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Abstract

Background/aim: Previous studies have revealed various subnormal visual functions in prematurely-born children. The present study aimed to determine the retinal macular thickness in prematurely-born children and compare with children born at term.

Methods: The eyes of 65 prematurely-born children aged 5-16 years, were examined with Stratus Optical coherence tomography (OCT) 3, and the results were compared with those of 55 children born at term. The retinal macular thickness in the nine EDTRS macular areas (A1-A9), the foveal minimum and the total macular volume were determined.

Results: The central macular thickness (A1 and foveal minimum) was significantly thicker in the prematurely-born children than in those born at term. There was no correlation between macular thickness and visual acuity or refraction. Children with previous retinopathy of prematurity (ROP) had significantly thicker central maculae than those without it. Prematurely born children without previous ROP had significantly thicker central macula than the control group. Multiple regression analyses showed that gestational age at birth was the only risk factor for a thick central macula.

Conclusion: Prematurely-born children had thicker central maculae than those born at term. Regardless of ROP, the degree of prematurity was the most important risk factor for abnormal foveal development.

Major neurological, pulmonary and ophthalmological dysfunctions are common in prematurely-born children. However, minor sequelae of preterm birth and their effects on daily life of these children as they grow up are less well-known. Visual impairment may occur

secondary to retinopathy of prematurity (ROP) and / or damage of the visual pathways. Although the prevalence of visual impairment is relatively low in high-income countries, population-based follow-up studies of prematurely-born children and adolescents have recently shown that a significant proportion of them have subnormal visual functions affecting visual acuity, contrast sensitivity, visual fields and stereopsis. [1-11] In a 10-year follow-up of children with a birth weight of 1500 grams or less in the Stockholm area of Sweden, the frequency of subnormal visual acuity was significantly higher than in a control group of children born at term. [6] It could not be determined whether the aetiology was cerebral or retinal.

Macular development is a very sophisticated process, including both a centrifugal displacement of inner retinal cells and a centripetal displacement of photoreceptors. [12-14] The development is not completed until about three to four years of life and the fovea is the last structure to become fully developed.[12] It is therefore not surprising that children with a history of various degrees of ROP have foveal abnormalities.[15-20] We hypothesized that preterm birth affects macular development and causes changes in the macular and foveal structures, even in infants without ROP. Recently, we reported on macular thickness with the help of optical coherence tomography (OCT) in full-term children.[20] The aim of the present study was to compare the macular thickness of prematurely-born children with that of full-term children and to determine whether the findings were related to prematurity and ROP.

Materials and Methods

The present study included 68 prematurely-born children with gestational ages (GA) of 32 weeks or less, who had been delivered at Uppsala University Hospital in Sweden between 1993 and 2000. All of them had been included in the routine ROP-screening, starting from the fifth postnatal week and performed every other week or more often, if necessary. The

screening continued until the retina was fully vascularized or in the case of ROP, until it had resolved completely. The criterion for treatment at that time was ROP stage 3 in at least four contiguous clock hours, even in the absence of plus disease. Mild ROP comprised stages 1-2 and severe ROP stages 3-5, which includes the children treated with laser or cryopexy.

The hospital records were used to locate the prematurely-born children and their caregivers and they were both asked by letter to participate in the study.

The control group included 55 children born in Uppsala County, Sweden, who were randomly selected from the birth register of the Swedish National Board of Health and Social Welfare. They were born at term (GA ≥ 37 weeks) with normal birthweights (BW ≥ 2500g). [20] One randomized eye from each child in the control group was used for comparison with the study group.[20]

Best-corrected visual acuity (VA) was assessed monocularly with linear LogMar charts. Cycloplegic retinoscopy was done after dilating the pupil with a mixture of phenylephrine 1.5 % and cyclopentholate 0.85%. The spherical equivalent was calculated. An eye examination, including ophthalmoscopy, was performed. A medical history was taken, including neurological complications defined as intraventricular haemorrhage, cerebal palsy, periventricular leukomalacia and epilepsy.

The macular thickness was measured with Stratus OCT 3, version 4.0.1. The fast macular map protocol was used, consisting of six scans arranged in a radial pattern over the macula with the fovea as a central point. During the scanning procedure, the examiner could observe

the fundus and continuously control fixation. The average retinal thickness is automatically calculated by an algorithm and presented as numeric values for nine ETDRS areas (Figure 1). The total area measured has a diameter of 6 mm and is divided into three concentric regions. The central region is 1 mm in diameter (A1) and the inner and outer circles are divided into four quadrants (A2-A9). The total macular volume and the foveal minimum were also calculated.

Most OCT assessments were performed by one of the authors (UE), and a few by another experienced examiner. Measurements with a signalstrength of at least five were required.

Informed consent was obtained from all caregivers before enrollment. The study was approved by the Ethics Committee of Uppsala University and was conformed to the tenets of the Declaration of Helsinki.

Statistical methods

The Kolmogorov-Smirnov test was used to test for a normal distribution. Prematurely-born and full-term children were compared using the independent t-test and one-way ANOVA for continuous data. As regards area A1 and foveal minimum, we used analyses of covariance, ANCOVA, with the covariates age, gender, VA and spherical equivalent. Pearson's correlation was used for bivariate correlations. In the prematurely-born children, forward stepwise multiple linear regression analyses were done to evaluate how much the variation in the area A1 and foveal minimum could be explained by GA, BW, ROP (yes/no), neurological complications, age at examination, gender, VA and spherical equivalent. Right (RE) and left eyes (LE) were analyzed separately and $p<0.05$ was considered statistically significant.

Results

Sixty-eight prematurely-born children were included in the study. All except one cooperated well in the assessments and two children were excluded due to technical problems. Therefore 65 REs and LEs were included. Of these, 22 REs and LEs had mild ROP and 7 REs and LEs severe ROP, including treated ROP (5 RE, 6 LE) . The values of macular thickness were compared with a control material of 55 eyes in healthy full-term children with normal birth weights.[20] Demographic data of both prematurely-born and full-term children are shown in Table 1. The range of ages was the same in the two groups although the mean age was slightly lower in the prematurely-born children (p=0.02). There was a statistically significant difference between the groups as regards VA (p < 0.001 RE and LE), but not the spherical equivalent. The proportion of boys and girls were similar in the two groups.

Table 1. Descriptive data of the 65 prematurely born children and the 55 children born at term.

	Gender	**Age**	**Gestational age**	**Birth weight**	**Visual acuity** (logMar)		**Spherical equivalent**	
	F/M	(years)	(weeks)	(grams)	Right eyes	Left eyes	Right eyes	Left eyes
Premature	31/34	8.6 (1.8)	28.6 (2.9)	1299 (497)	-0.006(0.08)	0.00(0.1)	1.0 (1.3)	0.9 (1.5)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
		5.0 - 16.0	22 - 32	453 - 2501	-0.1 - 0.3	-0.1 - 0.6	(-3.0)- (+4.75)	(-4.25) - (+5.5)
		Range	Range	Range	Range	Range	Range	Range
Control	28/27	10.1(3.1)			-0.08 (0.08)*		0.6 (0.7)*	
		Mean (SD)	≥37	≥2500	Mean (SD)		Mean (SD)	
		5.0 - 16.0			-0.2 - 0.0*		(-0.5) - (+3.0)*	

		Range			Range	Range

* 55 randomized eyes [20]

F=female, M=male

The mean values of macular thickness (A1-9, respectively) in prematurely-born and full-term children are given in Figure 2. The mean values of "foveal minimum" in the prematurely-born children were 196 (SD 28) μm in RE and 197 (SD 30) μm in LE and the mean values of "total macular volume" were 7.10 (SD 0.42) mm^3 in RE and 7.12 (SD 0.40) mm^3 in LE. The corresponding mean values in the full-term eyes were 166 (SD 15) μm and 7.11 (SD 0.35) mm^3, respectively.[20] All macular areas, foveal minimum and total macular volume were normally distributed in the prematurely-born and full-term children.[20] The central macula was significantly thicker in prematurely-born children than in full-term ones, as regards area A1 and foveal minimum ($p<0.001$ RE and LE, respectively), although the age at examination, gender, VA and spherical equivalent were taken into account. For illustration, see OCT image of one of the thickest maculae in the preterm group in comparison with an image of a child born at term (Figure 3). There was no difference between the groups as regards the inner (A2-A5) or outer (A6-A9) circles or the total macular volume.

Statistically significant differences in the central macula (A1) and foveal minimum were found between children with and without previous ROP, the former having a thicker central macula (A1 $p<0.001$ RE and LE, foveal minimum $p<0.001$ RE and LE). Moreover, the differences were also statistically significant between the children without previous ROP and the full-term children as regards A1 and foveal minimum (A1 $p=0.01$ RE and $p=0.01$ LE, foveal minimum $p=0.001$ RE and $p<0.001$ LE). The children with severe, including treated, ROP had the thickest central macula, but the difference was not statistically significant

compared to those with mild ROP. (Table 2, Figure 4).

Table 2. Central macular thickness (A1 and foveal minimum) in the 65 prematurely born children in relation to stage of ROP and in the 55 children born at term.

	No ROP		**Mild ROP**		**Severe ROP** incl. treated		**Controls**
	n=36		n=22		n=7		n=55*
	Right eyes	Left eyes	Right eyes	Left eyes	Right eyes	Left eyes	
A1 (μm)							
Mean (SD)	218 (20)	186 (24)	228 (17)	231 (19)	250 (32)	252 (34)	204 (19)
Range	181-268	179-271	194-265	195-269	213-310	212-320	162-234
Foveal min. (μm)							
Mean (SD)	187 (22)	186 (24)	199 (25)	205 (26)	230 (36)	233 (39)	166 (15)
Range	155-249	149-256	149-252	149-258	185-297	188-306	130-194

*55 randomized eyes.[20]

The thicknesses of A1-A9, foveal minimum and total macular volume showed no correlation with age at examination, VA or spherical equivalent. Boys had a thicker macula than girls, but the difference was not significant. The findings were similar in the full-term control group.[20]

In the prematurely-born children, low GA and BW (Figure 5) correlated significantly with a thicker central macula (A1) in the univariate analyses, (GA $r = -0.45$ $p<0.001$ RE, $r = -0.43$ $p<0.001$ LE; BW $r = -0.35$ $p = 0.004$ RE, $r = -0.33$ $p = 0.008$ LE). This correlation was also

true of the thickness in foveal minimum (GA r = -0.53 p<0.001 RE, r = -0.51 p<0.001 LE; BW r = -0.44 p<0.001 RE, r = -0.42 p = 0.001 LE). However, in a multiple regression analysis, including GA, BW, ROP (yes/no), neurological complications, age at examination, gender, VA and spherical equivalent, low GA was the only risk factor for a thicker central macula later in childhood (A1 p<0.001 RE and p<0.001 LE; foveal minimum p<0.001 RE and p<0.001 LE).

Discussion

This study presents the findings using OCT of the maculae in 65 prematurely-born children, with and without ROP. The data are compared with those of full-term children, with normal gestational ages and birth weights. [20] The prematurely-born children had thicker central foveas than those born at term. Among the prematurely-born children, the ones with previous ROP had thicker foveas than those without ROP. No correlation between macular thickness and visual acuity or refraction was detected. Gestational age at birth was the only significant risk factor for a thicker central macula in childhood/adolescence in a multiple regression analysis, even when ROP was taken into account.

Three features of the present study should be noted. First, it has a population-based control group of 55 children aged 5 – 16 years who were born at term in Uppsala County, -i.e. the same geographical area as that of the preterm group. [20] Secondly, all prematurely-born children were prospectively screened and, if necessary, treated for ROP in the neonatal period. Thirdly, this study includes more children than previous reports, [15, 17-19] and also a substantial number of children without any previous ROP (Table 3).

Table 3. OCT studies on macular thickness in prematurely-born and fullterm children and adults.

Author	**OCT type**	**Preterms** (n)	**Preterms With ROP** (n)	**Preterms Without ROP** (n)	**Fullterms** (n)	**Age**
Hammer et al [13]	FDOCT*	5	5	0	5	14 – 26 years
Reccia & Recchia [17]	Stratus OCT	12	12	0	0	8 – 38 years
Ecsedy et al [15]	Stratus OCT	30	20	10	10	7 – 13 years
do Lago et al [16]	Stratus OCT	13	12	1	0	1- 4 months
Present study	Stratus OCT	65	29	36	55	5 – 16 years

* FDOCT – Fourier domain OCT.

n=numbers

We found thicker foveas in the prematurely-born children than in those born at term, but no differences in the more ”peripheral” parts of the macula. Our findings accord with those of Hammer et al [15] and Ecsedy et al [17], who reported data in five and thirty prematurely-born children / adults respectively. The reason for the foveal abnormality in preterms is probably related to the foveal development, which seems to start around the 22nd week of gestation as a thickened region of ganglion cells. [12,13] In the 24th to 26th week, the ganglion cells and the inner nuclear layer cells move laterally, giving rise to the beginning of the foveal depression. This peripheral migration of cells does not seem to be completed until 15 – 45 months after birth. In contrast to peripheral migration, photoreceptors migrate centrally. [12,13] The number of foveal cone nuclei increases from a single layer at about 22 weeks to four to eight layers in the completely mature macula, but the cones gradually thin and

elongate for at least 45 months after birth. It is therefore not surprising that this complex foveal development is disturbed in the prematurely-born infant and results in thicker foveas than in the those born at term.

In accord with Recchia & Recchia [19] and Ecsedy et al [17], the inner retinal structures seemed to be preserved in the prematurely-born children. However, we could not evaluate the various retinal layers with our OCT technique. Hammer et al [15], using sophisticated techniques, showed that all inner retinal layers were present and contiguous across the central fovea in four of their five subjects with previous ROP.

In our study, ROP seemed to affect the development of the fovea. Children with previous ROP had significantly thicker foveas than those without ROP. Since only few children with previous ROP were included, no conclusion could be drawn about the effects of the stage of ROP on the foveal thickness. However, although not statistically significant, children with severe ROP, including those treated for ROP, had the thickest maculae. Our findings accord with the data reported in the OCT study by Ecsedy et al [17]. They are also in agreement with the delay in macular development in infants with ROP observed by Isenberg [21], who ascribed it to a direct macular insult by ROP.

We found no correlation between foveal thickness and refraction or visual acuity (VA) in the present study or in the full-term controls.[20] This concurs with the study of 12 children by Recchia & Recchia [19], who found no relation between a decrease in VA and absence of a foveal depression, preservation of inner retinal layers or an increase in foveal thickness. They

concluded that the increased foveal thickness may only reflect previous prematurity, and has no functional importance. This is in line with the view of Marmor et al [22], who states that abnormal foveal morphology is not always associated with a reduction in VA.

The present study, which consists of 36 prematurely-born children without ROP, enabled us to study the effect of prematurity per se on the foveal thickness. We found that children without previous ROP indeed had thicker foveas than those born at term . The role of preterm birth was also evaluated by Ecsedy et al [17], but they reached no definite conclusion because of the small size of their cohort.

Finally, our study showed that the degree of prematurity correlated with the thickness of the fovea. Moreover, in a multiple regression analysis which included GA and BW as continuous variables as well as ROP, neurological complications, refraction, VA and age at examination, gestational age at birth was the only risk factor for a thicker macula in prematurely-born children. Therefore, the degree of prematurity of the child seems to be of greatest importance for foveal development and more important than ROP. To our knowledge this has not been reported elsewhere.

In conclusion, we found, using OCT, that prematurely-born children have thicker central foveas than those born at term. We believe that this may be due to an arrest in the lateral migration of cells during normal development of the fovea. Infants with ROP seemed to be more prone to a delay in maturation than those without ROP. Regardless of ROP, however, the degree of prematurity was the most important risk factor for abnormal foveal

development.

Competing Interest**:** None declared.

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Figurelegends

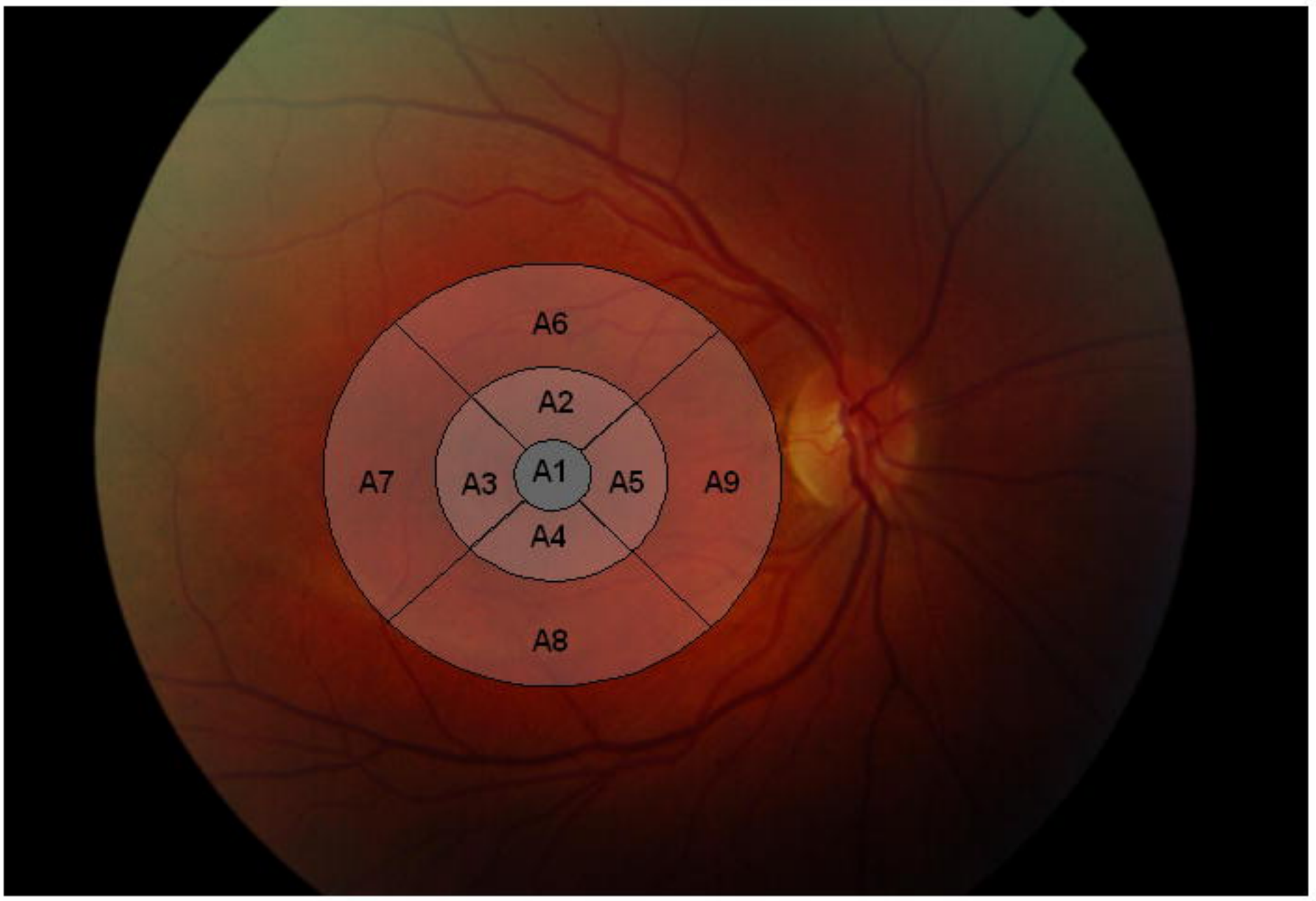
Figure 1. The nine macular areas defined 1985 by the Early Treatment Diabetic Retinopathy Study Reasearch Group,(ETDRS).

Figure 2, Retinal thickness (µm) in the 9 ETDRS areas, Mean (SD). A. Preterm group 65 right eyes. B. Preterm group 65 left eyes. C. Control group 55 randomly selected eyes (right or left).

Figure 3A. Optical coherent tomography (OCT) image from one of the thickest maculae in the preterm group. 3B. OCT image from a child born at term.

Figure 4. Central macular thickness (A1) in children born at term (control eyes) and prematurely born children without and with previous ROP (right and left eyes).

Figure 5. Central macular thickness (A1) in relation to gestational age at birth in the prematurely born children. A – right eyes, B – left eyes.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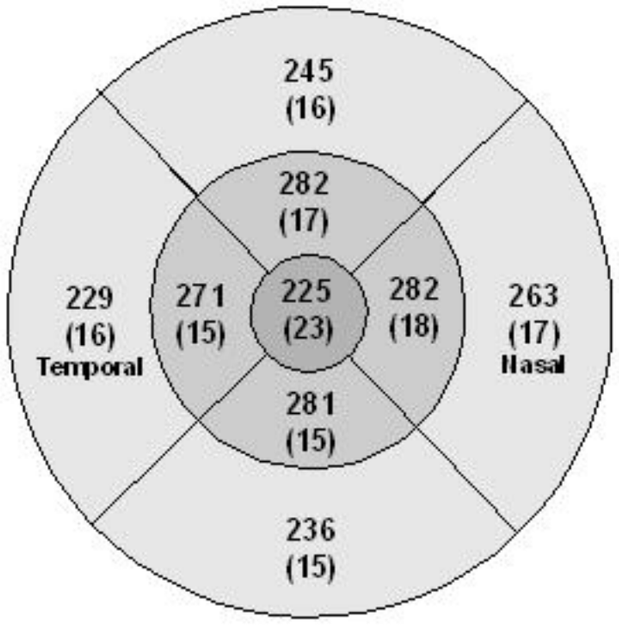
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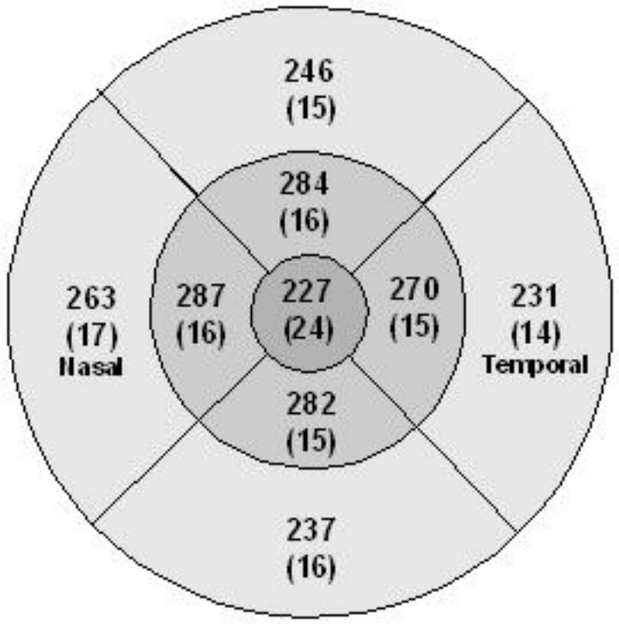
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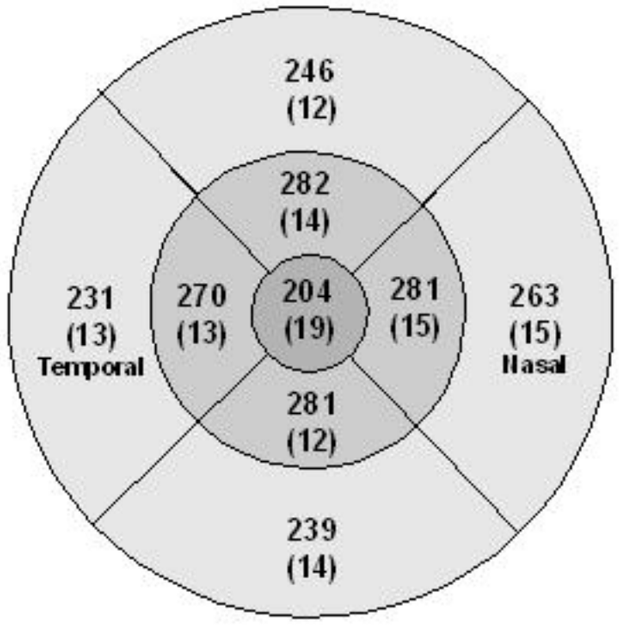
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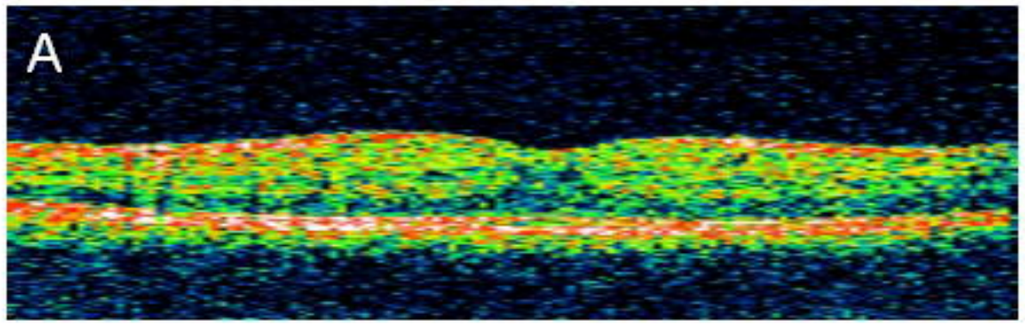
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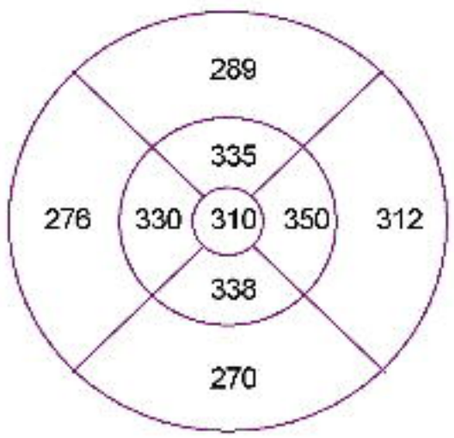
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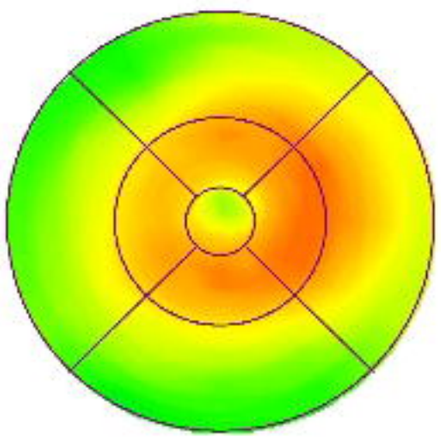

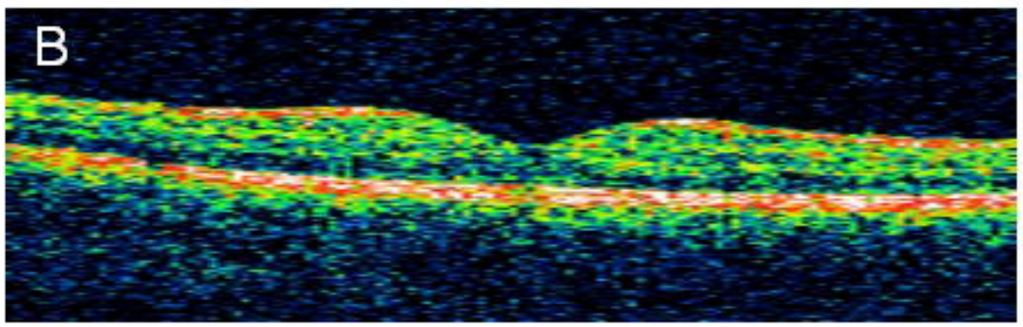
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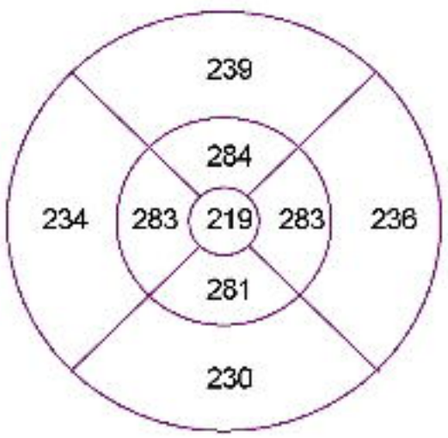
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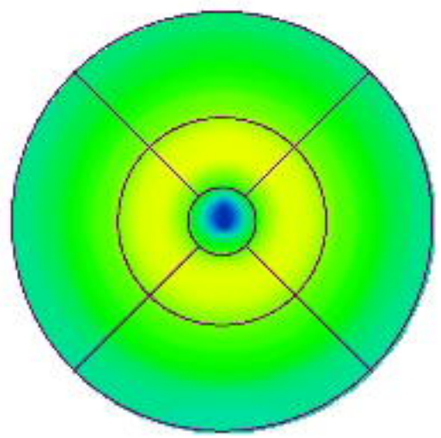

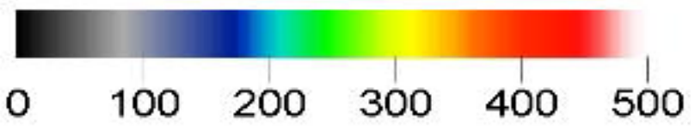
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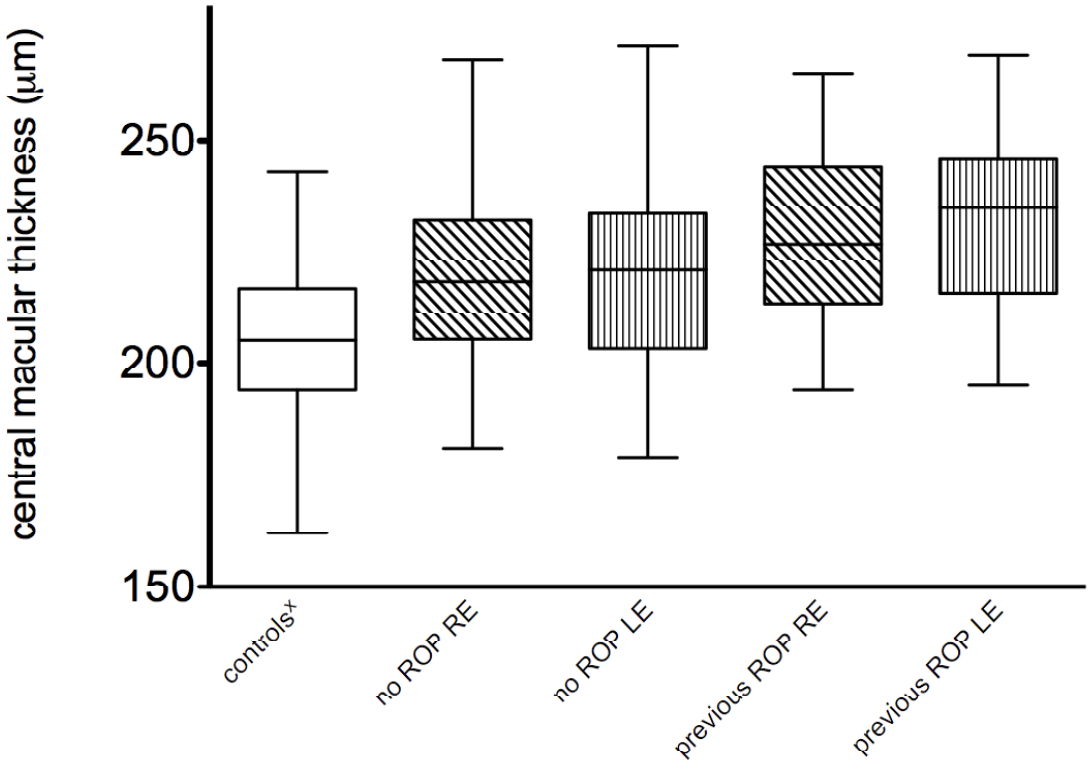
500

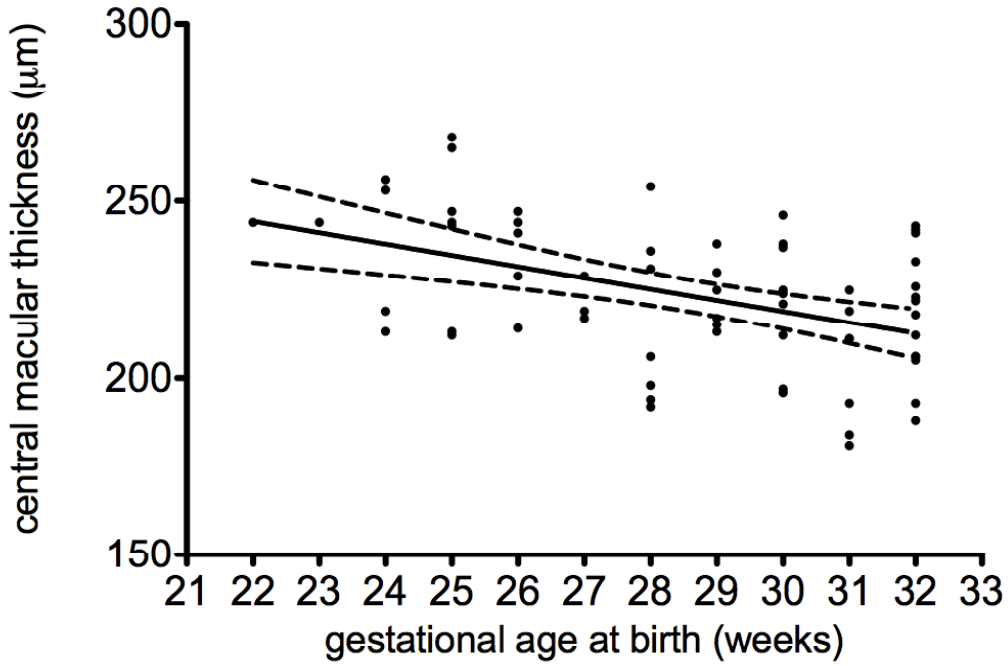


RE = right eye

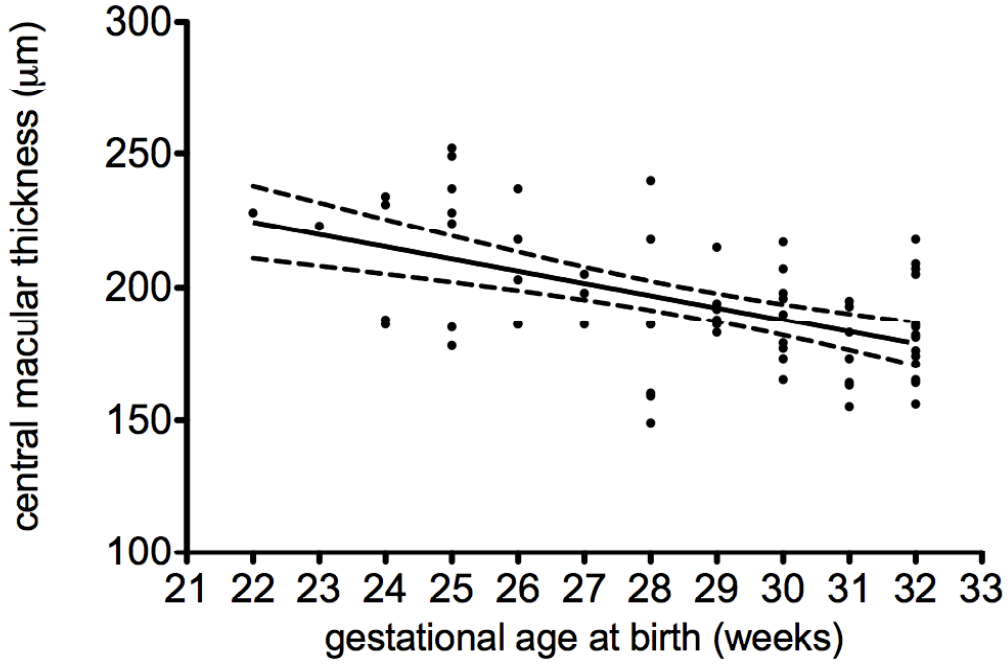
LE = left eye

X Eriksson et al 2009

A.


central macular thickness (μm)
300
250
200
150
21 22 23 24 25 26 27 28 29 30 31 32 33
gestational age at birth (weeks)

B.


central macular thickness (μm)
300
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21 22 23 24 25 26 27 28 29 30 31 32 33
gestational age at birth (weeks)