



Subfoveal choroidal thickness at age 9 years in relation to clinical and perinatal characteristics in the population-based Generation R Study

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ABSTRACT.

Purpose: To assess the association between clinical and perinatal characteristics and subfoveal choroidal thickness in 9-year-old children.

Methods: The study included data from the population-based Generation R cohort, whose participants underwent cycloplegic refractometry, ocular biometry, height, weight and subfoveal choroidal thickness measurements using a swept-source optical coherence tomography (SS-OCT) instrument. Birth parameters were obtained using medical records. Statistical analyses were performed using multivariate regression models adjusted for age, ethnicity and sex.

Results: A total of 1018 children (52.5% girls, 47.5% boys) with a mean age of 9.9 ± 0.3 years and a mean cycloplegic spherical equivalent refraction of 0.80 ± 1.1 D in boys and 0.81 ± 1.4 in girls were eligible for analysis. The subfoveal choroid was $17 \mu\text{m}$ thicker in girls ($298 \pm 60.6 \mu\text{m}$) than in boys ($281 \pm 55.0 \mu\text{m}$; $p < 0.001$), a difference of $9.1 \mu\text{m}$ persisting after adjustment for age, ethnicity and axial length ($p = 0.017$). Subfoveal choroidal thickness decreased with increasing ocular axial length ($-16.2 \mu\text{m}/\text{mm}$, 95% CI -21.2 to -12.4 , $p < 0.001$) and with increasing myopic refraction ($-10.0 \mu\text{m}/\text{D}$, 95% CI 6.8 – 13.1 ; $p < 0.001$, adjusted for age, ethnicity, axial length and sex) while it increased with increasing body height ($1.3 \mu\text{m}/\text{cm}$, 95% CI 0.8 to 1.9 , $p < 0.001$). Additionally, choroidal thickness increased with increasing birthweight ($13.0 \mu\text{m}/\text{kg}$; 95% CI 0.006 – 0.020 ; $p < 0.001$) and increasing size for gestational age ($8.2 \mu\text{m}/\text{kg}$; 95% CI 4.6 – 11.8 ; $p < 0.001$). Smoking up until the time that pregnancy became known was associated with a thinner choroid ($p = 0.016$). There was no detectable effect of alcohol consumption. The distributions of axial length, refraction and choroidal thickness were narrower than in older populations.

Conclusion: The subfoveal choroid was thicker in girls than in boys, and higher body height, higher birthweight and larger size for gestational age were associated with a thicker subfoveal choroid. The implications of these findings for myopia development need further evaluation in longitudinal studies.

Key words: children – choroidal thickness – optical coherence tomography – population study

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Introduction

Myopia or short-sightedness affects more than 50% of the population in several eastern Asian countries such as Japan and Singapore (Fredrick 2002; Resnikoff et al. 2008). Myopia is a failure of emmetropization, the process that balances the refractive components of the eye with the axial length of the eye to place the focus of distant objects on the retina without accommodation (Nickla & Wallman 2010). Axial length is closely related to both the spherical equivalent refraction of the eye, the thickness of the choroid and the thickness of the sclera. The choroid is suspected of playing a mediating role in the signalling chain that begins with the registration of the quality of the image cast upon the retina and ends with a change of the position of the retina effected by a change in thickness and rigidity of the sclera and the choroid (Goldenberg et al. 2012; Zhu et al. 2005; Read et al. 2013a,b). With the introduction of optical coherence tomography, anatomical characteristics of the choroid have become amenable to objective assessment. The present report describes associations of choroidal thickness with current and past ocular and systemic characteristics in a cross-sectional study.

Methods

Study design and participants

This study was embedded in the Generation R Study, a population-based prospective cohort study of pregnant women and their children in Rotterdam, the Netherlands. The complete methodology has been described elsewhere (Kooijman et al. 2016). Briefly, a total of 9778 pregnant women were included in the study, and children were born between April 2002 and January 2006. The children were invited at age 9 years for examination by trained nurses at the research centre. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20), and written informed consent was obtained from all participants. The research was conducted according to the Declaration of Helsinki.

Procedures

Study recruitment was based on inviting pregnant women who attended public health care clinics within a given geographic region during a specific period. A total of 1422 children of the population-based Generation R birth cohort from Rotterdam were eligible for examination between 1 June 2013 and 1 October 2014 using a swept-source optical coherence tomography instrument (SS-OCT; DRI-OCT-1, Topcon Corp., Tokyo, Japan) for imaging of the posterior segment of the eye. The methods of choroidal thickness measurement and data analysis were very similar to those used in the Copenhagen Child Cohort 2000 (CCC2000) Eye Study (Li et al. 2014a,b), with the exception that Generation R used cycloplegia and swept-source optical coherence tomography for imaging, whereas the CCC2000 used noncycloplegic refraction and spectral-domain optical coherence tomography. Scans were acquired by study nurses and other trained staff, who were instructed to reject scans of poor quality and to continue until optimum quality had been achieved in a given patient. All scans were manually segmented and subfoveal choroidal thickness measured by the same person (KZBK) who also rejected scans where the boundaries of the subfoveal choroid

could not be reliably identified. Subfoveal choroidal thickness was measured on seven-line horizontal transfoveal B scans, using the instrument manufacturer's proprietary software (3DOCT-2000, version 4.30.003.02, Tokyo, Japan). Additional scans available for the grader's visual assessment of the choriocleral boundary included a fovea-centred array of 128 B scans each made up of 512 A scans covering an area of 12.0 mm × 9.0 mm. The foveal centre was assumed to be found on the scan line with the deepest foveal depression and the most prominent bottom reflex (Fig. 1). Choroidal thickness was measured as the distance between Bruch's membrane and the inner surface of the choriocleral border, both determined by a trained operator (KZBK), who manually adjusted a software caliper feature that was precalibrated by the manufacturer. Intragrader repeatability was measured as the intraclass correlation coefficient (ICC) and found to be 0.983.

Objective refraction was measured using a hand-held automated refractometer (Retinomax-3, Right Mfg. Co., Ltd., Tokyo, Japan). Pupils were dilated using cyclopentolate 1% eye drops, two drops per eye as a standard and three in eyes with brown irides. Spherical equivalent refraction measurements and OCT measurements were made at least 30 min later. The pupil diameter was ≥6 mm at the time of the measurement. SE was calculated as the average spherical correction + half of the cylinder value. Only scans from right eyes were analysed, to avoid having data sets where some

parameters are the same for both eyes (age, weight, height etc.), whereas others are eye-specific (refraction, axial length), yet linked by identical genetics, etc. Weight was measured in lightweight clothes and without shoes using a mechanical scale. Height was measured in the standing position using a Harpenden stadiometer (Holtain Limited, Wales, UK). Body mass index (BMI) was calculated using the formula $BMI = \text{weight (kg)} / (\text{length (m)})^2$. Birth parameters were obtained from medical records (Kooijman et al. 2016). Gestational age-adjusted standard deviation birthweight scores were based on reference charts from a large North European birth cohort (Niklasson et al. 1991).

Optical coherence tomography was made in 1422 children. Exclusion criteria included missing OCT scans and scans of poor quality ($n = 333$), missing axial length measurement ($n = 3$), missing ethnicity information ($n = 29$), missing gestational age ($n = 5$), missing birthweight ($n = 2$) and being a twin ($n = 32$). This led to 404 children being excluded from the analysis. Only right eyes were included. Cycloplegic spherical equivalent refraction was available in 778 children.

Statistical analysis

Demographic data were presented as means and standard deviations for continuous data. Comparisons between sexes were made using Student's two-tailed *t*-test. One-way ANOVA was used to compare demographic characteristics between subgroups. The associations between subfoveal choroidal

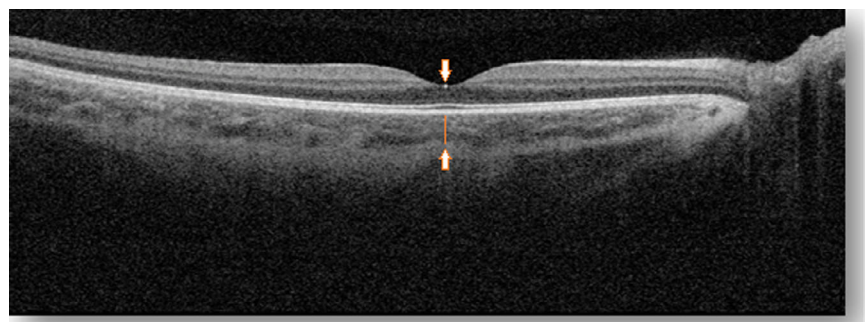


Fig. 1. Horizontal transfoveal optical coherence tomography scan from the right eye of a healthy study participant. The centre of the fovea was identified as the lowest point of the foveal depression (arrow pointing down). Subfoveal choroidal thickness (red line) was measured as the distance between Bruch's membrane and the inner surface of the choriocleral border (above arrow pointing up). When irregular scans were found, such as a sloping retina, the distance was measured at a right angle to Bruch's membrane.

thickness and relevant parameters were assessed using a general linear model. Homogeneity of variance of subfoveal choroidal thickness was assessed using Levene's test. Intragrader repeatability was evaluated by calculating the intra-class correlation coefficient using mixed models between repeated measurements of the horizontal choroidal scan in 130 randomly chosen children. Multivariate regression analysis was performed including parameters that were significantly associated with subfoveal choroidal thickness in univariate analyses and, invariably, parameters that are considered obligatory (age, ethnicity, sex). Because birthweight, gestational age and size for gestational age are highly correlated, adjustment for each of these parameters was not applied in one and the same model. The level of statistical significance was set to $p \leq 0.05$, and effect estimates are presented with 95% confidence intervals (95% CI). Statistical analyses were performed using the IBM-SPSS statistics software package version 21.0 (IBM-SPSS Inc., Chicago, IL, USA).

Results

This cross-sectional study included 1018 children (52.5% girls, 47.5% boys; Fig. 2) with a mean age of 9.9 ± 0.3 years and a mean cycloplegic spherical equivalent refraction of 0.80 ± 1.1 D in boys and 0.81 ± 1.4 in girls ($p = 0.85$; Table 1). Girls had a shorter mean axial length than boys (22.8 ± 0.8 mm versus 23.4 ± 0.8 ; $p < 0.001$), shallower anterior chambers (3.57 ± 0.2 mm versus 3.65 ± 0.3 ; $p < 0.001$) and steeper corneal radii of curvature (7.71 ± 0.2 versus 7.85 ± 0.3 ; $p < 0.001$). The subfoveal choroid was $17 \mu\text{m}$ thicker in girls ($298 \pm 60.6 \mu\text{m}$; range 136–485 μm) than in boys ($281 \pm 55.0 \mu\text{m}$; range 130–463 μm ; $p < 0.001$; Table 1), with a difference of $9.1 \mu\text{m}$ persisting after adjustment for age, ethnicity and axial length ($p = 0.017$; Table 2).

Subfoveal choroidal thickness decreased with increasing ocular axial length ($-16.2 \mu\text{m}/\text{mm}$, 95% CI -21.2 to -12.4 , $p < 0.001$; Table 2; Fig. 2) and with increasing myopic refraction ($10.0 \mu\text{m}/\text{D}$; 95% CI 6.8–13.1; $p < 0.001$, adjusted for age, ethnicity, axial length and sex; Table 2) while it increased with increasing body height ($1.3 \mu\text{m}/\text{cm}$ 95% CI 0.8–1.9,

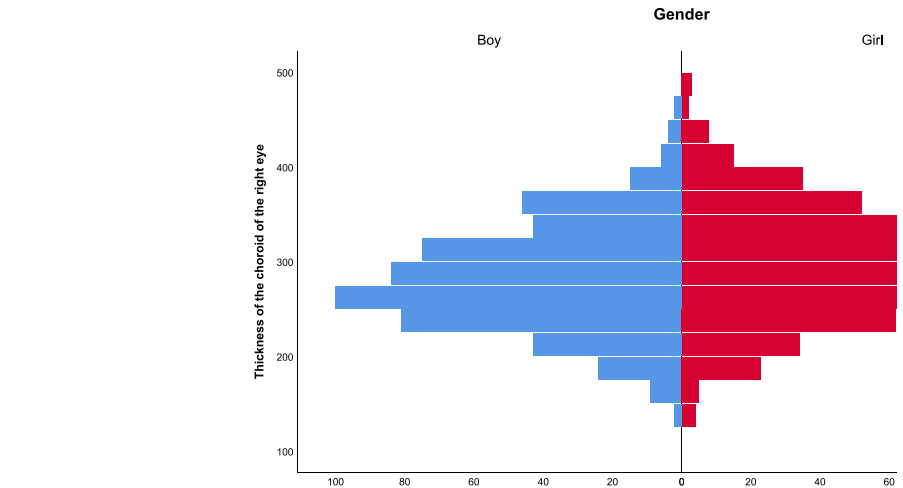


Fig. 2. The distribution of the choroidal thickness in girls (blue) and boys (green).

Table 1. Demographic and clinical characteristics of 1018 study participants from Generation R

Parameter	Boys, $n = 484$ (47.5%)	Girls, $n = 534$ (52.5%)	p^*
European/non-European, n , (%)	354/130 (73/27)	384/150 (72/28)	
Age, y	9.9 (0.3)	9.8 (0.3)	0.02
Refractive error, D	0.80 (1.1)	0.81 (1.4)	0.85
Axial length, mm	23.4 (0.8)	22.8 (0.8)	<0.001
Anterior chamber, mm	3.65 (0.3)	3.57 (0.2)	<0.001
Corneal radius of curvature, mm	7.85 (0.3)	7.71 (0.2)	<0.001
Height, cm	142.6 (6.5)	141.8 (6.5)	0.05
Weight, kg	35.7 (6.6)	36.1 (7.9)	0.44
Body mass index, kg/m^2	17.50 (2.5)	17.84 (3.0)	0.05
Subfoveal choroidal thickness, μm	281 (55.0)	298 (60.6)	<0.001
Birthweight, g	3535 (520)	3392 (528)	<0.001
Gestational age, weeks	40 (1.6)	40 (1.6)	0.35
Size for gestational age [†]	-0.01 (1.0)	-0.02 (1.0)	0.93

Values are mean and standard deviation (SD).

D = dioptres, y = years.

* Paired t -test.

[†] Index of birthweight to birth length normalized for sex and gestational age in newborn infants.

$p < 0.001$). Additionally, choroidal thickness increased with increasing birthweight ($13.0 \mu\text{m}/\text{kg}$; 95% CI 0.006–0.020; $p < 0.001$) and increasing size for gestational age ($8.2 \mu\text{m}/\text{kg}$; 95% CI 4.6–11.8; $p < 0.001$; confirmed in analysis including gestational age, size for gestational age and birthweight at the same time, Table 3).

Information about maternal smoking habits during pregnancy collected using a questionnaire was available for 885 children and alcohol consumption data during pregnancy for 784 children (Table 4). Children of mothers who smoked up until the time that the pregnancy became known had a thinner choroid than children from mothers who did not smoke during pregnancy ($p = 0.008$); the association persisted after adjusting for age, sex, axial length,

ethnicity and height ($p = 0.016$; Table 4). There was no detectable association between subfoveal choroidal thickness and alcohol consumption during pregnancy (Table 4).

Discussion

In this population-based child cohort of 9-year-old children, the subfoveal choroid was $17 \mu\text{m}$ thicker in girls than in boys. Additionally, choroidal thickness increased with increasing birthweight and size for gestational age and higher body height was associated with a thicker subfoveal choroid in both girls and boys.

The strong associations between axial length, refractive error and choroidal thickness found in previous studies of adults and older children were also

Table 2. Associations with subfoveal choroidal thickness in Generation R children

Parameter	Crude data			Adjusted age, ethnicity axial length and sex		
	Coefficient (CI ₉₅)	p	R ²	Coefficient (CI ₉₅)	p	R ²
Age, $\mu\text{m}/\text{y}$	11.1 (−2.1 to 24.3)	0.10	0.002	13.0 (−1.0 to 23.6)	0.05	0.070
European/non-European	−7.1 (−15.3 to 1.0)	0.09	0.003	−3.8 (−10.6 to 4.9)	0.35	0.070
Sex, girls versus boys, μm	16.8 (9.6 to 24.0)	<0.001	0.020	9.1 (1.5 to 16.1)	0.017	0.070
Axial length, $\mu\text{m}/\text{mm}$	−18.1 (−22.3 to −13.8)	<0.001	0.064	−16.2 (−21.2 to −12.4)	<0.001	0.070
Anterior chamber, $\mu\text{m}/\text{mm}$	−8.3 (−23.1 to 6.5)	0.27	0.001	17.7 (1.9 to 33.6)	0.03	0.084
Corneal Radius of curvature, $\mu\text{m}/\text{mm}$	−22.2 (−36.0 to −8.4)	<0.001	0.010	19.5(2.7 to 36.2)	0.02	0.078
Refractive error, $\mu\text{m}/\text{D}$	10.0 (6.8 to 13.2)	<0.001	0.045	10.0 (6.8 to 13.1)	<0.001	0.070
Body mass index, μm	−0.5 (−1.8 to 0.8)	0.44	0.001	−0.3 (−1.6 to 1.0)	0.66	0.07
Weight, $\mu\text{m}/\text{kg}$	0.18 (−0.3 to 0.7)	0.49	<0.001	0.4 (−0.1 to 0.9)	0.10	0.076
Height, $\mu\text{m}/10\text{ cm}$	0.8 (0.3 to 1.4)	0.003	0.009	1.3 (0.8 to 1.9)	<0.001	0.092
Birthweight, $\mu\text{m}/\text{kg}$	6.0 (0 to 13.0)	0.07	0.003	13.0 (6.0 to 20.0)	<0.001	0.086
Gestational age, $\mu\text{m}/\text{weeks}$	0.7 (−1.6 to 3.0)	0.54	<0.001	1.1 (−1.2 to 3.3)	0.35	0.074
Size for gestational age [†]	5.7 (2.1 to 9.4)	0.002	0.009	8.2 (4.6 to 11.8)	<0.0001	0.091

Univariate regression analysis (left) of choroidal thickness in relation to single descriptive variables and multivariate regression analysis (right) of same descriptive parameter, but adjusted for age, ethnicity axial length and sex.

[†] Index of birthweight to birth length normalized for sex and gestational age in newborn infants.

Table 3. Subfoveal choroidal thickness in relation to birth parameters in Generation R children

Crude data	Age and sex adjusted		Multivariate adjustment	
	Estimate (CI ₉₅)	p	Estimate (CI ₉₅)	p
Birthweight, kg	0.009 (0.002 to 0.016)	0.010	0.01 (0.003 to 0.017)	0.007
Gestational age, weeks	1.0 (−1.3 to 3.2)	0.395	0.7 (−1.5 to 2.9)	0.547
Size for gestational age, SDS	5.8 (2.2 to 9.4)	0.002	6.5 (2.8 to 10.2)	0.001

Multivariate adjustment included age, sex, ethnicity, axial length and height.

present in the Generation R cohort (Zhu et al. 2005; Niklasson et al. 1991). Thus, increasing axial length and more myopic refraction was associated with a thinner subfoveal choroid. The association between refraction and choroidal thickness persisted after inclusion of axial length in the analysis, despite the close association between refraction and axial length.

The shift in choroidal thickness of −16.2 μm per mm increase in axial length in 9-year-old children was considerably smaller than the −28.1 μm per mm found in 11- to 12-year-old children

in the CCC2000 Eye Study (Li et al. 2014a,b) and far lower than the −58.2 μm per mm observed in 20- to 33-year-old adults (Li et al. 2011). Nevertheless, this cross-study comparison may be seen as evidence that the steepness of the relation increases as the ocular length distribution expands when children grow older. This phenomenon may be important for myopia risk prediction, and it therefore needs further consideration in prospective studies. It should be noted that there may be a systematic offset between the present study's use of cycloplegia and swept-source optical

coherence tomography (SS-OCT) instead of the CCC2000's use of spectral-domain optical coherence tomography (SD-OCT) without cycloplegia. The SS-OCT instrument been reported to find an approximately 20- μm -thinner choroid than the SD-OCT instrument (Philip et al. 2016). Cycloplegia has been reported to increase choroidal thickness (Öner et al.).

In adults, men have a thicker choroid than women (Zhu et al. 2005; Li et al. 2014a,b; Zeng et al. 2012; Gupta et al. 2015). In the present study of children aged 9 years, girls had thicker choroids than boys. In the CCC2000 Eye Study of children aged 11–12 years, girls who had entered puberty had thicker choroids than boys and less developed girls. This may suggest a potential effect of sex or growth hormones on the development of the choroid (Liu et al. 2000). This is supported by animal studies which have reported that insulin-like growth factor 1 (IGF-1) promotes both

Table 4. Subfoveal choroidal thickness in relation to maternal smoking and alcohol consumption during pregnancy.

Mean choroidal thickness (μm)	Age and sex adjusted		Multivariate adjustment	
	Estimate (CI ₉₅)	p	Estimate (CI ₉₅)	p
Maternal smoking during pregnancy, <i>n</i> = 885				
Smoked until pregnancy was known, <i>n</i> = 73	274 (63)		−19 (−33 to −5) μm	0.008
Never smoked during pregnancy, <i>n</i> = 680	292 (59)		Reference	
Continued smoking in pregnancy, <i>n</i> = 132	284 (53)		−9 (−19 to 2) μm	0.120
Maternal alcohol during pregnancy, <i>n</i> = 784				
Alcohol until pregnancy was known, <i>n</i> = 98	286 (61)		−1 (−13 to 13) μm	0.994
Never alcohol in pregnancy, <i>n</i> = 307	287 (56)		Reference	
Alcohol continued in pregnancy, <i>n</i> = 379	291 (60)		−7 (−3 to 14) μm	0.210

Multivariate adjustment, adjusted for age, sex, axial length, ethnicity, height and birthweight.

elongation of the eye and thickening of the choroid (Penha et al. 2011; Zhu & Wallman 2009).

Previous studies have found a correlation between growth spurt, pubertal development and myopia, indicating that myopic children and young adults were more likely to be taller, heavier and more physically mature compared to age-matched controls (Yip et al. 2012). However, others found little or no effect of height or growth spurt (Northstone et al. 2013).

Subfoveal choroidal thickness increased with increasing birthweight and size for gestational age, in agreement with the findings of the CCC2000 Eye Study, thus supporting the notion that intrauterine growth conditions have lasting effects on choroidal thickness.

A link with myopia was suggested by the British 1958 cohort which reported that adult myopia was associated with low birthweight for gestational age and maternal smoking in early pregnancy (Rahi et al. 2011). According to an analysis of the associations of active and passive smoking in the Generation R study (Jaddoe et al. 2008), there was a significant association of active maternal smoking with low birthweight and preterm birth. Cessation of active smoking after pregnancy had been confirmed was associated with a higher birthweight compared with continued smoking.

An analysis of the associations of smoking and choroidal thickness comparing smoking and nonsmoking mothers found that maternal smoking until pregnancy had been confirmed was associated with a thinner choroid, but there was no association between smoking throughout pregnancy and choroidal thickness. This paradox suggests that the issue should be studied in a meta-analysis with larger power than the present study.

The strengths of the present study include the population-based recruitment and data collection from foetal life onwards. This study is limited by occasional poor definition of the chorioscleral border on the optical coherence tomography images (Gupta et al. 2015) which led to a relatively high number of disqualified images. Nevertheless, the intraclass correlation coefficient for renewed assessment of

choroidal thickness was high, indicating uniformity of the scan analysis process.

In conclusion, this study found, in a younger group of children than previously studied, that subfoveal choroidal thickness increased with increasing birthweight and with increasing size for gestational age. We also found a thinner choroid at the age of 9 years than in a comparable study of 11- to 12-year-old children and a narrower distribution of axial lengths. Future follow-up of the cohort may possibly reveal the extent to which these anatomical effects have an impact on the development of refraction.

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