in childhood myopia are consistent with axial elongation in myopia being associated with a dragging of the optic disc in the temporal direction (Kim et al., 2012). We hypothesise that this mechanism may at least in part explain some of the choroidal thinning we have observed, since a temporal dragging of the optic disc with increasing axial length would be expected to result in a thinning of the choroid adjacent to the optic nerve, particularly in the nasal region. It should be noted however, that our current study is cross-sectional in nature, which means we cannot attribute causation or know the time-course of these changes in choroidal thickness associated with refractive error.

A number of previous studies have reported upon the normal peripapillary RNFL thickness in children using spectral domain OCT (Tariq et al., 2012; Tsai et al., 2012; Turk et al., 2012; Barrio-Barrio et al., 2013; Yanni et al., 2013). These studies (most of which have analysed the RNFL thickness data from a 3.5 mm diameter circle centred on the optic nerve head centre) examining populations of children with mean ages ranging from 9 to 17 years and using a range of different OCT devices, have reported mean RNFL thickness values between 97 µm and 108 µm. This compares
closely to our reported mean RNFL thickness in the outermost annulus of 103 ± 8 μm. Although the mean RNFL thickness was very similar between our myopic and non-myopic children, some differences in the distribution of RNFL thickness around the optic nerve head associated with refractive error were observed. Interestingly, the myopic children had a significantly thinner RNFL in the nasal sector, but a significantly thicker RNFL in the temporal, superior-temporal and inferior-temporal sectors. A significant negative association between axial length and RNFL thickness was found in the nasal sector, whereas a significant positive association between these parameters was found in the temporal sector. These findings are consistent with a redistribution of retinal nerve fibres occurring with increasing axial length in myopia. Previous studies of RNFL in both children (Tsai et al., 2012) and adults (Kang et al., 2010; Kim et al., 2010,) with myopia have shown similar results, with a thicker temporal RNFL and thinner nasal RNFL noted to be associated with increasing myopia/longer axial length. We also found choroidal thickness exhibited a significant negative association with axial length in the nasal regions and that additionally, RNFL thickness and choroidal thickness were significantly correlated in this region (but not in the temporal regions), which suggests that similar mechanisms may be underlying the changes in the RNFL and the choroid associated with myopia in the nasal peripapillary region.

A strength of our current study is that our OCT image analysis utilised a range of tools such as automated segmentation algorithms, and individual adjustments to account for ocular magnification factors and the disc-fovea angle, that are likely to reduce the inter-subject variability of the data. These approaches have not been used universally in previous studies of the peripapillary RNFL and choroidal
thickness, although there is evidence that accounting for these factors can result in a reduction of inter-subject variability in certain OCT derived thickness parameters (Amini et al., 2014; Nowroozizadeh et al., 2014). The volumetric scanning protocol used also provides a more comprehensive assessment of the variations in thickness across the peripapillary region, compared to analysis of a single circle scan. Our scanning and analysis approach also has the advantage of not being influenced by errors in manual scan circle placement since the region of analysis within the volume scan is determined based upon the position of the BMO, and this means that the analysis regions for all subjects are in a consistent location with respect to the anatomical landmark of the BMO. Although all thickness measures for each subject were taken at the same radial distance from BMO, the larger BMO diameter in the myopic children, means that the area of each annulus analysed was slightly larger on average in the myopic children. However this difference in annulus area was small, and represented less than 4% of the average annulus area.

A limitation of our study is the relatively small sample size and range of ages examined. Therefore, future work utilising larger populations of children with a wider range of ages will help to further our understanding of the normal peripapillary choroid in childhood. A further limitation of this study is the lack of cycloplegic refraction measures, which may reduce the reliability of refraction data in children, and can result in the underestimation of hyperopic refractive errors (Choong et al., 2006). However, there is evidence that topical cycloplegic agents can result in small changes in choroidal thickness (Kara et al., 2014; Sander et al., 2014) and the effect of cycloplegia upon the choroidal thickness of pediatric subjects has not previously been investigated. For these reasons, cycloplegia was not used in our current study.
to ensure that the primary outcome measure of choroidal thickness was not confounded by the potential influence of cycloplegia.

5. Conclusions

In conclusion, this study presents new data regarding the normal thickness of the peripapillary choroid and its distribution in healthy children. Given the previously documented changes in peripapillary choroidal thickness associated with a variety of ocular diseases in adults (Roberts et al., 2012; Vujosevic et al., 2012; Lee et al., 2014; Park et al., 2014), these normative values documented in children in our current study provide important comparative values for future research exploring potential changes in the peripapillary choroid associated with pediatric eye disease. Our results also provide insights into the peripapillary choroidal changes associated with childhood refractive error, demonstrating choroidal thinning, particularly in the nasal and temporal sectors around the optic disc occurs in myopic children. Future longitudinal studies will help to further our understanding of the nature and time-course of the peripapillary choroidal thinning associated with myopia in childhood.

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References


Figure Captions:

**Figure 1**: Illustration of the scanning protocol used to image the peripapillary region (a), and an example OCT image (b). A 15° by 15° volumetric scan, centred on the optic nerve head was collected for each subject. The volume scan consisted of 37 horizontal cross-sectional OCT images (with each OCT image consisting of 20 averaged B-Scans, each with 768 A-scans). All OCT images were segmented using an automated algorithm (with manual correction) to define the position of the inner limiting membrane (ILM), retinal nerve fibre layer (RNFL), retinal pigment epithelium/Bruch’s membrane complex (RPE) and the choriocapillaris interface (CSI) (c). The location of the edge of the optic nerve head was also defined manually in each of the OCT images through the optic nerve head, as the point of termination of Bruch’s membrane (i.e. Bruch’s membrane opening) (white arrows in b).
Figure 2: Overview of analysis procedure carried out on the OCT data for each subject. Following the capture of the peripapillary OCT images and segmentation of each of the 37 horizontal OCT images (a), peripapillary choroidal thickness and retinal nerve fibre layer (RNFL) thickness maps in the 15° by 15° region surrounding the optic nerve head were derived for each subject (b). The angle between horizontal and the line joining the centre of the optic nerve head (green dot) to the centre of the fovea (red dot-F) was then determined (b-bottom). The thickness maps were then rotated according to each subject’s individual disc-fovea angle (c). Each rotated thickness map was then analysed to derive the average choroidal and RNFL thickness across 8 sectors [superior (S), superior temporal (ST), temporal (T), inferior temporal (IT), inferior (I), inferior nasal (IN), nasal (N) and superior nasal (SN)], within 5 concentric annuli of 0.25 mm width from the edge of the optic nerve head (d).
Figure 3: Average peripapillary choroidal thickness for all children in the study (n = 93). Choroidal thickness averaged across each of the 5 concentric, 0.25 mm wide annuli (a), and across each of the 8 sectors [temporal (T), superior temporal (ST), superior (S), superior nasal (SN), nasal (N), inferior nasal (IN), inferior (I), and inferior temporal (IT)] (b), and within each of the individual sectors in each of the annuli (c) in the peripapillary region is illustrated. Error bars represent the standard error of the mean.
Figure 4: Average peripapillary choroidal thickness for the myopic (n = 37) and non-myopic (n = 56) children in the study. Choroidal thickness averaged across each of the 5 concentric, 0.25 mm wide annuli (a), and across each of the 8 sectors [temporal (T), superior temporal (ST), superior (S), superior nasal (SN), nasal (N), inferior nasal (IN), inferior (I) and inferior temporal (IT)] (b), and within each of the individual sectors in each of the annuli (c) in the peripapillary region for the myopic and non-myopic children is shown. The mean choroidal thickness difference between the myopic and non-myopic children is also illustrated (d) (myopic minus non-myopic, where negative thickness difference values indicate a thinner choroid in the myopic children). Error bars represent the standard error of the mean. Asterisks indicate a significant difference in choroidal thickness between myopic and non-myopic children (p<0.05).
Figure 5: Average peripapillary retinal nerve fibre layer (RNFL) thickness for all children in the study (n = 93). RNFL thickness averaged across each of the 5 concentric, 0.25 mm wide annuli (a), and across each of the 8 sectors [temporal (T), superior temporal (ST), superior (S), superior nasal (SN), nasal (N), inferior nasal (IN), inferior (I) and inferior temporal (IT)] (b), and within each of the individual sectors in each of the annuli (c) in the peripapillary region is illustrated. Error bars represent the standard error of the mean.
Figure 6: Average peripapillary retinal nerve fibre layer (RNFL) thickness for the myopic (n = 37) and non-myopic (n = 56) children in the study (n = 93). RNFL thickness averaged across each of the 5 concentric, 0.25 mm wide annuli (a), and across each of the 8 sectors [temporal (T), superior temporal (ST), superior (S), superior nasal (SN), nasal (N), inferior nasal (IN), inferior (I) and inferior temporal (IT)](b), and within each of the individual sectors in each of the annuli (c) in the peripapillary region for the myopic and non-myopic children is shown. The mean RNFL thickness difference between the myopic and non-myopic children is also illustrated (d) (myopic minus non-myopic, where negative thickness difference values indicate a thinner RNFL in the myopic children). Error bars represent the standard error of the mean. Asterisks indicate a significant difference in RNFL thickness between myopic and non-myopic children (p<0.05).
Tables:

**Table 1:** Results from stepwise multiple regression analysis examining the association between choroidal thickness with ocular biometry measures (central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT) and axial length (AXL)) in each of the considered peripapillary annuli. RNFL thickness did not exhibit any significant association with any of the ocular biometry measures for any of the peripapillary annuli (all p>0.05).

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<tr>
<th>Choroidal Thickness</th>
<th>Standardised Regression Coefficients (p-value)</th>
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<tr>
<td></td>
<td>0.25 mm Annulus</td>
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<tr>
<td>CCT</td>
<td>NS</td>
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<tr>
<td>ACD</td>
<td>0.214 (p = 0.039)</td>
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<tr>
<td>LT</td>
<td>NS</td>
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<tr>
<td>AXL</td>
<td>NS</td>
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*a NS indicates non-significant association (p>0.05)*
Table 2: Results from stepwise multiple regression analysis examining the association between choroidal thickness and RNFL thickness with ocular biometry measures (central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT) and axial length (AXL)) in each of the considered peripapillary sectors.

<table>
<thead>
<tr>
<th>Choroidal Thickness</th>
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<td>Temporal Superior-Superior</td>
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<th>RNFL Thickness</th>
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*NS indicates non-significant association (p>0.05)