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Choroidal Thickness Profiles and Associated Factors in Myopic Children

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TITLE: Choroidal Thickness Profiles and Associated Factors in Myopic Children

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ABSTRACT

Significance: This study addresses the lack of choroidal thickness (ChT) profile information available in European children and provides a baseline for further evaluation of longitudinal changes in ChT profiles in myopic children as a potential biomarker for myopia treatment and identifying children at risk of myopic progression.

Purpose: To investigate ChT profiles and associated factors in myopic children.

Methods: Baseline data of 250 myopic children aged 6-16years in the Myopia Outcome Study of Atropine in Children clinical trial were analysed. ChT images were obtained using swept source optical coherence tomography (DRI-OCT Triton Plus). The macula was divided into 9 Early Treatment of Diabetic Retinopathy Study (ETDRS) locations with diameters of 1mm, 3mm, and 6mm corresponding to the central fovea, parafoveal, and perifoveal regions. Multiple linear regression models were used to investigate determinants of ChT.

Results: ChT varied across the macular ETDRS locations (P<.001); thickest in the perifoveal superior region (mean±SD: 249.0±60.8μm) and thinnest in the perifoveal nasal region (155.1±50.3μm). On average, ChT was greater in all parafoveal (231.8±57.8μm) compared to perifoveal (218.1±49.1μm) regions except superiorly where the ChT was greater in the perifoveal region. Longer axial length (AL) and higher myopic spherical equivalent refraction (SER) were consistently associated with thinner ChT at all locations in the multiple linear regression models. Asian race was significantly associated with thinner ChT only at para- and peri-foveal superior regions following Bonferroni correction (P=.004 and P=.001, respectively).

Conclusions: ChT was thinnest in the nasal macular region and varied systematically across all macular locations, with AL and SER being the strongest determinants of ChT. Longitudinal evidence will need to evaluate whether any differences in ChT profiles are predictive of myopic progression and to determine the role of ChT measurements in identifying myopic children most in need of myopia control treatment.

Keywords: Choroidal thickness; Choroidal thickness profiles; Myopia; Optical Coherence Tomography

INTRODUCTION

The choroid is a highly vascularized layer found between the sclera and retina of the human eye.[1] Aside from its essential, primary function of supplying nutrients and oxygen to the avascular outer retina, the choroid is also involved in regulating eye growth and emmetropisation.[1,2]

Clinically, excessive thickening/thinning of the choroid is potentially important in the development of retinal disease, such as chorioretinal atrophy, choroidal neovascularisation, and retinal degeneration.[3] Changes in the choroidal architecture occur from childhood throughout adulthood and individuals with myopia are at higher risk of vision loss from chorioretinal disease such as myopic maculopathy.[4] Within the myopic population, a thinner choroid has been associated with higher risk of myopic choroidal neovascularisation[5] and lacquer cracks,[6] and the risk of chorioretinal disease in highly myopic individuals is much higher in older adults.[7] Importantly, a recent study showed that choroidal thickness was associated with higher risk of progression of myopic maculopathy, independent of axial length.[8] The choroid is known to thin in response to myopia-inducing visual stimuli[9–11] and choroidal thinning is proposed to precede axial elongation and, ultimately, myopia progression.[2,12]

The advent of Swept Source Optical Coherence Tomography has allowed detailed, repeatable, *in vivo* analyses of choroidal thickness within the macular area. In children, studies have shown that there is regional variation of choroidal thickness within the macular area.[13–15] The limited European data available, however, mostly describes subfoveal choroidal thickness in children,[16,17] with little information describing choroidal thickness within different macular locations in a myopic cohort. For example,

a study by Herrera et. al. on macular choroidal thickness in Spanish children included just 29 myopic eyes,[17] while another Spanish study recruited only highly myopic adults with a mean age of 54.4 years.[18] Anecdotal evidence suggests that current clinical measurements of choroidal thickness predominantly focus on the subfoveal region, however, it is important to gain a better understanding of choroidal thickness profiles in myopic children. If the choroid is indeed involved in modulating myopia progression and the development of chorioretinal disease,[3,5,12] it is worth exploring whether choroidal thickness measurements across the macular area could provide a useful biomarker for identifying children at risk. This requires detailed analyses of the cross-sectional relationship between choroidal thickness and relevant parameters such as age, gender, race, refraction and axial length in myopic children.

This study addresses the lack of choroidal thickness profile information available in European children. Specifically, the study was designed to describe the macular choroidal thickness profiles and investigate possible determinants of choroidal thickness among children with different degrees of myopia. This initial cross-sectional evaluation exploits data derived from myopic children recruited to the Myopia Outcome Study of Atropine in Children clinical trial in Ireland and will provide a baseline for further evaluation of longitudinal changes in choroidal thickness profile and response to 0.01% atropine treatment for the purpose of myopia control.

MATERIALS AND METHODS

Study Participants

Baseline data of 250 myopic children aged 6-16 years and enrolled in the Myopia Outcome Study of Atropine clinical trial (ISRCTN36732601) were analyzed. The

Myopia Outcome Study of Atropine study was approved by the Research Ethics Committees at the Mater Misericordiae University Hospital, Ireland and Technological University Dublin, Ireland and adhered to the tenets of the Declaration of Helsinki. Participants and their parents provided written informed assent and consent, respectively, to participate in the study. The Myopia Outcome Study of Atropine study is a randomized clinical trial exploring the mechanisms of action of 0.01% atropine for treatment of myopia progression – details of this study have previously been published.[19] Participants with at least -0.50D spherical equivalent refraction in both eyes were recruited during the period July 2019 to September 2020. All the participants used single vision spectacle correction prescribed by their eye care practitioner and had not previously used any myopia control treatment. Under- or over-correction was defined as spherical equivalent refraction difference of at least 0.25D less or more spectacle correction, compared to our cycloplegic autorefraction results, respectively. This definition was chosen to reflect a clinically meaningful change in visual acuity. Participants who had other ocular morbidities, astigmatism $\geq$ 2.50D in either eye, strabismus, hypersensitivity to atropine and other significant health problems were excluded from the study. All data used for this study is from the baseline visit, prior to beginning any study medication.

Ocular Health Assessment, Axial Length and Refractive Error Measurement

Eligible participants underwent ocular health examination including visual acuity, slit lamp examination, and indirect fundus biomicroscopy. Corrected visual acuity was measured using a randomised letterset of the MultiQuity (MiQ 720) computerised logMAR chart. Axial length and other ocular biometric measurements, including anterior chamber depth, central corneal thickness, and lens thickness, were measured

with a low-coherence interferometry biometer (Aladdin HW3.0, Visia Imaging S.r.l., San Giovanni, Valdarno, Italy). Five readings of axial length were obtained per measurement and the mean recorded. After axial length measurement, 1 drop of 1% cyclopentolate hydrochloride (Bausch and Lomb Minims; Laboratoire Chauvin, France) was instilled in both eyes 5 minutes after corneal anaesthesia with topical 0.5% proxymetacaine hydrochloride (Bausch and Lomb Minims; Laboratoire Chauvin, France). Cycloplegic refraction was measured after 30 minutes using the Grand Seiko Open Field autorefractor (WAM-5500 Auto Ref/Keratometer, Kagawa, Japan). Five readings were taken and the calculated average was recorded. Spherical equivalent refraction was calculated as the sum of sphere and half of the cylindrical power.

Choroidal Thickness Measurement

Choroidal thickness images were obtained using Swept Source Optical Coherence Tomography (DRI-OCT Triton Plus, Topcon Corporation, Tokyo, Japan) after cycloplegia. While we did not strictly control participant activities prior to the optical coherence tomography scan, participants waited in the examination room and did not engage in intense near work activities or rigorous exercise but tended to occasionally talk with their parent/carer or move around the room in a manner that likely reflected “real-world” clinical practice. Participants immediate past two weeks near work activities (i. e., average time spent per day on mobile phone, tablet/kindle/iPad, or reading printed material) were analyzed to investigate any potential impact of their near work behavioral patterns on choroidal thickness. Measurements were taken throughout the day from 9am to 4pm and to minimize the effect of eye movements, participants were asked to concentrate on the fixation target within the equipment. Participants’ axial length, corneal curvature, and spherical and cylindrical

measurements were input into the in-built optical coherence tomography software to adjust for the effects of transverse magnification errors as described by Iwase et al.[20] Choroidal thickness was measured as the distance between Bruch's membrane and choroidal-scleral interface (Figure 1A). The Topcon Advanced Boundary Software was used for automated choroidal segmentation and thickness analysis. Automated segmentation was reviewed, and errors were manually corrected (37 scans were manually corrected) by a trained observer/technician when the software was judged to have incorrectly delineated the borders of the layers. Optical coherence tomography images required an image quality rating of at least 70/100 to be included in the analysis. The macula was divided into 9 sectors using macular Early Treatment of Diabetic Retinopathy Study grid, centred on the fovea, with circle diameters of 1mm, 3mm, and 6mm corresponding to the central fovea (subfoveal; central circle of 1mm diameter), parafoveal (the area between 1mm and 3mm eccentric to the fovea), and perifoveal (the area between 3mm and 6mm eccentricity from the fovea) regions, respectively (Figure 1B). The parafoveal and perifoveal regions were further divided into four quadrants – superior, inferior, temporal, and nasal – and average choroidal thickness measurements within each of the 9 Early Treatment of Diabetic Retinopathy Study sectors were extracted using the Fast Map Data Export tool.

Statistical Analyses

Statistical analyses were performed with R version 4.1.2 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). To characterize choroidal thickness and other ocular and anthropometric characteristics according to myopia severity and age, myopia was categorized into three subgroups: low myopia (-0.50D

to -3.00D), moderate myopia (<-3.00D to >-6.00D) and high myopia (≤-6.00D); participants were grouped into younger (6-11 years) and older (12-16 years) children. To investigate the choroidal thickness distribution for participants with short, medium, and long eyes, respectively, axial length was categorized into three groups around clinically relevant cut-off values of ≤24mm, >24mm to <26mm and ≥26mm.

One-way Analysis of Variance, independent samples t-test or their non-parametric alternatives (Wilcoxon signed-rank and Kruskal-Wallis tests) were used to evaluate differences in subfoveal choroidal thickness and other ocular biometrics within different subgroups. Repeated measures Analysis of Variance with two between-subjects factors (age and sex) was used to explore the variations in choroidal thickness at different macular locations. Pearson correlation was used to analyze relationships between subfoveal choroidal thickness and continuous variables. Variables associated with choroidal thickness at all macular locations at the *P*<.05 level after univariable analyses were included in a multiple linear regression model. The final model included age, sex, and other significant covariates (axial length, spherical equivalent refraction, and race) and was adjusted for multiple comparisons using Bonferroni correction.

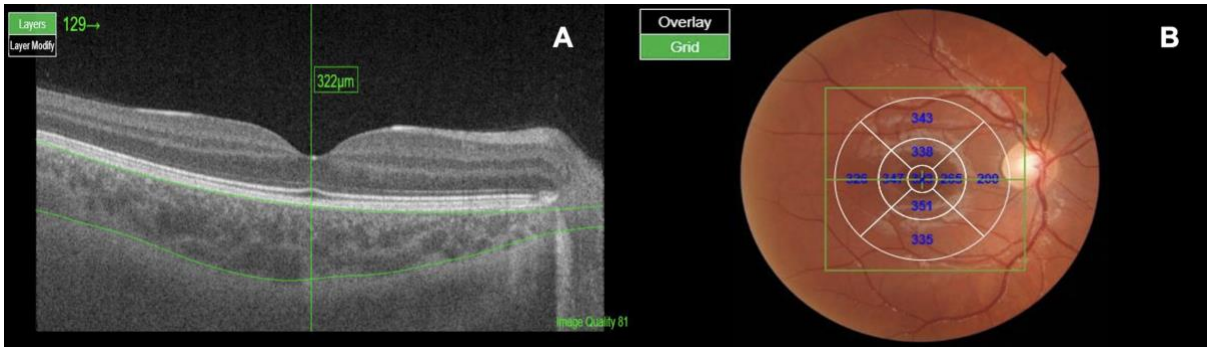

Figure 1: Optical coherence tomography scan of the retina and choroid. (A) Choroidal thickness measured from Bruch's membrane to the choroidal-scleral interface (green horizontal lines). (B) Average choroidal thickness measurements within the 9 Early Treatment of Diabetic Retinopathy Study locations.

RESULTS

Participant characteristics

The racial profile of study participants reflected the Irish population, and comprised 82.8% White, 8.8% Asian, 6.8% Mixed, and 1.6% Black children, with overall mean±SD age of 11.3±2.4 years (range: 6-16 years; 62% female). Table 1 summarizes the general, anthropometric, and ocular biometric characteristics of study participants. Ethnicity was not significantly associated with axial length (F (3, 246), P=.08), post-hoc analysis showed no significant difference in axial length for White and Asian race (24.9mm vs 25.2mm; P=.97); however, Asians were significantly more myopic than Whites (-5.00D vs -3.28D; P<.001), but no significant differences in spherical equivalent refraction were observed between Asians and Blacks (-5.00D vs -3.50D; P=.39), or Asians and Mixed race (-5.00D vs -3.52D; P=.05). Asians spent approximately 80 more minutes per day reading printed material compared to Whites (P=.003), however, there was a non-statistically significant near work activity by race interaction on choroidal thickness, suggesting that the effect of near work activities on choroidal thickness did not vary between the different races ($F_{14,\ 227} = 1.076$, P=.38). Compared to our cycloplegic autorefraction (which has its own limitations as a comparator) results, 15.6% and 56% were under- and over-corrected by 0.55D and 0.68D on average, respectively, in their single vision spectacles. There were no significant associations between under- and over-corrected single vision lenses and choroidal thickness (P=.34) after adjusting for age, sex, and axial length.

Subfoveal Choroidal Thickness

There was a strong correlation between subfoveal choroidal thickness (Intraclass Correlation Coefficient [ICC]=0.89; *P*<.001), AL (ICC=0.97; *P*<.001), and spherical equivalent refraction (ICC=0.96; *P*<.001) between the right and left eyes. Therefore, only data from right eyes were used for analysis. Overall mean±SD subfoveal choroidal thickness was 234.9±63.7μm (range: 78.6 to 391.1μm). Subfoveal choroidal thickness was negatively correlated with axial length, each additional millimeter in axial length equated to a 21μm thinner choroidal thickness (R = -0.35, *P*<.001); and positively correlated with spherical equivalent refraction, with each additional dioptre of myopia equating to a 10μm thinner choroidal thickness (R = 0.30, *P*<.001) (Figure 2). There was no significant association between time of day and subfoveal choroidal thickness (*P*=.13). As shown in figure 3, longer eyes and high myopic individuals exhibited thinnest subfoveal choroidal thickness, with their respective distributions showing a slight positive skew; however, there were overlapping ranges of subfoveal choroidal thickness among the different axial length and myopia groups.

Table 1. Characteristics of study participants according to sex and degree of myopia.

Variables	Total	Male	Female	*P*-value	Low Myopia (-0.50 D to -3.00 D)	Moderate Myopia (<-3.00 D to > -6.00 D)	High Myopia (≤ -6.00D)	*P*-value
	N = 250	N = 94	N = 156		N = 116	N = 112	N = 22	
Age, mean (SD) years	11.3 (2.4)	11.0 (2.5)	11.5 (2.3)	.12[a]	10.6 (2.3)	11.8 (2.3)	12.4 (2.4)	**.001[b]**
AL, mean (SD) mm	24.87 (1.09)	25.1 (1.10)	24.8 (1.08)	**.04[a]**	24.2 (0.84)	25.3 (0.87)	26.3 (0.84)	**<.001[b]**
SER, mean (SD) dioptres	-3.45 (1.80)	-3.10 (1.76)	-3.67 (1.81)	**.02[a]**	-1.89 (0.69)	-4.33 (0.79)	-7.11 (1.10)	**<.001[b]**
[†]Subfoveal ChT, mean (SD) μm	234.9 (63.7)	231.0 (58.1)	237.6 (66.9)	.45[a]	250.3 (61.8)	227.5 (61.5)	193.0 (61.8)	**<.001[b]**
CCT, mean (SD) mm	0.54 (0.03)	0.54 (0.03)	0.54 (0.03)	.96[a]	0.54 (0.03)	0.54 (0.04)	0.55 (0.03)	.48[b]
ACD, mean (SD) mm	3.84 (0.27)	3.92 (0.26)	3.77 (0.26)	**<.001[a]**	3.83 (0.28)	3.85 (0.26)	3.78 (0.21)	.47[b]
[‡]LT, mean (SD) mm	3.43 (0.21)	3.39 (0.19)	3.47 (0.22)	**.02[a]**	3.44 (0.23)	3.45 (0.18)	3.42 (0.22)	.91[b]
logMAR VA, mean (SD)	-0.03 (0.09)	-0.04 (0.09)	-0.02 (0.09)	.48[a]	-0.04 (0.08)	-0.02 (0.09)	0.00 (0.11)	.14[b]
Height, mean (SD) cm	151.0 (14.3)	150.9 (16.4)	151.1 (13.0)	.88[a]	147.3 (14.0)	154.2 (13.6)	154.3 (15.6)	**.001[b]**
Weight, median (IQR) kg	43.3 (34.9 – 53.7)	41.8 (33.3 – 54.1)	44.4 (36.1 – 53.5)	.23[c]	40.6 (33.0 – 49.7)	45.2 (37.9 – 55.4)	50.8 (40.0 – 62.9)	**.002[d]**
BMI, median (IQR) kg/m^2	18.6 (16.8 – 20.8)	18.1 (16.5 – 19.9)	18.8 (17.0 – 21.2)	.10[c]	18.2 (16.5 – 20.3)	18.7 (16.8 – 20.9)	19.8 (17.7 – 23.6)	.07[d]
IOP, mean (SD) mmHg	14.76 (3.28)	14.8 (3.38)	14.8 (3.22)	.94[a]	14.8 (3.22)	14.5 (3.27)	15.8 (3.56)	.25[b]

Significance testing: [a]Independent samples t-test; [b]One-Way ANOVA; [c]Wilcoxon signed-rank test; [d]Kruskal-Wallis test. Bold *P*-values are statistically significant.

AL = axial length; SER = spherical equivalent refraction; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity; BMI = body mass index; IOP = intraocular pressure; CCT = central corneal thickness; ACD = anterior chamber depth; [†]Subfoveal ChT = choroidal thickness (valid data was available for 249 participants); [‡]LT = lens thickness (valid data was available for 215 participants); SD = standard deviation; IQR = interquartile range; μm = micrometer; mm = millimeter; cm = centimeter; kg = kilogram; mmHg = millimeter of mercury; kg/m^2 = kilogram per square meter

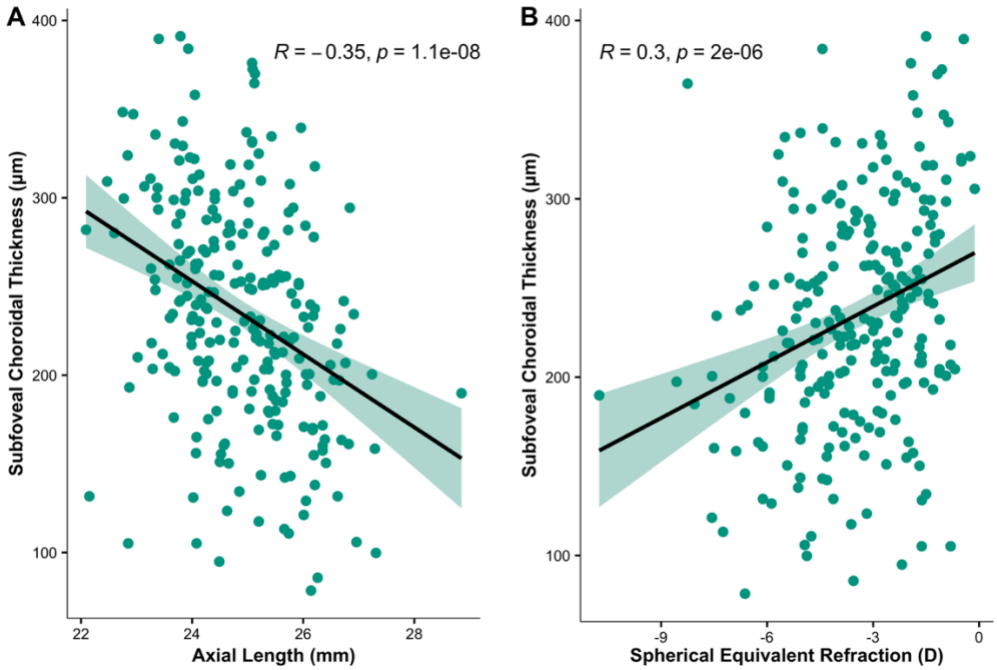

Figure 2: (A) Inverse correlation between subfoveal choroidal thickness and axial length. (B) Positive correlation between subfoveal choroidal thickness and spherical equivalent refraction. Shaded area represents 95% confidence interval around the regression line.

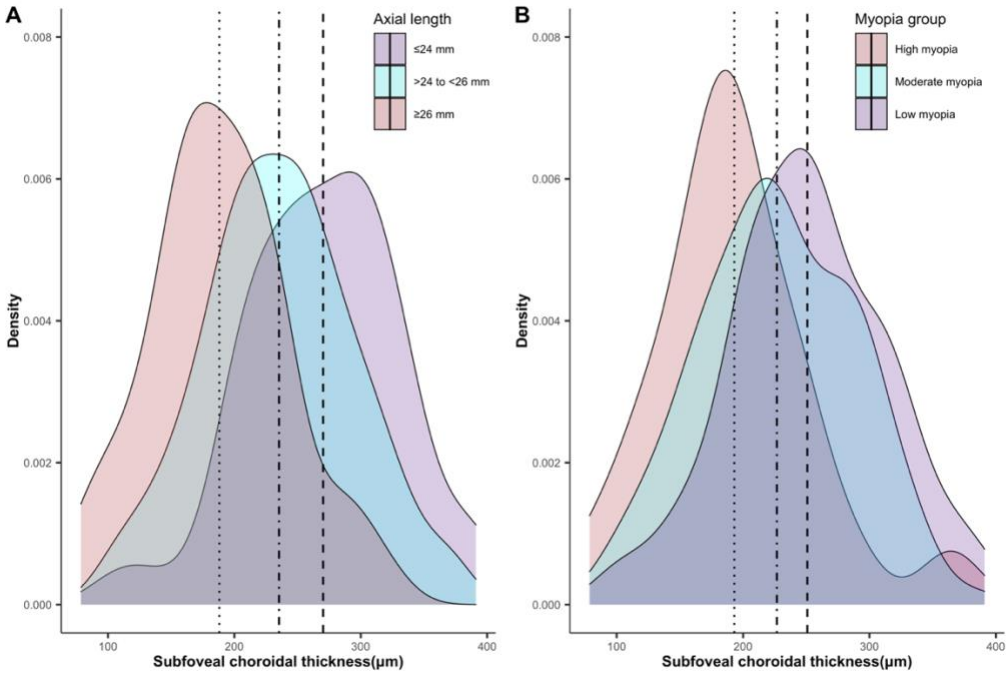

Figure 3. Density plot showing the distribution of subfoveal choroidal thickness across different (A) Axial length and (B) Myopia groups, illustrating thinner subfoveal choroidal thickness in longer and high myopic eyes. The black lines – dotted, dotdashed, and dashed – indicates the mean choroidal thickness for long eyes and high myopia, medium eyes and moderate myopia, and short eyes and low myopia, respectively.

Topographical distribution of choroidal thickness

Overall, repeated measures analysis of variance showed that choroidal thickness varied significantly across the macular locations (F (8, 1928) = 431.6, P<.001); thickest in the perifoveal superior region (mean±SD: 249.0±60.8μm) and thinnest in the perifoveal nasal region (155.1±50.3μm). This was consistent for low and moderate myopia, but the parafoveal temporal region was thickest in high myopia (211.1±60.3μm) (Figure 4B). On average, choroidal thickness was greater in all parafoveal compared to perifoveal regions except superiorly where the choroidal thickness was greater in the perifoveal region. There was no sex (P=.89) or age (P=.82) by choroidal thickness interaction at any of the macular locations. Table 2 summarizes the distribution of choroidal thickness in the macular locations among different sex and age groups.

Table 2. Choroidal thickness distribution by sex and age group

Variables	Total N = 249	Male N = 94	Female N = 155	*P-value	6-11 N = 129	12-16 N = 120	*P-value
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Subfoveal Region							
Subfoveal	234.9 (63.7)	231.0 (58.1)	237.6 (66.9)	.45	241.8 (59.7)	227.4 (67.3)	.08
Parafoveal Region							
Parafoveal Temporal	246.4 (58.6)	241.1 (54.2)	249.6 (61.1)	.27	251.8 (54.0)	240.5 (62.9)	.13
Parafoveal Superior	246.6 (62.7)	242.4 (55.7)	249.2 (66.7)	.41	252.6 (57.4)	240.2 (67.5)	.12
Parafoveal Inferior	230.5 (60.5)	224 (56.1)	234.4 (62.8)	.19	235.1 (56.8)	225.6 (64.0)	.22
Parafoveal Nasal	203.9 (60.5)	199.8 (57.3)	206.4 (62.4)	.40	209.6 (57.1)	197.7 (63.6)	.12
Parafoveal overall average	231.8 (57.8)	226.8 (53.0)	234.9 (60.5)	.29	237.3 (52.9)	226.0 (62.4)	.13
Perifoveal Region							
Perifoveal Temporal	242.6 (50.9)	236.1 (47.8)	246.6 (52.4)	.11	247.7 (47.1)	237.1 (54.3)	.10
Perifoveal Superior	249.0 (60.8)	243.4 (54.7)	252.5 (64.1)	.25	253.9 (54.3)	243.8 (66.9)	.19
Perifoveal Inferior	225.7 (54.6)	219.1 (52.4)	229.7 (55.7)	.14	229.9 (50.3)	221.2 (58.7)	.21
Perifoveal Nasal	155.1 (50.3)	151.7 (48.3)	157.1 (51.6)	.41	158.4 (48.6)	151.4 (52.2)	.28
Perifoveal overall average	218.1 (49.1)	212.6 (45.7)	221.5 (51.4)	.17	222.5 (44.6)	213.4 (53.9)	.15

Significance testing: *Independent samples t-test

Axial length and Myopia

Participants with longer axial length (≥26mm) exhibited significantly thinner choroidal thickness compared with shorter ≤24mm) and medium (>24mm to <26mm) axial length at all locations (*P*<.001 for all) (Figure 4A). The high myopia group had significantly thinner choroidal thickness compared with low myopia group at all locations with the biggest and smallest mean differences between high and low myopia observed in the subfoveal (-57.3μm) and perifoveal nasal (-32.8μm) regions, respectively (*P*<.001 for all) (Figure 4B). There was a significant difference in choroidal thickness between low and moderate myopia in five out of the nine locations (subfoveal, perifoveal inferior, parafoveal inferior, nasal, and temporal regions; *P*<.05 for all) and between high and moderate myopia groups in only three out of the nine locations (parafoveal superior, perifoveal superior and temporal regions; *P*<.05 for all).

Sex, Age and Race

Similar choroidal thickness profiles were observed between males and females (Table 2); and between older (12-16 years) and younger (6-11 years) children (Table 2), with no significant differences in choroidal thickness between groups at any location.

Overall, race was significantly associated with choroidal thickness at all macular locations (*P*<.01 for all). Blacks had the thickest subfoveal choroidal thickness (n=4; 279.8±32.9μm) followed by Mixed race (n=16; 239.1±48.1μm), Whites (n=207; 237.8±64.5μm), and Asians (n=22; 196.6±58.0μm). Asians exhibited significantly thinner choroidal thickness compared to Whites (*P*<.001 for all) in all locations (biggest and smallest mean difference in choroidal thickness were observed in perifoveal superior and nasal regions [mean±SE; -10.52±7.12μm vs -5.45±6.59μm, respectively]) (Figure 4C). Compared to Mixed race, Asians exhibited significantly

thinner choroidal thickness at five out of nine macular locations (perifoveal inferior, superior, temporal and parafoveal inferior and superior regions; *P*<.05 for all); no significant differences in choroidal thickness were found between Whites and Mixed race at all locations (*P*>.05 for all).

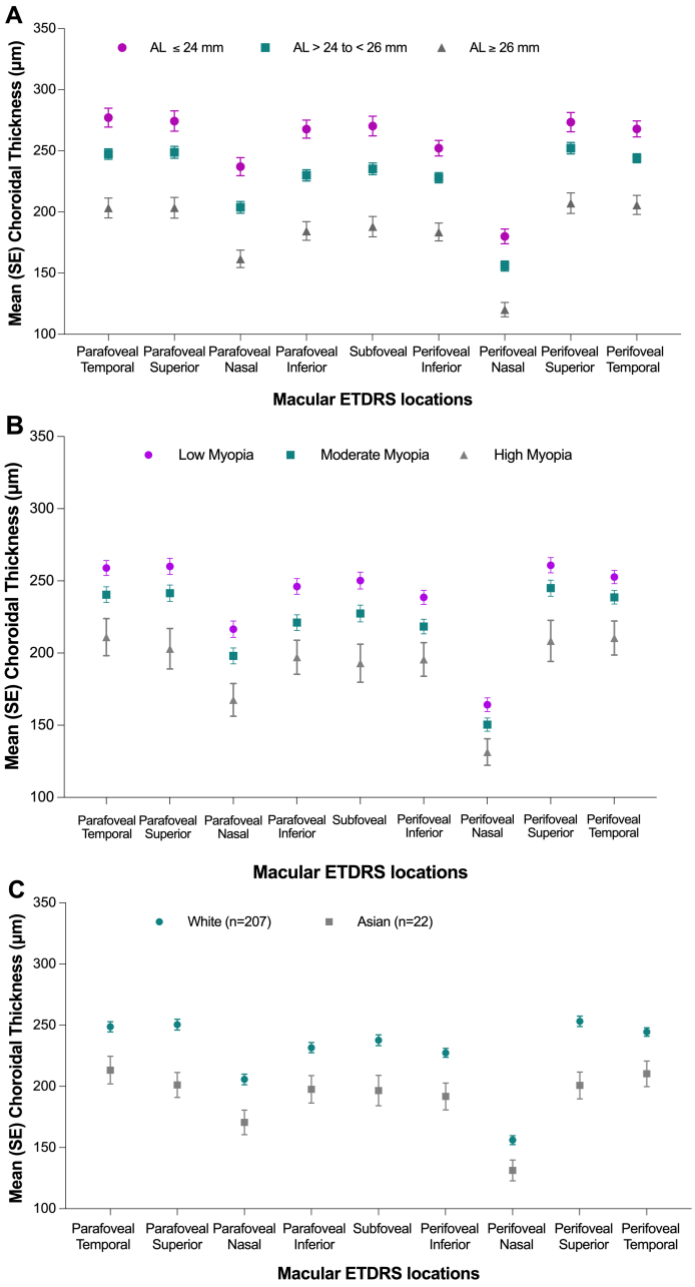

Figure 4. Graph showing distribution of choroidal thickness at all macular locations across different (A) Axial length, (B) Myopia groups, and (C) Whites and Asians. Error bars indicate standard error of mean (SE). Differences are statistically significant at all locations (P<.001 for all).

Multivariable analysis

Race, axial length, and spherical equivalent refraction were associated with choroidal thickness on univariable analysis and were further investigated in multiple linear regression models. Age and sex were additionally included as covariates. Axial length and spherical equivalent refraction were included separately in two different models due to high multicollinearity between the two variables (variance inflation factors of 1.87 and 1.98, respectively). On univariable analysis, axial length appeared to account for slightly more of the variance in subfoveal choroidal thickness than spherical equivalent refraction (R^2 = 12.4% [all locations, range = 7% to 15%] and 8.8% [all locations, range = 5% to 9.8%], respectively).

Longer axial length and higher myopic spherical equivalent refraction were consistently associated with thinner choroidal thickness at all locations in the multiple linear regression models. Asian race was significantly associated with thinner choroidal thickness only at para- and peri-foveal superior regions following Bonferroni correction (*P*=.004 and *P*=.001, respectively; Table 3), where the mean difference in choroidal thickness between Asian and White participants was nearly twice as large as at other locations. Although included in the model, age and sex were not significantly associated with choroidal thickness at any of the locations.

Table 3. Multiple linear regression† analysis of associations with choroidal thickness, by macular location, for axial length, spherical equivalent refraction, and race (White versus Asian).

Macular locations	Axial length		SER		‡Race (Reference, White)	
	Estimate, μm (SE)	*P*-value	Estimate, μm (SE)	*P*-value	Estimate, μm (SE)	*P*-value
Subfoveal	-19.88 (3.74)	<.001*	9.79 (2.31)	<.001*	-34.40 (13.40)	.011
Parafoveal Temporal	-17.68 (3.47)	<.001*	8.29 (2.15)	<.001*	-30.30 (12.30)	.048
Parafoveal Superior	-17.13 (3.13)	<.001*	8.37 (2.29)	<.001*	-43.50 (13.30)	.004*
Parafoveal Inferior	-21.60 (3.48)	<.001*	10.24 (2.17)	<.001*	-26.80 (12.50)	.032
Parafoveal Nasal	-17.91 (3.58)	<.001*	8.71 (2.21)	<.001*	-29.10 (12.80)	.024
Perifoveal Nasal	-13.61 (3.02)	<.001*	6.51 (1.86)	.001*	-20.20 (10.80)	.063
Perifoveal Inferior	-17.48 (3.17)	<.001*	8.70 (1.96)	<.001*	-29.80 (11.40)	.009
Perifoveal Superior	-15.13 (3.61)	<.001*	7.32 (2.21)	.001*	-47.40 (12.90)	.001*
Perifoveal Temporal	-13.42 (3.01)	<.001*	6.33 (1.85)	<.001*	-29.70 (10.80)	.006

†Although included in the model, age and sex have not been presented since there was no significant association with choroidal thickness at any of the locations.
‡Only results for Asian race are presented in the table because there were no significant associations with Mixed and Black race at any of the locations.
**P*-values with asterisk (*) are considered statistically significant (<0.006 [0.05/9]) after Bonferroni adjustment.
SER = spherical equivalent refraction; SE = standard error

DISCUSSION

In this cohort of myopic children, choroidal thickness was thinnest in the nasal macular region while thickest in the perifoveal superior region for low and moderate myopia and in the parafoveal temporal region for highly myopic children. Axial length and spherical equivalent refraction were the key determinants of choroidal thickness, each accounting for approximately 10% of the variance in subfoveal choroidal thickness. After adjusting for axial length and spherical equivalent refraction, choroidal thickness in participants of Asian race was generally thinner compared to White participants, but this was only significant in the superior regions.

Compared to other studies of myopic children, the mean subfoveal choroidal thickness (234.9 ± 63.7μm) in our study was thinner than reported in children from Australia[21] (303.6 ± 79 μm) and Spain[16,17] (300.34 ± 54.34μm and 310 ± 62μm, respectively). Although these studies used a different scanning technique (Spectral Domain Optical Coherence Tomography), differences probably arise because children in our study were more myopic on average (mean SER of -3.45 ± 1.80D) compared to the studies in Australia (-2.39 ± 1.51D) and Spain (-2.61 ± 1.28D and -2.44 ± 2.52D). In Asia, compared to our study, both thinner[15,22] (207 – 227μm) and thicker[14,23] (252.8 – 294.2μm) subfoveal choroidal thickness have been reported in myopic children. The contrasting findings in Asia could be attributable to the choroidal thickness measurement and scanning techniques (i. e. Swept Source- vs Spectral Domain-Optical Coherence Tomography), age (8-11years;[14] 7-13years;[15] 9-16years;[22] 6-16years[23]), and SER (means: -2.88D;[14] -2.00D;[15] -2.96D;[22] -2.68D[23]) of the study cohorts.

Mean choroidal thickness varied across the macular area with the superior and nasal regions exhibiting the thickest and thinnest choroidal thickness, respectively. While similar findings of overall thickest choroidal thickness in the superior region have been reported in studies in adults[24,25] and children,[21,26,27] others have reported thickest choroidal thickness in the temporal region.[15,28,29] The nasal quadrant showed the largest decrease in choroidal thickness with increasing eccentricity; but, compared to the subfovea, choroidal thickness was actually thicker in the superior and temporal parafoveal and perifoveal regions. Vascular distribution of choroidal blood vessels,[30] regional contraction of choroidal nonvascular smooth muscles,[31] and embryological developmental characteristics[32] of the choroid have all been postulated to account for the topographical variations in choroidal thickness. Additionally, the hypothesised watershed zone phenomenon also makes the nasal region vulnerable to ischaemic changes particularly in myopic eyes,[33] although this may be unlikely in children. Despite the topographical variations in choroidal thickness observed within the macular area, future longitudinal evaluation of the changing profile of choroidal thickness in growing children will be critical to understanding the value of choroidal thickness profile information in informing clinical decision making.

Although mean choroidal thickness was significantly different between the three axial length groups (≤24mm, >24mm to <26mm, and ≥26mm), there was a large amount of overlap in the distributions of choroidal thickness. This indicates that even myopic children with a relatively short axial length may have thin choroidal thickness or that myopic children with a long axial length may have a relatively thick choroidal thickness. It is expected that with increasing age the choroidal thickness will become thinner, potentially exposing even low myopic children with thinner choroidal thickness to

potential chorioretinal disease and consequent vision loss. Thinner subfoveal choroidal thickness was an important predictor of myopic maculopathy progression, independent of axial length, in a cohort of highly myopic individuals (including children).[8] The mean baseline subfoveal choroidal thickness of Chinese myopic children of ages 7-18 years who showed progression of their high myopia in their study over a two-year period was 93.3μm.[8] Thus, assessment of choroidal thickness may provide additional information to assist in identifying myopic children most at risk of myopic progression or future chorioretinal disease. Further follow-up will however determine if rates of myopia progression in our study differ between low and high myopic children with short and long axial length or who exhibit thinner choroidal thickness at baseline. Additional work is also required to explore the relationship between choroidal thickness and risk of myopia complications, particularly in low and moderate myopia.

The observed association between choroidal thickness and both spherical equivalent refraction and axial length is well-known and may be bi-directional. Increasing axial length may mechanically stretch and thin the choroid, or changes in the choroid may precede an increase in axial length.[2,34] Consistent with reports from previous studies,[35–37] race did appear to have an impact on choroidal thickness, being thinner at all macular locations in Asians compared to Whites in univariable analysis. Asians are generally more susceptible to myopia progression and typically exhibit longer axial length compared to Whites,[37,38] so this was expected. After adjusting for axial length, race remained significantly associated with choroidal thickness in the superior regions, suggesting this relationship may be independent of axial length or myopia severity. These findings could be underpinned by genetic or behavioral factors such as near

work activities between the two races as Asians were found to spend approximately 80 more minutes per day reading printed material compared to Whites (*P*=.003), however, an interaction term between near work activities and race was not statistically significant, suggesting that the effect of near work activities on choroidal thickness did not vary between the different races. Few Asian participants were recruited to the current study, so this relationship requires further exploration in a larger study with more Asian participants.

There were some limitations to this study; for instance, only 22 highly myopic children were included, compared to 112 moderate myopic and 116 low myopic children. The Myopia Outcome Study of Atropine in Children clinical trial was not designed to recruit high, moderate, and low myopic children equally – this variation therefore reflects that high myopia is less common in the general population. Choroidal thickness measurements were taken throughout the course of the day and not at a fixed time. Although the choroidal thickness measurements could have been influenced by diurnal variation,[39–41] the number of measurements in our study were nearly balanced throughout the day (16 early morning, 82 mid-morning, 73 early afternoon, 78 late afternoon), with no significant associations observed between time of day and choroidal thickness measurements (*P*=.13). Despite the equivocal evidence about the effect of cyclopentolate-induced cycloplegia on choroidal thickness – some studies have reported thinner[42] or thicker[43] choroidal thickness post cyclopentolate-induced cycloplegia – it is important to acknowledge that the use of cyclopentolate (to eliminate the potential effects of accommodation on choroidal thickness and improve image quality of the optical coherence tomography scan and fundus image) in our study may have impacted the choroidal thickness measurements. Transient thinning in choroidal

thickness in the range of -1 to -9μm in response to 3D to 6D induced accommodation retinal defocus have been reported previously.[44,45] Even though our study did not strictly control for the effects of retinal defocus (which could potentially influence choroidal thickness), it is unlikely that participants in this study may have been exposed to that level of blur as highlighted, for instance, by the small amount of under- and over-correction of their spectacles. Our findings may thus be more generalisable to clinical settings in Ireland as our study protocol simulated the typical clinical environment, where children's activities prior to entering the examination room are not controlled. A significant strength, however, is the high sample size of 250 myopic children recruited from eye care centres throughout the Republic of Ireland – this represents one of the few studies in a relatively large myopic cohort in Europe and may adequately reflect the choroidal thickness profiles of myopic children who require myopia control treatment in the studied population. The findings of this study will underpin the analysis of longitudinal choroidal thickness profile changes with and without low dose atropine treatment and provide a baseline for understanding the potential value of choroidal thickness in predicting myopic progression in children using atropine and placebo eye drops.

In conclusion, the current study described the profile of choroidal thickness in a cohort of myopic children. Choroidal thickness was thinnest in the nasal macular region and varied systematically across all macular locations, with axial length and spherical equivalent refraction being the strongest determinants of choroidal thickness after adjusting for potential confounders. Choroidal thickness was generally thinner in Asian, compared to White participants, but was only significantly different in the superior regions. Longitudinal evidence will need to evaluate whether any differences

in choroidal thickness profiles are predictive of myopic progression and also help to determine the role of choroidal thickness measurements in identifying myopic children most in need of treatment.

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Competing interests

No conflicting relationship exists for any author.

Availability of data and materials

The dataset(s) supporting the conclusions of this article is/are available on reasonable request from the corresponding author.

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Figure 1: Optical coherence tomography scan of the retina and choroid. (A) Choroidal thickness measured from Bruch's membrane to the choroidal-scleral interface (green horizontal lines). (B) Average choroidal thickness measurements within the 9 Early Treatment of Diabetic Retinopathy Study locations.

Figure 2: (A) Inverse correlation between subfoveal choroidal thickness and axial length. (B) Positive correlation between subfoveal choroidal thickness and spherical equivalent refraction. Shaded area represents 95% confidence interval around the regression line.

Figure 3. Density plot showing the distribution of subfoveal choroidal thickness across different (A) Axial length and (B) Myopia groups, illustrating thinner subfoveal choroidal thickness in longer and high myopic eyes. The black lines – dotted, dotdashed, and dashed – indicates the mean choroidal thickness for long eyes and high myopia, medium eyes and moderate myopia, and short eyes and high myopia, respectively.

Figure 4. Graph showing distribution of choroidal thickness at all macular locations across different (A) Axial length, (B) Myopia groups, and (C) Whites and Asians. Error bars indicate standard error of mean (SE). Differences are statistically significant at all locations (P<0.001 for all).