Macular thickness assessed with spectral domain OCT in a population-based study of children: normative data, repeatability and reproducibility and comparison with time domain OCT

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ABSTRACT.
Purpose: **To collect data on macular thickness assessed with Cirrus OCT in healthy children in a population-based study, to examine the repeatability and reproducibility, and to compare the values with Stratus OCT.**
Methods: **Fifty-eight 6- to 15-year-old children, born at term, were examined. Best-corrected visual acuity and refraction were assessed. One examiner performed three OCT assessments, and the repeatability was calculated. Thereafter, a second examiner repeated the examinations to calculate the reproducibility. One eye was randomized to be included in the normal material. Finally, the second examiner assessed the macular thickness with the Stratus OCT.**
Results: **The mean value (±SD) of central macular thickness was 255 ± 17 μm, and the total macular volume was 10.3 ± 0.5 mm^3. No correlations were found between macular thickness and age, gender or refraction. The coefficients of variance (CoVs) for both repeatability and reproducibility were <1.21%, and the intraclass correlations (ICCs) were over 0.86. The Cirrus OCT showed a 29% thicker central macular thickness than the Stratus OCT.**
Conclusion: **Normal values for macular thickness assessed with Cirrus OCT in healthy full-term children in a population-based study were reported. The assessments showed high repeatability and reproducibility. The values of Cirrus and Stratus OCT differed and the techniques were not interchangeable.**

Key words: children – normal values – optical coherence tomography – repeatability – reproducibility

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Introduction

Optical coherence tomography (OCT) was first used in a human eye in 1995 (Hee et al. 1995). Since its introduction, the technique has evolved rapidly and is nowadays routinely used in ophthalmological clinical practice. The first version, the time domain system (TD-OCT), has a slow mechanical scan speed and builds up two-dimensional images of the retina. The later generation of OCT, the spectral domain technology (SD-OCT), gives three-dimensional images, has a faster speed scan, and a higher axial resolution. OCT has been used to demonstrate morphological changes in the retina, which are sometimes subtle and can be missed with traditional ophthalmoscopy. It also makes possible quantitative measurements of retinal thickness, including the retinal nerve fibre layer thickness. This non-invasive and fast technology has been found to be a useful tool in the investigation of children with different macular pathologies (Eriksson et al. 2004; Holmström et al. 2010), and, when monitoring OCT abnormalities, knowledge of normal values of retinal thickness in children is of great importance. As the OCT software does not provide such data, studies on normal children are important. Several studies on healthy children regarding Stratus TD-OCT have previously been published (Huynh et al. 2006; Eriksson et al. 2009), revealing good repeatability and reproducibility (Wang et al. 2007; Eriksson et al. 2009). Studies on adults, however, have shown that measurements with the older TD-OCT are not interchangeable with measurements assessed with the newer SD-OCT (Menke et al. 2009; Bentaleb-Machkour et al. 2012). Therefore, there is a need to build a new database of normal values for children using SD-OCT.

The primary aim of this study was to collect data of macular thickness and volume, assessed with Cirrus SD-OCT, in a population-based cohort of full-term healthy children. The second aim was to examine the intra- and interobserver variability in the Cirrus OCT assessments of the macula. The third and final aim was to compare the values of macular thickness in children assessed with both Stratus (TD) and Cirrus (SD) OCT.

Materials and Methods

The study group encompassed children aged between 6 and 15 years, born at term (≥37 weeks of gestation), and with normal birthweights (≥2500 grams). Children living in Uppsala County were randomly chosen from the birth register with the help of the Swedish National Board of Health and Welfare. The parents of the participating children had to provide written consent. Ethical approval for the study was obtained from the Regional Ethical Board of Uppsala, Sweden.

Examinations were performed from September 2012 through December 2013 at the Department of Ophthalmology, University Hospital, Uppsala, Sweden. First, a medical and ophthalmologic history for each child was recorded. The inclusion criteria were as follows: normal health, without any eye disease; a best-corrected visual acuity of at least 0.1 logMAR; a spherical equivalent of between +3.0 and −3.0; and astigmatism of <2.0 dioptres (D).

All children underwent monocular visual acuity (VA) testing of both eyes. Linear logMAR charts were routinely used. If the child was not able to read the letters, an HVOT chart read at 3 metres was used (Hedin & Olsson 1984). Autorefraction in cycloplegia was performed after dilating the pupils with a mixture of phenylephrine 1.5% and cyclopentolate 0.85%, and a fundus examination was performed.

The macular thickness was measured with spectral domain Cirrus, version 6.0.2.81 and Stratus OCT 3, version 4.0.1 (both Carl Zeiss Medite, Inc., Dublin, CA, USA). The measurements with the Cirrus OCT were obtained using the macular cube 512 × 128 protocol. The fast macular map protocol was used with the Stratus OCT. Both devices use an interferometric technique and near-infrared light. Stratus uses a time domain system (TD-OCT) with a mechanical reference arm that measures the retina in a radial pattern over the macula. In the fast protocol, 768 (128 × 6) A-scans build up a two-dimensional cross-sectional B-scan. Cirrus OCT has a Fourier frequency domain system (SD-OCT) and measures the interferometric signal as a function of optical frequencies. This new technique provides retinal images approximately 50 times faster, and with a higher resolution than the time domain system. Three-dimensional images can also be acquired with SD-OCT.

The OCT scans were performed on each child, through dilated pupils by two examiners. First, three examinations of the macula were performed by one of the authors (A.M.) using Cirrus OCT. These assessments were then repeated by another experienced examiner (E.N.). Finally, three measurements were performed with the Stratus OCT (by E.N.). The macular thickness data are presented in the nine ETDRS areas with both techniques (A1 = central, A2 = inner superior, A3 = inner temporal, A4 = inner inferior, A5 = inner nasal, A6 = outer superior, A7 = outer temporal, A8 = outer inferior, A9 = outer nasal area) (Early Treatment Diabetic Retinopathy Study Research Group 1985). The central subfield (A1) measures 1 mm in diameter, the inner (A2–A5) and outer (A6–A9), 3 and 6 mm, respectively. In addition, the total macular volume (CV) and macular cube average thickness (CAT) for Cirrus OCT were noted. The inclusion criteria for the scans were as follows: a signal strength of 7 or more, fovea as a central point, no artefacts, no great vertical or horizontal eye movement, no great eye movement along the scanning beam, and no blink over the measured area. Regarding the blinks, only the affected area was removed. Both eyes were examined and recorded.

Statistical methods

Statistics were analysed using SPSS version 21 (IBM Corp., Armonk, NY, USA). Two examiners (A.M. and E.N.) performed three measurements on each child. The mean values of the three measurements for each examiner were calculated. Right (RE) and left eyes (LE) were initially analysed separately and were compared with the paired sample t-test. Then, to describe the normal material, one eye of each child was randomly chosen. In two children, one eye (one RE and one LE) was excluded and the other eye was included in the analyses and was therefore not randomized. The descriptive values for right and left eyes and for randomized eyes were based on the assessments of one of the examiners (A.M.). The Kolmogorov–Smirnov test was used for analysing normal distributions. Correlations between the eyes and between randomized eye and age and refraction were performed using the Pearson correlation test. The independent t-test was used for analysing differences between boys and girls in the randomized eye. Regarding the thickness of the inner macular circle, a multivariate regression analysis was performed including age and gender. For comparison of Stratus OCT and Cirrus OCT in both right and left eyes, a paired sample *t*-test was used.

Repeatability (intra-observer variability) was calculated using the three measurements performed by the first examiner (A.M.) in the randomized eye. Reproducibility (interobserver variability) was calculated by comparing the mean values of the randomized eye of the two examiners (A.M., E.N.). The repeatability and reproducibility were expressed as a coefficient of variance (CoV) (the standard deviation, divided by the mean) and an intraclass correlation (ICC). A CoV close to 0 and an ICC close to 1.0 are regarded as perfect. The repeatability was also illustrated by a Bland–Altman plot (Bland & Altman 1986).

Results

Fifty-eight children accepted the invitation to participate in the study. There were 28 girls and 30 boys. The mean age of the children was 10.6 years (SD: 2.9, range 6–15). The distribution of ages is illustrated in Table 1. The mean value of VA in the REs was −0.043 logMAR (SD: 0.09, range −0.2–0.1) and in the LEs −0.047 logMAR (SD: 0.07, range −0.2–0.1). Regarding refraction, the mean spherical equivalents were 0.95 D (SD: 0.63, range - 0.5–2.75) and 0.93 D (SD: 0.71, range 0.75–3.0) in the RE and LE, respectively.

For two children, one eye had to be excluded. The left eye of one boy was excluded due to astigmatism of 2.5 D. For one 6-year-old girl, all measurements of the right eye were excluded due to great movements with the scanning beam.

Due to technical problems with the Stratus OCT, only 14 REs and 11 LEs were examined with this device.

Table 1. Mean values, standard deviations (SD) and ranges of visual acuity, refraction and macular retinal thickness and volume in 58 randomized eyes.

Years (no)	All ages (58)	6–7 (12)	8–9 (8)	10–11 (12)	12–13 (15)	14–15 (11)
Visual acuity (SD)	−0.04 (0.07)	0.02 (0.04)	−0.04 (0.06)	−0.05 (0.09)	−0.11 (0.08)	−0.04 (0.11)
Range	−0.2–0.1	0.0–0.1	−0.1–0.0	−0.2–0.1	−0.2–0.0	−0.2–0.1
Spherical equivalent (SD)	0.91 (0.66)	1.57 (0.67)	1.09 (0.67)	0.78 (0.41)	0.75 (0.57)	0.42 (0.41)
Range	−0.5–3.0	0.8–3.0	0.5–2.5	0.1–1.4	−0.1–2.1	−0.5–1.0
A1 μm (SD)	255 (17)	252 (15)	255 (16)	243 (11)	262 (20)	263 (18)
Range	218–303	218–267	230–275	223–262	227–303	243–293
A2 μm (SD)	330 (16)	325 (15)	330 (16)	323 (13)	336 (16)	335 (18)
Range	299–369	302–347	304–354	307–352	312–367	299–369
A3 μm (SD)	316 (16)	309 (13)	316 (15)	310 (14)	322 (17)	321 (18)
Range	281–353	293–331	293–335	292–346	296–353	281–350
A4 μm (SD)	325 (16)	321 (14)	322 (17)	318 (13)	331 (15)	331 (16)
Range	295–361	304–339	299–351	307–352	309–361	295–357
A5 μm (SD)	330 (17)	324 (16)	332 (18)	322 (14)	336 (18)	336 (19)
Range	300–377	302–344	300–358	308–360	312–370	302–377
A6 μm (SD)	290 (15)	291 (14)	288 (15)	281 (13)	293 (16)	292 (14)
Range	254–319	271–319	266–312	254–299	272–317	259–310
A7 μm (SD)	273 (14)	269 (10)	273 (15)	267 (11)	277 (16)	277 (16)
Range	240–303	258–290	254–299	252–292	253–303	240–295
A8 μm (SD)	277 (14)	278 (10)	279 (18)	271 (12)	279 (14)	281 (15)
Range	245–310	260–289	258–310	255–302	259–309	245–300
A9 μm (SD)	307 (15)	305 (11)	308 (16)	299 (14)	312 (18)	311 (14)
Range	275–344	285–323	288–337	275–384	287–344	283–331
CV mm^3 (SD)	10.3 (0.5)	10.3 (0.4)	10.4 (0.53)	10.1 (0.39)	10.5 (0.51)	10.5 (0.49)
Range	9.3–11.3	9.8–10.7	9.7–11.3	9.5–11.1	9.8–11.23	9.3–11.1
CAT μm (SD)	289 (13)	288 (10)	290 (15)	283 (11)	293 (14)	293 (14)
Range	260–315	273–299	270–315	266–311	274–315	260–312

A1 = central area, A2 = inner superior area, A3 = inner temporal area, A4 = inner inferior area, A5 = inner nasal area, A6 = outer superior area, A7 = outer temporal area, A8 = outer inferior area, A9 = outer nasal area, CV = cube volume, CAT = cube average thickness.

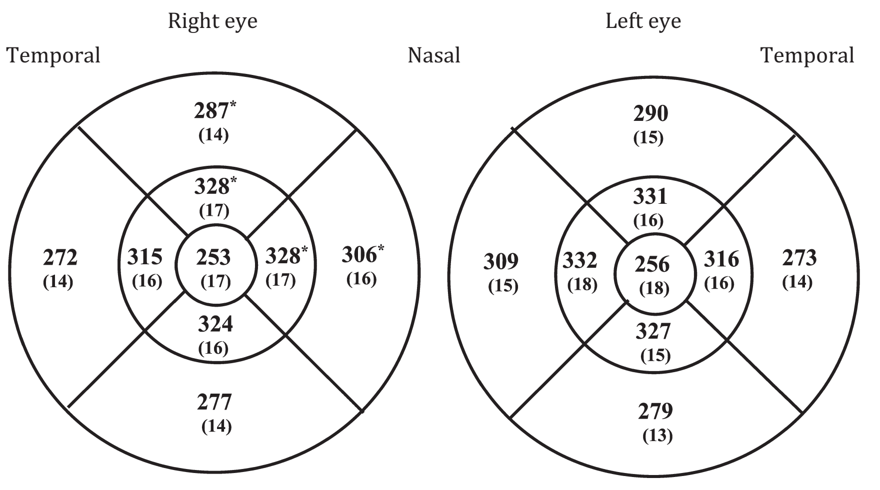

Fig. 1. Mean macular thickness (μm) in right eyes and left eyes in the nine macular areas (A1–A9). *Significant differences from left eyes p < 0.05.

The mean retinal thicknesses of the right and left eyes for Cirrus OCT are shown in Fig. 1. The thickness in each area (A1–9), as well as the CV and CAT, were normally distributed (Kolmogorov–Smirnov test). The values for the right and left eyes were statistically correlated (0.80–0.93), $p < 0.001$, in all areas, with the highest correlation in the central part (A1) (0.93). Although there were small differences between the eyes, there was a statistically interocular difference in some areas (see Fig. 1).

To present the normal material, eyes were randomized and the mean values of Cirrus OCT measurements are presented in Table 1. The central macular thickness was the thinnest of all the areas. The mean value of the inner circle (A2–A5) was 325 μm (SD: 16, range 294–363) and for the outer circle (A6-A9) 287 μm (SD: 14, range 257–316).

There was no statistically significant correlation between the VA or spherical equivalent and the EDTRS areas, inner- and outer circles, CAT or CV.

No statistically significant correlations were found between age and central macular thickness, outer macular circle, CAT or CV. Regarding age and inner macular circle, a significant positive correlation was found ($r = 0.27$, $p = 0.04$). Being male was associated with a greater thickness in all areas, but the differences were not significant, except for the inner macular circle (boys 329 μm [SD13] and girls 321 μm [SD 17], $p = 0.03$). When performing a multivariate analysis including age and gender, the statistical significance did not remain.

The intra-observer measurement variations (repeatability) are illustrated in Table 2A and the Bland–Altman plot in Fig. 2. Table 2B shows the interobserver variability (reproducibility).

Measurements with Stratus revealed a significantly thinner retinal thickness in all ETDRS areas ($p < 0.001$), see Table 3.

Table 2. Repeatability (intra-observer) (A) and reproducibility (interobserver) (B) of Cirrus OCT measurements in 58 randomized eyes, expressed as a coefficient of variance (CoV) with standard deviation (SD) and intraclass correlation (ICC) with confidence interval (CI), lower bound (LB) and upper bound (UB).

Area	CoV (%)	SD (%)	ICC	CI (LB − UB)
(A)				
A1	1.01	0.91	0.968	0.948–0.981
A2	0.84	0.78	0.956	0.931–0.973
A3	0.86	0.87	0.952	0.925–0.970
A4	1.20	2.85	0.953	0.925–0.970
A5	0.74	0.72	0.968	0.950–0.980
A6	1.19	0.90	0.923	0.882–0.953
A7	0.98	0.83	0.949	0.920–0.969
A8	1.15	0.88	0.929	0.890–0.956
A9	0.66	0.59	0.975	0.961–0.985
CV	0.63	0.54	0.968	0.948–0.981
CAT	0.62	0.52	0.970	0.961–0.985
(B)				
A1	0.92	0.78	0.973	0.954–0.984
A2	1.20	0.86	0.916	0.861–0.950
A3	1.05	0.82	0.935	0.892–0.961
A4	1.23	1.49	0.857	0.769–0.914
A5	0.99	0.75	0.948	0.913–0.969
A6	1.37	1.05	0.872	0.791–0.923
A7	1.21	0.92	0.917	0.863–0.951
A8	1.18	1.02	0.904	0.840–0.943
A9	1.12	0.90	0.925	0.875–0.955
CV	0.84	0.70	0.936	0.892–0.963
CAT	0.84	0.68	0.939	0.896–0.964

A1 = central area, A2 = inner superior area, A3 = inner temporal area, A4 = inner inferior area, A5 = inner nasal area, A6 = outer superior area, A7 = outer temporal area, A8 = outer inferior area, A9 = outer nasal area, CV = cube volume, CAT = cube average thickness.

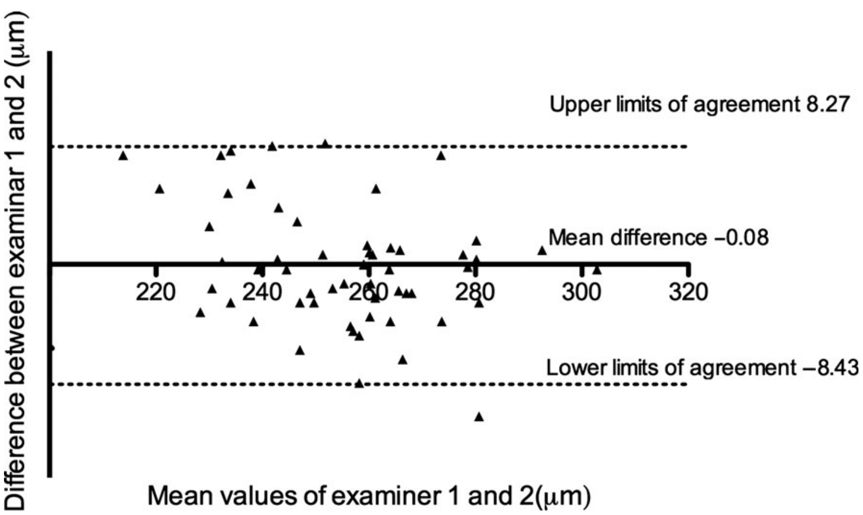

Fig. 2. Repeatability (intra-observer variability) expressed as a Bland–Altman plot.

Discussion

In the present population-based study, we report normative data for macular thickness and volume, assessed with Cirrus OCT in 58 full-term, healthy children aged between 6 and 15 years. The central area was the thinnest, followed by the outer macular circle, whereas the inner macular circle was the thickest. The repeatability (intra-observer) and reproducibility (interobserver) were good, with high intraclass correlations and low coefficients of variance in all macular areas. There were no correlations with age, refraction or sex in this age group. The correlations between right and left eyes were good, and the differences between the eyes were small. In comparison with Stratus OCT, the Cirrus OCT showed an approximately 30% thicker central macula.

Many OCT studies have been performed regarding normal values in children. In most of these studies, TD-OCT was used (Huynh et al. 2006; Eriksson et al. 2009). However, only a few studies of macular thickness using SD-OCT in normal children have been published (see Table 4). In the present study, we used the Cirrus OCT, as in three other studies performed by Altemir et al. (2013), Barrio-Barrio et al. (2013) and, most recently, Al-Haddad et al. (2014a). Altemir et al. assessed the average macular thickness and macular volume using the 200 × 200 volume cube protocol in 6- to 11-year-old children. Like the present study, Barrio-Barrio et al. and Al-Haddad et al. reported on all macular areas (A1–9), together with the average macular thickness and macular volume in 4- to 17-year-old children and 6- to 17-year-old children respectively, using the 512 × 128 protocol. Our results very much resemble theirs (see Table 4). The central area (A1) was the thinnest, and the inner macular circle (A6–9) was the thickest. The nasal areas were thicker than the temporal ones, which probably accords with the normal convergence of the retinal nerve fibres into the optic nerve (Eriksson et al. 2009; Barrio-Barrio et al. 2013).

Boys had slightly thicker maculae than girls in the present study, in accordance with the findings of studies by Barrio-Barrio et al. and Al-Haddad et al., although, after multivariate analyses, they were only statistically significant in the study by Al-Haddad et al. A difference between boys and girls has previously been shown with the older Stratus OCT in children (Huynh et al. 2006), and also between men and women using Cirrus OCT (Liu et al. 2011).

A positive correlation between age and central macular thickness was reported by Barrio-Barrio et al. (2013), as it was by Al-Haddad et al. (2014a) regarding the inner macular circular. After a multivariate analysis, such a correlation could not be found in the present study, although the youngest children (6–7 years old) had relatively thicker central maculae than those in adolescence (14–15 years old) (see Table 1). Our results were in

Table 3. Mean values and standard deviations (SD) of retinal thickness in the nine EDTRS areas, assessed with Cirrus and Stratus OCT, in 14 right and 11 left eyes.

	Right eye Mean values (SD) μm no = 14		Left eye Mean values (SD) μm no = 11	
	Cirrus	Stratus	Cirrus	Stratus
A1	258 (13)	200 (12)	258 (10)	201 (8.1)
A2	328 (17)	283 (13)	330 (17)	282 (12)
A3	316 (18)	269 (14)	314 (16)	267 (13)
A4	325 (17)	280 (14)	324 (18)	280 (15)
A5	330 (16)	280 (12)	330 (18)	279 (13)
A6	288 (16)	247 (14)	290 (18)	249 (14)
A7	271 (17)	233 (14)	271 (17)	229 (14)
A8	278 (18)	243 (16)	276 (17)	242 (15)
A9	306 (17)	264 (15)	306 (17)	264 (15)

SD = standard deviation, no = number, A1 = central area, A2 = inner superior area, A3 = inner temporal area, A4 = inner inferior area, A5 = inner nasal area, A6 = outer superior area, A7 = outer temporal area, A8 = outer inferior area, A9 = outer nasal area.

accordance with a previous study by our group, which examined children of the same age and from the same area of Sweden as in the present study, but using Stratus OCT (Eriksson et al. 2009). The annual increase of central macular thickness has been reported as being rather small (Barrio-Barrio et al. 2013; Al-Haddad et al. 2014a). Consequently, we believe that, in the age span of 6- to 15-year-old children, one does not have to take the age into consideration in clinical practice.

There was no correlation between macular thickness and refraction in the present study, which accords with the studies by Barrio-Barrio et al. (2013) and Al-Haddad et al. (2014a). In all studies, children with high refractive errors were excluded, which could be a bias. High refractive errors might interfere with OCT measurements, because studies in adults have reported a correlation between refraction and macular thickness (Song et al. 2014).

When evaluating monocular macular disease, it is important to know whether there is any difference between normal right and left eyes. We studied the interocular difference regarding macular thickness and found a good correlation between the eyes. Although statistically different in a few areas, the interocular differences were small. The difference in the central area (A1) was 3 μm and, in the inner and outer ring, it was between 1 and 4 μm (Fig. 1). The interocular difference, using Cirrus OCT, has previously been studied in children in another paper by Al-Haddad et al. (2014b), who found even smaller differences between the eyes. In accordance with Al-Haddad et al., we found a significant difference in the nasal areas, but, in contrast to their results in which the inferior areas were different, we found differences in the upper sectors (A2 and A6). Although these were small differences between the eyes, we believe that randomization of one eye to be included in the normal material was a good alternative.

In a previous study, we found good repeatability using TD-OCT (Stratus) in children (Eriksson et al. 2009). Regarding SD-OCT, studies in adults have shown both good repeatability and reproducibility (Garcia-Martin et al. 2011), but to our knowledge, there is only one previous study analysing the intra- and interobserver variability of Cirrus OCT in children, which is Altemir et al. (2013). Regarding the average macular thickness and volume, Altemir et al. found CoVs from 0.82–1.0 and ICCs from 0.940–0.949, which was in accordance with our study. In the present study, we also found good repeatability and reproducibility in all macular areas (A1–9) (Table 2). The low CoVs and high values of ICC with narrow confidence intervals suggest that one could rely on one examination in a clinical situation and also that assessments performed by different examiners are reliable.

In adults, studies have shown higher values of macular thickness using Cirrus OCT than Stratus OCT (Menke et al. 2009; Bentaleb-Machkour et al. 2012). The borders of the measured retinal thickness are different for the

Table 4. Studies of macular thickness using SD-OCT in children.

Author (Year of publication)	Number of participants	Subjects Years*	OCT device	Central macular thickness (μm) Mean ± SD	Average Macular thickness (μm) Mean ± SD	Cube volume (mm^3) Mean ± SD	Inner Circle (μm) Mean	Outer Circle (μm) Mean
Turk et al. (2012)	107	10.46 ± 2.94	Spectralis SD OCT	258.6 ± 17.2	326.4 ± 14.17	0.257 ± 0.011	328.2	341.7
Yanni et al. (2013)	83	5–15	Spectralis SD OCT	271.2 ± 2.0	–	–	336.7	–
Altemir et al. (2013)	100	9.15 ± 1.05	Cirrus OCT	–	282.9 ± 11.83	10.18 ± 0.43	–	–
Barrio-Barrio et al. (2013)	283	9.58 ± 3.12	Cirrus OCT	253.9 ± 19.76	283.6 ± 14.08	10.2 ± 0.49	318.2	285.1
Al-Haddad et al. (2014a)	108	10.7 ± 3.1	Cirrus OCT	249.1 ± 20.2	279.6 ± 12.5	10.1 ± 0.5	317.3	278
Current study (2015)	58	10.6 ± 2.9	Cirrus OCT	255.1 ± 17.4	289.4 ± 13.0	10.3 ± 0.5	325.2	286.6

* Mean ± SD or range.
Spectralis SD OCT (Heidelberg Engineering).
Cirrus OCT (Carl Zeiss Meditec).

two devices. In Stratus OCT, the retinal thickness is defined as the distance between the vitreoretinal interface and the highly reflective band adjacent to the pigment epithelium, which is suspected to be the inner/outer cone segment junction. In Cirrus OCT, the boundary of the outer retina is in the highly reflective pigment epithelium, and therefore values of the retinal thickness become different (Mylonas et al. 2009). To the best of our knowledge, comparisons between Cirrus and Stratus OCTs have not yet been investigated in children. In this study, we could compare Cirrus OCT and Stratus OCT in 14 REs and 11 LEs, and the results were similar to those in adults. Cirrus OCT showed 29% (REs) and 28% (LEs) higher values than Stratus OCT in the central macular area (A1), and between 14 and 18% higher values in the inner and outer macula (A2–9). Thus, also for children, Cirrus and Stratus OCT are not interchangeable.

Conclusion

This population-based study reports normative data for macular thickness assessed with Cirrus OCT in 58 full-term, healthy children, aged between 6 and 15 years. The repeatability (intra-observer) and reproducibility (interobserver) were good. There were no correlations with age, refraction or sex in this age group. In comparison with Stratus OCT, the Cirrus OCT showed an approximately 30% thicker central macula, on average.

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