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Five-Year Change in Choroidal Thickness in Relation to Body Development and Axial Eye Elongation: The CCC2000 Eye Study

Mathias Hvidtfelt Hansen,[1,2] Xiao Qiang Li,[1] Michael Larsen,[1,2] Else Marie Olsen,[3,4] Anne Mette Skovgaard,[5] Line Kessel,[1,2] and Inger Christine Munch[6]

[1]Department of Ophthalmology, Rigshospitalet-Glostrup, Copenhagen, Denmark
[2]Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[3]Institute of Public Health, University of Copenhagen, Copenhagen, Denmark
[4]Center for Clinical Research and Disease Prevention, Capital Region, Copenhagen, Denmark
[5]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[6]Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark

Correspondence: Mathias Hvidtfelt Hansen, Department of Ophthalmology, Rigshospitalet, Valdemar Hansens Vej 1-23, Glostrup 2600, Denmark;
mhan0884@regionh.dk.

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Purpose. We describe changes in choroidal thickness from age 11 to 16 years and its association with ocular biometrics and body development.

Method. In this longitudinal, population-based observational study, choroidal thickness was measured subfoveally and 1- and 3-mm temporal thereof using enhanced depth imaging spectral domain optical coherence tomography. Analyses were stratified by sex and adjusted for age and the time of day that the scan was performed.

Results. The study included 687 participants (304 boys). Median (interquartile range [IQR]) age was 11.5 (0.6) years at baseline and 16.6 (0.3) years at follow-up. Mean increase in choroidal thickness was 33, 27, and 11 μm at the three respective locations. The subfoveal choroid thickened less in eyes whose axial length increased more (boys, $\beta = -85$ μm/mm; 95% confidence interval [CI], −104 to −66, $P < 0.0001$; girls, $\beta = -105$ μm/mm; 95% CI, −121 to −89, $P < 0.0001$) and in eyes with a more negative refractive development (boys, 11 μm/diopters [D]; 95% CI, 4.0 to 18, $P = 0.0022$; girls, 22 μm/D; 95% CI, 16 to 27, $P < 0.0001$). Subfoveal choroidal thickness increased less in girls who underwent early puberty (Tanner stage 4 vs. 1; −39 μm' 95% CI, −72 to −5.9, $P = 0.021$) and who had a longer baseline axial length ($\beta = -8.6$ μm/mm; 95% CI, −15 to −2.7, $P = 0.0043$), and more in girls who grew taller ($\beta = 0.9$ μm/cm; 95% CI, 0.1 to 1.7, $P = 0.026$).

Conclusions. The choroid increased in thickness from age 11 to 16 years. The increase was greater in girls with later sexual maturation and smaller in eyes that added more axial length and had a relatively negative refractive development.

Keywords: choroidal thickness changes, longitudinal study, cohort study, axial eye growth

Choroidal thickness is associated with the eye's axial length[1–3] and refractive status[3,4] so that long and myopic eyes have thin choroids. Also, choroidal thickness is abnormal in conditions, such as glaucoma,[5] diabetic retinopathy,[6] amblyopia,[7] and central serous chorioretinopathy.[8] Thus, it is involved in several visual disorders, but sparse information exists on the normal changes in choroidal thickness through life. Only within the most recent decade has means of in vivo quantification of choroidal thickness been available[9] and most of the current data are limited to cross-sectional studies. Some of them indicate that choroidal thickness decreases during adult life.[4,10–13] In children and adolescents, cross-sectional studies suggest an increase in thickness with age in European and Australian cohorts,[14–16] whereas a decrease has been noted in Asian child cohorts.[1,17–20] Given this complexity, it is obvious that prospective studies are particularly valuable.[21–23] Previous longitudinal studies have been relatively small and mainly investigated populations with high myopia rates.[21,22] We describe changes in choroidal thickness from the age of 11 to 16 years in a prospective cohort study, and its association with baseline parameters and various aspect of ocular and systemic development during the observation period.

Methods

Participants

The analysis includes participants from the Copenhagen Child Cohort 2000 (CCC2000) Eye Study[24,25] that is an addition to the CCC2000 study; a prospective, population-based, observational birth cohort study of 6090 children born in the year 2000 in 16 municipalities of Copenhagen County, Denmark.[26] The cohort has been found representative of all children born in Denmark that year regarding key perinatal characteristics.[27] All eligible children from the original cohort were invited to the examinations in 2011–2012 and in 2016–2017. Eye examinations in 2011–2012 included 1406 participants.[25] Compared to the initial 6090 children, the children participating in the 2011–

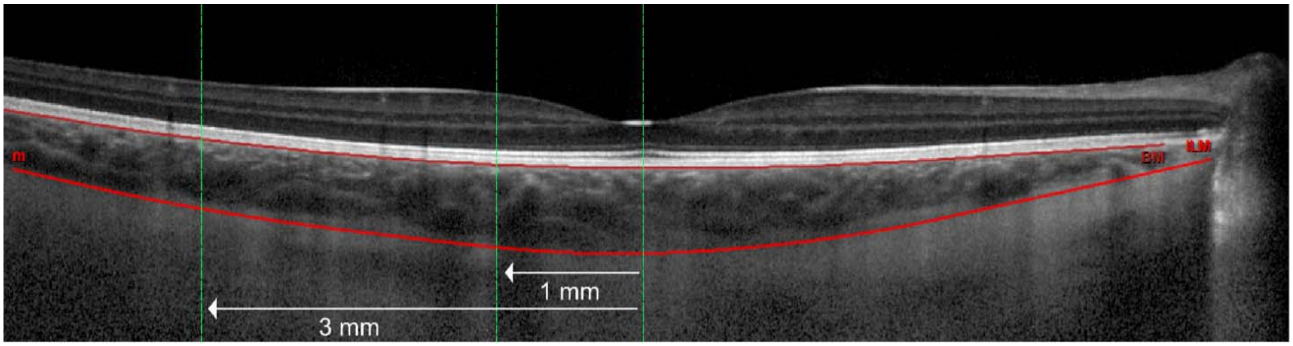

FIGURE 1. Outlines of Bruch's membrane (BM) and the sclerochoroidal border (ILM) as traced manually using software functions available for the OCT system used in our study. Choroidal thickness was measured at three locations: under the foveal center, and 1 and 3 mm temporal thereof.

2012 examination included more girls, and more children born at term, living with both parents at birth, and having more well-educated parents with higher annual household income.[28] In 2016–2017, 1445 subjects participated in the eye examination, including 741 participants who both attended the 2011–2012 and 2016–2017 examination. The follow-up rate was 412 of 733 (56%) for girls and 329 of 673 (49%) for boys. There was no significant difference between children who attended both visits and those who attended only the 2011–2012 examination in body height, axial length, choroidal thickness, or regarding key perinatal characteristics ($P > 0.3$, Student's *t*-test). Medical history was obtained from the participants, their parents, or legal guardians.

We excluded participants with a best corrected visual acuity (BCVA) <80 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters at age 16 ($n = 8$). Additionally, 46 participants with missing data from one or more of the following parameters were excluded: optical coherence tomography (OCT) scans ($n = 4$), axial length ($n = 3$), corneal curvature ($n = 29$), and refractive data ($n = 15$). A total of 687 participants were included in the analysis.

Procedures

We measured BCVA using ETDRS charts (4-meter original series; Precision-Vision, La Salle, IL, USA). Subjective refraction was guided by noncycloplegic autorefraction (in 2011, Retinomax K-plus; Right MFG Co., Ltd., Tokyo, Japan; in 2016, Nidek AR-660A; NIDEK CO., LTD., Gamagori, Japan). Using the correction found by the autorefractor, the children read as many letters on an ETDRS chart as possible. Hereafter, positive lens power (+0.5 diopters [D]) was added until significant blur occurred, followed by reduction in steps of –0.25 D until optimal acuity was achieved.

The choroid was imaged using enhanced depth imaging spectral domain OCT (EDI-SD-OCT; Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The scanning protocol included a horizontal raster with seven scan lines within a $5° \times 30°$ rectangle and a 30° four-line radial scan. The built-in eye tracking feature was used, and scans were obtained in the high-resolution mode and centered on the fovea. Each scan line consisted of the average of 25 B-scans. The eye examination was performed immediately after a 1-hour interview of the child or adolescent by a psychiatrist. Thus, the participants were physically inactive for at least 1 hour in advance of the OCT scan. We used the participants' refractive status and corneal curvature as scaling factors to adjust for transverse magnification. The scaling factors were entered in the OCT apparatus before the scans were obtained. As a 30° four-line radial scan was not performed in all participants at the baseline visit in 2011–2012, we only used horizontal scan lines in the evaluation of choroidal thickness. We selected the horizontal scan line from either the horizontal raster or the radial scan with the deepest foveal depression and the presence of a pronounced foveal center specular reflex for measurement of subfoveal choroidal thickness (Fig. 1). The follow-up function from the manufacturer's software (Heidelberg Eye Explorer, version 1.6.1.0; Heidelberg Engineering) was used when performing the examinations in 2016–2017 to ensure that the follow-up scans were from the same location as the baseline scans. The same software was used to measure choroidal thickness by manually moving the segmentation line that is automatically set at the inner limiting membrane to the choroidoscleral border. Choroidal thickness was measured at three locations: subfoveal, 1 mm temporal of the foveal center, and 3 mm temporal of the foveal center (Fig. 1).

All scans from 2011–2012 were evaluated by one grader (XQL) and all scans from 2016–2017 by another (MHH). The 2011–2012 intragrader variability was 1.8 ± 7.9, range –17 to 14 µm ($P = 0.22$).[24] The 2016–2017 intragrader variability was tested by MHH in 30 random participants showing a mean difference of 1.2 µm, $P = 0.23$, with 95% limits of agreements ($\pm 1.96 \times \text{SD}$) –9 to 12 µm. Intergrader variability between XQL and MHH was tested by regrading 30 random participants from the 2011–2012 examination showing a mean difference of 0.3 µm, $P = 0.90$ with 95% limits of agreement being –23 to 23 µm.

Axial length and corneal curvature were measured using a partial coherence interferometry device (IOL-Master, version 3.01.0294; Carl Zeiss Meditec, La Jolla, CA, USA).

Participants' body height and weight were measured using a wall-mounted altimeter (Height Measuring Rod, Soehnle Professional GmbH & Co., Backnang, Germany) and an electronic scale (2011 examination, "Exact/personal scale 6295"; OBH Nordica Denmark A/S, Taastrup, Denmark; 2016 examination, TBF 300A; Tanita Europe BV, Amsterdam, The Netherlands), respectively. Body height measurements were missing in three boys and four girls in 2011 and in one boy in 2016. Body weight measurements were missing in four boys and two girls in 2011 and in 1 girl in 2016. Puberty stage was self-evaluated by participants in 2011 using illustrations of Tanner stages 1 through 4 developments of pubic hair, genitals, and breasts, with stage 1 being prepubertal and stage 4 late puberty. Data of Tanner stages were missing in nine boys and five girls.

Signed informed consent was obtained from all parents or legal guardians in the 11- to 12-year examination. In the 16- to 17-year examination, only the participants signed the consent after the participants and their parents or legal guardians had received written information regarding the examinations. The protocol was approved by the Danish Data Protection Agency (jr.nr. CSU-FCFS-2016-004) and assessed by the local medical ethics committees in 2011 (jr.nr. H-3-2011-028) and 2016 (protocol number 16023242) with the verdict that approval was not required. The study adhered to the tenets of the Declaration of Helsinki.

Statistics

Normally distributed data were reported as mean ± SD and Student's *t*-test was used when comparing boys with girls. Nonnormally distributed data were reported as median ± interquartile range (IQR) and the Wilcoxon Rank Sum was used when comparing the sexes. Baseline parameters' effect on the 5-year change in choroidal thickness from baseline to follow-up and the association between the change in choroidal thickness and the 5-year change in spherical equivalent refraction, axial length, body height, and body mass index (BMI) were analyzed using general linear models stratified for sex and adjusted for age at baseline and time of day OCT scans were performed at baseline and follow-up.

Participants with missing body height ($n = 8$), weight ($n = 7$), and Tanner stage ($n = 14$) measurements were only excluded from the analyses that included the respective parameters.

Main analyses were performed using subfoveal choroidal thickness. Potential differences between the three choroidal locations (subfoveal, 1 mm temporal, and 3 mm temporal) in the associations between the 5-year change in choroidal thickness, and the exposure variables were analyzed as the interaction between choroidal location and the variables in mixed models with choroidal location as a repeated effect and using the unstructured covariance structure.

Spherical equivalent refraction was calculated by adding half the cylindrical refraction to the subjective refraction, BMI by dividing the weight in kilograms with the squared height in meters, and corneal curvature as the average between the steepest and flattest corneal meridian. The 5-year change in choroidal thickness, axial length, spherical equivalent refraction, corneal curvature, body height, body weight, and BMI from age 11 to 16 years was calculated as the difference between the two measurements divided by the follow-up time and multiplied by five.

The intergrader (between MHH and XQL) and intragrader (MHH) variability in the grading of subfoveal choroidal thickness was analyzed using Bland-Altman plots and paired Student's *t*-tests.

The level of statistical significance was set to $P < 0.05$.

We used the SAS Enterprise Guide statistical software package (version 7.2; SAS Institute, Cary, NC, USA) for all statistical analyses.

RESULTS

The analyses included 687 participants (304 boys / 383 girls) with a median (IQR) age of 11.5 (0.6) years at baseline, 16.6 (0.3) years at follow-up (Table 1), and a median (IQR) follow-up of 5.0 (0.5) years. Average (SD, range) scanning time was 1:54 PM (±2.5 hours, 8:20 AM–8:20 PM) in 2011–2012 and 3:19 PM (±3.2, 8:00 AM–10:00 PM) in 2016–2017 (mean difference = 1.4 hours; 95% confidence interval [CI], 1.1–1.7, $P < 0.0001$, paired *t*-test).

The mean (SD) 5-year change in choroidal thickness was a 33 (44), 27 (42), and 11 (35) μm increase under the foveal center, and at 1 and 3 mm temporal of the foveal center, respectively (Fig. 1). The increase was significantly higher in boys than in girls under the fovea ($P = 0.015$) and at 3 mm ($P < 0.0001$) but not at 1 mm temporal of the foveal center ($P = 0.10$; Table 1).

Five-Year Change in Choroidal Thickness in Relation to Baseline Parameters

Longer eyes at baseline increased less in subfoveal choroidal thickness over the 5 years in girls, with a subfoveal choroidal thickness increase of 8.6 (95% CI, −15 to −2.7, $P = 0.0043$) μm less for each mm longer baseline axial length (Table 2). This effect remained significant when adjusting for baseline subfoveal choroidal thickness and baseline spherical equivalent refraction ($P = 0.025$; data not tabulated). We found no significant effect of baseline axial length in boys ($P = 0.052$).

Subfoveal choroidal thickness increased 6.2 μm (95% CI, 0.4–12, $P = 0.036$) more per 100 μm thicker baseline choroid in girls (Table 2), whereas no such association with baseline choroidal thickness was found in boys ($P = 1.00$). The association in girls was not significant when adjusted for baseline axial length ($P = 0.21$; data not tabulated).

The subfoveal choroid of girls increased 5.6 (95% CI, 0.5–11, $P = 0.033$) μm more in thickness for each diopter more positive refractive power at baseline (Table 2). The association was not significant after adjusting for baseline axial length ($P = 0.37$; data not tabulated). We found no association between changes in subfoveal choroidal thickness and baseline spherical equivalent refraction in boys ($P = 0.60$; Table 2).

Subfoveal choroidal thickness increased 39 (95% CI, −72 to −5.9, $P = 0.021$) μm less among girls in Tanner stage 4 at baseline compared to girls in Tanner stage 1 (Table 2). Baseline pubertal stage had no effect on the 5-year change in choroidal thickness in boys (Table 2).

We found no effect of baseline body height or BMI on the subsequent 5-year change in subfoveal choroidal thickness among boys or girls (Table 2).

The effect of the baseline parameters on choroidal thickness changes did not differ among the three choroidal locations. All *P* values for interaction between choroidal location and the respective parameters were >0.09 (data not tabulated).

Associations Between Five-Year Changes in Choroidal Thickness and Five-Year Changes in Axial Length, Spherical Equivalent Refraction, Body Height, and BMI

The median (IQR) 5-year increase in axial length was 0.25 (0.22) mm and higher among girls than boys ($P = 0.046$; Table 1). Higher 5-year axial elongation was associated with less thickening of the subfoveal choroid in the eyes of boys and girls (Table 3; Fig. 2). Thus, the subfoveal choroid increased 85 (95% CI, −104 to −66, $P < 0.0001$) μm less in thickness for each 1 mm increase in axial length in boys' eyes and 105 (95% CI, −121 to −89, $P < 0.0001$) μm less per mm increase in girls' eyes. In girls, the choroidal thickness change per mm axial length increase was greater at the subfoveal location compared to 1 and 3 mm temporally ($P < 0.01$; Fig 2). In boys, the effect was greater at the subfoveal location compared to 3 mm temporally ($P < 0.0001$), but not compared to 1 mm temporally ($P = 0.21$; Fig. 2).

The median (IQR) spherical equivalent refractive error became 0.25 (0.8) D more myopic, with no differences between sexes ($P = 0.14$, Table 1). The subfoveal choroid increased 11 (95% CI, 4.0–18, $P = 0.0022$) μm and 22 (95% CI, 16–27, $P < 0.0001$) μm more in thickness for each diopter more hyperopic shift in refraction in boys and girls, respectively (Table 3). This effect was more pronounced subfoveally compared to 3 mm temporally ($P = 0.015$ in boys and $P < 0.0001$ in girls). There was no difference between the effect subfoveally and 1 mm temporally in boys or girls ($P > 0.05$; data not tabulated).

Table 1. Demographic Characteristics of the Study Participants and Their Right Eyes

Parameter	Boys (*n* = 304)	Girls (*n* = 383)	*P* Value
11–12 years examination			
Age, median (IQR), years	11.5 (0.6)	11.5 (0.6)	0.91
BCVA, mean (SD), ETDRS letters	89 (3)	89 (3)	0.30
Spherical equivalent refractive error, median (IQR), D	0.0 (0.5)	0.0 (0.6)	0.16
Axial length, mean (SD), mm	23.46 (0.7)	22.92 (0.7)	<0.0001
Corneal curvature, mean (SD), mm	7.87 (0.2)	7.75 (0.2)	<0.0001
Choroidal thickness, mean (SD), µm			
Subfoveal	351 (73)	369 (77)	0.0021
1 mm temporal	346 (70)	365 (71)	0.0006
3 mm temporal	319 (65)	330 (66)	0.030
Body height, mean (SD), cm	151 (8)	152 (7)	0.09
Body weight, median (IQR), kg	40.6 (10)	41.1 (11)	0.27
BMI, median (IQR), kg/m^2	17.6 (3)	17.7 (3)	0.98
Pubertal development, Tanner stages, No. (%)	*n* = 295	*n* = 378	
Tanner 1	85 (29)	70 (19)	
Tanner 2	163 (55)	190 (50)	
Tanner 3	47 (16)	109 (29)	
Tanner 4	− (−)	9 (2)	<0.0001
16–17 years examination			
Age, median (IQR), years	16.6 (0.3)	16.6 (0.3)	0.63
BCVA, mean (SD), ETDRS letters	92 (4)	91 (3)	0.0003
Spherical equivalent refractive error, median (IQR), D	−0.13 (0.5)	−0.13 (0.6)	0.41
Axial length, mean (SD), mm	23.75 (0.8)	23.23 (0.9)	<0.0001
Corneal curvature, mean (SD), mm	7.88 (0.2)	7.77 (0.2)	<0.0001
Choroidal thickness, mean (SD), µm			
Subfoveal	389 (84)	398 (94)	0.18
1 mm temporal	376 (78)	389 (88)	0.038
3 mm temporal	335 (69)	336 (75)	0.95
Body height, mean (SD), cm	180 (7)	168 (6)	<0.0001
Body weight, median (IQR), kg	67 (14)	60 (12)	<0.0001
BMI, median (IQR), kg/m^2	20.5 (4)	21.3 (4)	0.0027
Five-year change from age 11 to 16			
Spherical equivalent refractive error, median (IQR), D	−0.24 (0.7)	−0.26 (0.8)	0.14
Choroidal thickness, mean (SD), µm			
Subfoveal	38 (40)	29 (47)	0.015
1 mm temporal	30 (39)	25 (45)	0.10
3 mm temporal	17 (35)	5.9 (34)	<0.0001
Axial length, median (IQR), mm	0.24 (0.2)	0.26 (0.2)	0.046
Corneal curvature, mean (SD), mm	0.01 (0.03)	0.02 (0.03)	0.0021
Body height, mean (SD), cm	28 (5)	15 (6)	<0.0001
Body weight, mean (SD), kg	26 (7)	19 (7)	<0.0001
BMI, mean (SD), kg/m^2	3.0 (2)	3.7 (2)	<0.0001

Table 2. Linear Regression Analysis of Effects of Baseline Characteristics at Age 11–12 Years on Subsequent 5-Year Change in Subfoveal Choroidal Thickness

	Subfoveal Choroidal Thickness Change, µm			
	Boys		Girls	
11-Year Parameter	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Subfoveal choroidal thickness, 100 µm	0.0 (−6.8 to 6.8)	1.0	6.2 (0.4 to 12)	0.036
Axial length, mm	−6.8 (−14 to 0.1)	0.052	−8.6 (−15 to −2.7)	0.0043
Spherical equivalent refraction, D	1.9 (−5.2 to 8.9)	0.60	5.6 (0.5 to 11)	0.033
Body height, cm	0.5 (−0.1 to 1.2)	0.12	0.1 (−0.5 to 0.7)	0.70
BMI, kg/m^2	0.9 (−1.0 to 2.7)	0.36	−0.7 (−2.4 to 0.9)	0.38
Pubertal development, Tanner stage				
Tanner 2 vs. 1	-8.5 (−19 to 2.2)	0.12	4.2 (−9.0 to 17)	0.46
Tanner 3 vs. 1	6.0 (−9.4 to 21)	0.45	7.5 (−7.1 to 22)	0.31
Tanner 4 vs. 1	–	–	−39 (−72 to −5.9)	0.021

Multivariable analyses stratified by sex and adjusted for age at baseline and time of day OCT scans were performed at baseline and follow-up.

Table 3. Linear Regression Analysis of Associations Between 5-Year Change in Subfoveal Choroidal Thickness and Changes in Other Biometric Variables

	Subfoveal Choroidal Thickness Change, µm			
	Boys		Girls	
5-Year Change	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Axial length, mm	−85 (−104 to −66)	<0.0001	−105 (−121 to −89)	<0.0001
Spherical equivalent refraction, D	11 (4.0 to 18)	0.0022	22 (16 to 27)	<0.0001
Body height, cm	−0.7 (−1.8 to 0.4)	0.21	0.9 (0.1 to 1.7)	0.026
BMI, kg/m^2	−0.5 (−2.9 to 1.9)	0.69	−0.4 (−2.4 to 1.6)	0.69

Multivariable analyses stratified by sex and adjusted for age at baseline and time of day OCT scans were performed at baseline and follow-up.

The mean (SD) 5-year growth in body height was 21 (8) cm, with boys adding 13 (95% CI, 12–14, $P < 0.0001$) cm more than girls (Table 1). In girls, the 5-year increase in subfoveal choroidal thickness was 0.9 (95% CI, 0.1–1.7, $P = 0.026$; Table 3) µm greater for each additional centimeter they added in body height. No association was found between the subfoveal choroidal thickness change and growth in body height among boys ($P = 0.21$; Table 3). We found no locational differences in the association between choroidal thickness changes and body height growth ($P = 0.95$ in boys, $P = 0.65$ in girls; data not tabulated).

The 5-year change in subfoveal choroidal thickness was not associated with the 5-year increase in BMI ($P = 0.69$ in boys, $P = 0.69$ in girls) and the association did not differ among the three choroidal locations ($P = 0.062$ in boys, $P = 0.73$ in girls).

DISCUSSION

We examined the change in choroidal thickness from age 11 to 16 years in 687 participants from a Danish birth cohort. Relative to baseline thickness, the choroid increased by 9% under the foveal center, and 8% at 1 mm and 3% at 3 mm temporal thereof. Choroidal thickness increased more in boys than in girls. In girls, choroidal thickness changes were associated with baseline pubertal stage, axial length, and growth in body height. These parameters had no association with choroidal thickness changes in boys. Choroidal thickness changes also were associated with axial length elongation and changes in refractive power in both sexes. Thus, choroidal thickness increased less, and in some eyes thinned, in long eyes that underwent more axial elongation, and in eyes that became relatively more myopic.

We found regional differences in the changes in choroidal thickness. The choroid increased more under the foveal center and less with increasing distance in the temporal direction, away from the fovea. Likewise, choroidal thinning, when it happened, was more likely to do so temporal of rather than under the fovea. This confirms a tendency observed in a study performed by Read et al.,[21] who followed 41 myopic and 60 nonmyopic Australian children aged 10 to 15 years over an 18-month period. They found less choroidal thickness increase in parafoveal zones, especially the temporal zones, compared to the central fovea and inner macula, but without statistical power to fully support that finding. Consequently, regional differences in choroidal thickness seem to emerge, or increase, with maturation of the eye.

The finding of a choroidal thickness increase from age 11 to 16 years corresponds to cross-sectional observations from white European and Australian children,[14–16] and the magnitude of subfoveal choroidal thickness increase in our study was similar that of Read et al.[21] We also confirmed a reduced increase in choroidal thickness—in some cases choroidal thinning—in eyes that added more axial length.[21,23] While Asian studies in general report a mean decrease in choroidal thickness with increasing age in children,[1,17–20,23] a recent cross-sectional study of 3001 Chinese children aged 6 to 19 years only found choroidal thinning in myopic eyes, whereas the choroid increased in thickness in nonmyopic eyes.[20] Additionally, a 1-year follow-up study of 118 Chinese children aged 7 to 12 years found choroidal thinning in eyes with a myopic shift in refraction, but not in eyes without such shift.[22] Consequently, the choroid appears to thicken in normally-developing young eyes and thin in eyes that have myopia. Our finding of a decreased thickening of the choroid in eyes that had a negative refractive development supports this association. Therefore, the differences between European and Asian children could be caused by the higher prevalence of myopia in Asian populations.

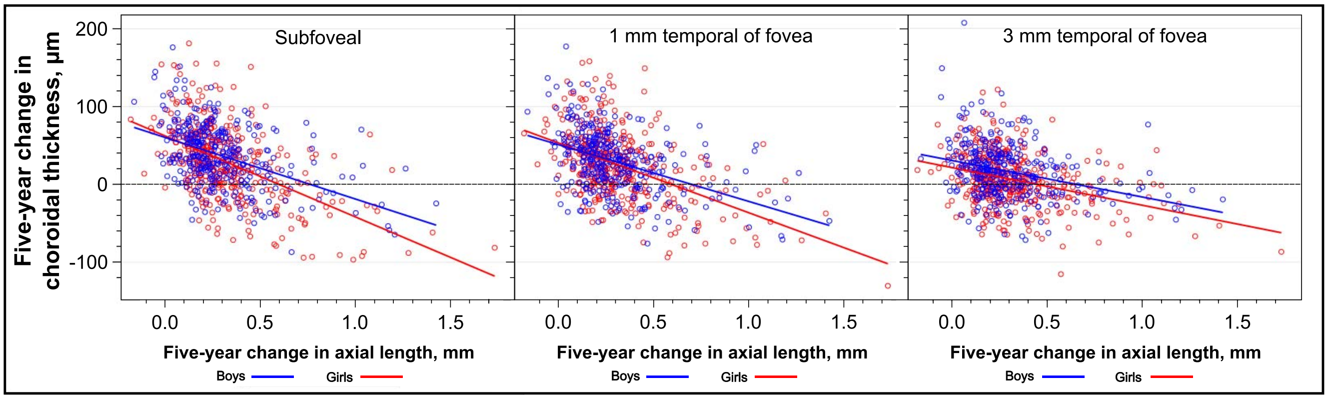

Figure 2. Association between 5-year change in choroidal thickness and axial length stratified by sex and divided by choroidal location.

We have previously shown that, at age 11 years, the subfoveal choroid was thicker in taller girls and in girls at Tanner stage 4 compared to girls in Tanner stage 1.[25] The present study showed that choroidal thickness grew less in girls who had reached Tanner stage 4 at age 11 years compared to those who were still at Tanner stage 1. Additionally, we observed greater choroidal thickening in girls who added more in body height. These findings suggest that the development of the choroid follows the general development of the body—especially the pubertal growth spurt. It supports the notion of a general increase in choroidal thickness during childhood and adolescence in normal developing eyes. The lack of association with body growth among boys is likely explained by most boys being prepubertal or in early puberty when aged 11 years. Thus, most boys entered pubertal growth spurt within the study period, making it difficult to detect possible differences in growth. The greater increase in choroidal thickness among boys could be explained by this delayed development, as there was no difference in choroidal thickness between sexes at age 16 years.

Future studies with objective measurements of pubertal development and more frequent follow-up examinations of both body height, pubertal stage, and choroidal thickness are needed to confirm these associations.

A major strength of our study is its design as a longitudinal observational study of a large and well-described population-based cohort. To our knowledge, it is the largest longitudinal study evaluating choroidal thickness changes in adolescence and the first study to describe the association with body development. Subjective refraction with fogging instead of with cycloplegia is a limitation, as on average it will underestimate hyperopia and overestimate myopia.[29–32] The follow-up rate was limited to 52% of participants from the baseline examination participating in the follow-up study.

CONCLUSIONS

In our study cohort, the choroid increased in thickness from age 11 to 16 years. In girls this increase was associated with general body development. The choroid increased less in eyes that grew more in axial length and had a relatively myopic refractive development and actually thinned in the eyes that elongated the most. These results showed that in healthy subjects the choroid grows during adolescence in concert with general body development and that the maturation of general body development and growth arrest at the end of puberty is accompanied by a retardation or cessation of choroidal growth. Thinning of the choroid is linked to the most pronounced cases of myopic refractive development and axial elongation.

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References

1. Zhang JM, Wu JF, Chen JH, et al. Macular choroidal thickness in children: The Shandong Children Eye Study. *Invest Ophthalmol Vis Sci*. 2015;56:7646–7652.
2. Li XQ, Larsen M, Munch IC. Subfoveal choroidal thickness in relation to sex and axial length in 93 Danish university students. *Invest Ophthalmol Vis Sci*. 2011;52:8438–8441.
3. Jin P, Zou H, Zhu J, et al. Choroidal and retinal thickness in children with different refractive status measured by swept-source optical coherence tomography. *Am J Ophthalmol*. 2016;168:164–176.
4. Ding X, Li J, Zeng J, et al. Choroidal thickness in healthy Chinese subjects. *Invest Ophthalmol Vis Sci*. 2011;52:9555–9560.
5. Zhang X, Cole E, Pillar A, et al. The effect of change in intraocular pressure on choroidal structure in glaucomatous eyes. *Invest Ophthalmol Vis Sci*. 2017;58:3278–3285.
6. Rewbury R, Want A, Varughese R, Chong V. Subfoveal choroidal thickness in patients with diabetic retinopathy and diabetic macular oedema. *Eye (Lond)*. 2016;30:1568–1572.
7. Hansen MH, Munch IC, Li XQ, et al. Visual acuity and amblyopia prevalence in 11- to 12-year-old Danish children from the Copenhagen Child Cohort 2000. *Acta Ophthalmol*. 2019;97:29–35.
8. Chen G, Tzekov R, Li W, Jiang F, Mao S, Tong Y. Subfoveal choroidal thickness in central serous chorioretinopathy: a meta-analysis. *PLoS One*. 2017;12:e0169152.
9. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2008;146:496–500.
10. Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. *Invest Ophthalmol Vis Sci*. 2010;51:2173–2176.
11. Kim M, Kim SS, Koh HJ, Lee SC. Choroidal thickness, age, and refractive error in healthy Korean subjects. *Optom Vis Sci*. 2014;91:491–496.
12. Wei WB, Xu L, Jonas JB, et al. Subfoveal choroidal thickness: the Beijing Eye Study. *Ophthalmology*. 2013;120:175–180.
13. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. *Am J Ophthalmol*. 2009;147:811–815.
14. Bidaut-Garnier M, Schwartz C, Puyraveau M, Montard M, Delbosc B, Saleh M. Choroidal thickness measurement in children using optical coherence tomography. *Retina*. 2014;34:768–774.
15. Read SA, Collins MJ, Vincent SJ, Alonso-Caneiro D. Choroidal thickness in childhood. *Invest Ophthalmol Vis Sci*. 2013;54:3586–3593.
16. Mapelli C, Dell'Arti L, Barteselli G, et al. Choroidal volume variations during childhood. *Invest Ophthalmol Vis Sci*. 2013;54:6841–6845.
17. Park KA, Oh SY. Choroidal thickness in healthy children. *Retina*. 2013;33:1971–1976.
18. He X, Jin P, Zou H, et al. Choroidal thickness in healthy Chinese children aged 6 to 12: the Shanghai Children Eye Study. *Retina*. 2017;37:368–375.
19. Zhu D, Wang Y, Zheng YF, et al. Choroidal thickness in school children: the Gobi Desert Children Eye Study. *PLoS One*. 2017;12:e0179579.
20. Xiong S, He X, Deng J, et al. Choroidal thickness in 3001 Chinese children aged 6 to 19 years using swept-source OCT. *Sci Repair*. 2017;7:45059.
21. Read SA, Alonso-Caneiro D, Vincent SJ, Collins MJ. Longitudinal changes in choroidal thickness and eye growth in childhood. *Invest Ophthalmol Vis Sci*. 2015;56:3103–3112.
22. Jin P, Zou H, Xu X, et al. Longitudinal changes in choroidal and retinal thicknesses in children with myopic shift. *Retina*. 2019;39:1091–1099.
23. Ohsugi E, Mitamura Y, Shinomiya K, et al. Changes in choroidal thickness in healthy pediatric individuals: a longitudinal study. *Int J Ophthalmol*. 2018;11:1179–1184.
24. Li XQ, Munkholm A, Larsen M, Munch IC; Copenhagen Child Cohort Study Group. Choroidal thickness in relation to birth parameters in 11- to 12-year-old children: the Copenhagen Child Cohort 2000 Eye Study. *Invest Ophthalmol Vis Sci*. 2015;56:617–624.

25. Li XQ, Jeppesen P, Larsen M, Munch IC. Subfoveal choroidal thickness in 1323 children aged 11 to 12 years and association with puberty: the Copenhagen Child Cohort 2000 Eye Study. *Invest Ophthalmol Vis Sci*. 2014;55:550–555.
26. Skovgaard AM, Olsen EM, Houmann T, et al. The Copenhagen County child cohort: design of a longitudinal study of child mental health. *Scand J Public Health*. 2005;33:197–202.
27. Olsen EM, Skovgaard AM, Weile B, Jorgensen T. Risk factors for failure to thrive in infancy depend on the anthropometric definitions used: the Copenhagen County Child Cohort. *Paediatr Perinat Epidemiol*. 2007;21:418–431.
28. Munkholm A, Olsen EM, Rask CU, et al. Early predictors of eating problems in preadolescence-a prospective birth cohort study. *J Adolesc Health*. 2016;58:533–542.
29. Choong YF, Chen AH, Goh PP. A comparison of autorefraction and subjective refraction with and without cycloplegia in primary school children. *Am J Ophthalmol*. 2006;142:68–74.
30. Jan C, Congdon N, Zhou W, Ross B, Wang N, Liang Y. The value of cycloplegia in optometric refraction of adults in a population study. *Acta Ophthalmol*. 2019;97:e484–e486.
31. Funarunart P, Tengtrisorn S, Sangsupawanich P, Siangyai P. Accuracy of noncycloplegic refraction in primary school children in southern Thailand. *J Med Assoc Thai*. 2009;92:806–811.
32. Hashemi H, Khabazkhoob M, Asharlous A, et al. Cycloplegic autorefraction versus subjective refraction: the Tehran Eye Study. *Br J Ophthalmol*. 2016;100:1122–1127.