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ORIGINAL ARTICLE

All retinas are not created equal: Fovea-to-macula thickness ratio and foveal microvasculature in healthy young children

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Abstract

Purpose: Markers for the relationships between structural and microvasculature measures given by optical coherence tomography angiography are necessary to increase the diagnostic and prognostic value of this technique. The aim of this study was to investigate relationships between structural and microvasculature measures around the fovea in healthy eyes of healthy children.

Methods: Observational cross-sectional study involving children aged 8–17 years, born at full-term, with no eye disease. The better of two 3 × 3 mm macular scans obtained with a Cirrus 5000HD-OCT was analysed. Images were corrected for lateral magnification errors. Vessel density and perfusion were measured with ImageJ/Fiji software for the superficial capillary plexus. Structural measures including foveal and macular thicknesses were performed manually.

Results: The sample included 86 participants, 51 (59%) females. Mean age was 12.4 years (SD = 2.5); mean best-corrected acuity was −0.10 logMAR (SD = 0.09); mean refractive error was +0.59 D (SD = 1.3) and mean axial length was 23.1 mm (SD = 0.86). Mean area of the foveal avascular zone (AFAZ) was 0.20 mm^2 (SD = 0.88); median fovea-to-macula thickness ratio (FMTR) was 0.63 (IQR = 0.08); mean central vessel density was 12.42 mm^{-1} (SD = 2.78) and mean central perfusion was 38.66% (SD = 3.83). AFAZ was correlated with central vessel density ($p < 0.001$), perfusion ($p < 0.001$), foveal thickness ($p < 0.001$) and FMTR ($p < 0.001$). Central vessel density was correlated with foveal thickness ($p < 0.001$) and FMTR, ($p = 0.01$). Central perfusion was correlated with foveal thickness ($p < 0.001$) and FMTR, ($p = 0.003$).

Conclusion: In this study, foveal thickness, FMTR and foveal microvasculature measurements were correlated. Clinicians need to be aware that shallow foveal pits and persistent foveal microvasculature are likely to occur in optical coherence tomography angiography images. In healthy eyes from healthy children, an atypical high FMTR and a small AFAZ may be associated with incomplete foveal development. The mechanism and functional implications of this remain unknown.

KEYWORDS
children, fovea, foveal avascular zone, foveal pit, optical coherence tomography angiography

INTRODUCTION

Retinal structure and microvasculature in children born pre-term, with or without retinopathy of prematurity (ROP), is usually abnormal.[1–5] Anatomical characteristics of the retinal vascular network including the foveal avascular zone (FAZ) are important to understand the impact of prematurity on the development of the fovea.[3] Premature children are more likely to present with a poorly defined foveal pit and a reduced or absent FAZ, known as foveal hypoplasia or fovea plana. Fovea plana has been suggested in cases where there is anatomical and functional cone specialisation but the foveal pit is absent.[6,7] However, fovea plana has also been found in full-term children for reasons that are currently unclear.[7–12] Therefore, to increase the diagnostic and prognostic value of retinal microvasculature measures given by optical coherence tomography angiography (OCTA, sometimes referred as functional OCT)[13] in paediatric patients, it is necessary to characterise the spectrum of normal findings.

Studies involving mostly pre-term children have attributed a reduced or absent FAZ and increased foveal thickness to subnormal postnatal development of the foveal area of the macula.[5] However, it is currently unclear if a reduced or absent FAZ will lead to future problems.[14] There are also other conditions such as nanophthalmos that can lead to a small FAZ. In addition, characteristics of the FAZ can also be affected by myopia (larger FAZ)[15] or sex (larger among females).[11,16] Most studies have found negative correlations between foveal thickness and the area of the FAZ (AFAZ), as well as between retinal vessel density and foveal thickness. This is unsurprising, as thinner foveae should have less need for inner retinal vasculature. However, a recent study has shown that amblyopic eyes have thicker inner retinal layers and reduced vessel density when compared with non-amblyopic fellow eyes, suggesting that thicker foveae are not necessarily associated with increased vessel density.[17]

Foveal thickness alone does not give information about the structure of the foveal pit, which is a marker for good foveal development and advantageous for visual acuity.[18,19] The centrifugal displacement of inner retinal layers forming the foveal pit reduces the light scattering at neuronal structures and blood vessels and allows a nearly direct illumination of the photoreceptors. The distribution of neurons along the walls of the foveal pit also increases the number of cells processing the light at the fovea.[20] Therefore, the fovea-to-macula thickness ratio (FMTR)[21] might be a good way to quantify the development of the fovea. FMTR can be used when investigating correlations with microvasculature to better understand the normal or subnormal development of the fovea and to monitor changes over time.

Key points

- Children born full term with normal visual acuity can have microvasculature in the fovea, an area that has traditionally been considered avascular in healthy eyes.
- The thickness of the fovea, compared with the thickness of the macula, was higher in eyes with persistent microvasculature at the fovea.
- Microvasculature and structural measures of the fovea revealed by optical coherence tomography angiography are useful to assess the development of the fovea.

Further understanding of the characteristics of the retinal microvasculature in children is also necessary to understand retinal vascular disorders in adults.[12,22–24] For example, it may help to disentangle congenital foveal microvasculature from acquired vascular disorders associated with conditions such as age-related macular degeneration or diabetic retinopathy.[25]

Most previous studies have used incorrectly scaled images to measure OCTA parameters in children. Scaling errors due to the axial length deviating from the standard assumed by the OCTA are to be expected in children because the axial length is typically different from a standard adult eye.[26] The aim of this study was to investigate structural and microvasculature measures in healthy eyes of healthy children. We hypothesised that structural and microvasculature measures provided by OCTA are correlated. The results of the current study revealed a spectrum of areas of foveal avascular zones (AFAZ) that were correlated with foveal thickness and fovea-to-macula thickness ratio. Findings are discussed based on existing theories of foveal development; high FMTR together with low AFAZ may be linked to incomplete foveal development.

METHODS

Participants and clinical evaluation

This was a cross-sectional study performed in schoolchildren aged 8 to 17 years living in Kalmar Län, Sweden, who were participating in a longitudinal study, details of which have been described in our previous publication.[27] Exclusion criteria included: (1) visual acuity (VA) worse than 0.10 logMAR in either eye; (2) strabismus and/or amblyopia; (3) any

pre-existing condition affecting refractive development of the eye, for instance, retinopathy of prematurity or diabetes; (4) any systemic disease; (5) use of or a need for any systemic medication or topical medications that may alter normal ocular findings; (6) use of medications that may affect normal ocular health and physiology and (7) any previous eye surgery. The research protocol was approved by the Regional Committee for Medical Research Ethics in Linköping, Sweden (Dnr 2018/423-31) and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Visual acuity was determined by an internally illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) chart viewed at 3 m and scored letter-by-letter.[28] Cycloplegia was achieved using two drops of cyclopentolate 1% (Cyclogyl, Alcon, alcon.com), administered 10 min apart. Refractive error was measured 30 min after the second drop of cyclopentolate using an open-field autorefractor (NVision-K 5001, Shin-Nippon, shin-nippon.jp). Axial length was measured with a non-contact optical coherence biometer IOLMaster 500 (Carl Zeiss Meditec, zeiss.com), and intraocular pressure (IOP) was measured with the Icare ic100 (ICARE, icare.world.com).

Optical coherence tomography angiography (OCTA) image acquisition

Functional and structural measures were obtained with a Cirrus 5000HD-OCT with Angioplex (SW version 11.0.0.2994, Carl Zeiss Meditec, zeiss.com), a system which has been proven accurate and repeatable.[29,30] Two 3×3 mm scans centred at the fovea were obtained in succession from right eyes approximately 30 min after instillation of cyclopentolate. The Cirrus 5000HD acquires images at speed between 27,000–68,000 A-scans/sec with an active tracking system (FastTrac) to reduce motion artifacts.[31] Images with inadequate quality that had a signal-to-noise ratio (SNR) of less than or equal to 9 and/or images having visible artifacts after visual inspection were excluded from the analysis. When both scans were of acceptable quality then the better of the two was used. If both scans were of inadequate quality, then the participant was excluded.

Optical coherence tomography angiography (OCTA) image magnification correction

The Littman and Bennett formulae were used to calculate the true image size of the OCTA scans.[17,32,33] In short, the relationship between the measured OCTA image diameter (D*m*) and the true diameter of the fundus (D*t*) was computed using the equation:

$$Dt = p \times q \times Dm \quad (1)$$

where $p \times q$ was the overall image magnification factor, p was the magnification factor of the imaging system and q was that of the eye. Factor q was determined from the Bennett formula: $q = 0.01306 \times (AL - 1.82)$, where 1.82 is a constant related to the distance between the corneal apex and the second principal plane, and AL is the axial length of the eye. Factor p was computed from the Bennett formula if the axial length at which D*t* = D*m* is known. For the CIRRUS 5000HD the axial length was set as 24.7 mm, the standard axial length provided by the manufacturer. When D*t* = Dm, then $p = 1/q$, and p was computed as: $p = 1/[0.01306 \times (24.7–1.82)] = 3.347$. Values of p and q were replaced in Equation (1) to compute the true size of the scan: $Dt = 3.347 \times 0.01306 \times (AL - 1.82) \times 3$, assuming an initial scan size D*m* = 3 mm, the AL is specific for each participant in millimetres. To compute the correct size of the scan and all other parameters, we used the ImageJ/Fiji software (ImageJ, imagej.net/software/fiji/).[34] The macro to compute the correct size of the scan is given in the Supplementary Methods. The resulting image is provided in Figure 1 (top-right image), with the new size in mm given inside the red square.

Vessel density, perfusion, area of the foveal avascular zone (AFAZ) and structural measures

As shown in Figure 1, macular microvascular measurements were taken from the central 1 mm diameter of the scan and from the total scan (including the central 1 mm). Statistics for the microvasculature measures of the superficial capillary plexus were recomputed using the ImageJ/Fiji software (not the CIRRUS Angioplex software) to correct for the size of the scan.

Perfusion was defined as perfused vasculature per unit area in a region of measurement, expressed as a percentage. For example, in Figure 1 (top-right image), perfusion corresponds to the percentage of white pixels in the binary image (with grey pixels being converted to black or white according to their intensity). Vessel density was defined as the total length of perfused vasculature per unit area in the region of measurement, in mm/mm^2 or mm^{-1}.[31] This was performed after binarization by "skeletonising" the images and measuring the length of the capillaries with the Measure Skeleton Length Tool plugin. The foveal avascular zone was detected by the Angioplex software and the area of the foveal avascular zone (AFAZ) was measured using ImageJ/Fiji software. An example of the resulting image is given in the Supplementary Information. When the avascular zone was too small to be detected automatically, the detection was performed manually by author AFM.

Macular thickness was measured manually at the two thickest points in the parafovea, defined following manual segmentation of the central horizontal scan - slice 122 (see Supplementary Information for additional description). Foveal thickness (at the foveal pit) and macular thickness (taken at the two thickest points of the parafovea) were used to compute the fovea-to-macula thickness ratio. Microvasculature and structural measures were taken from

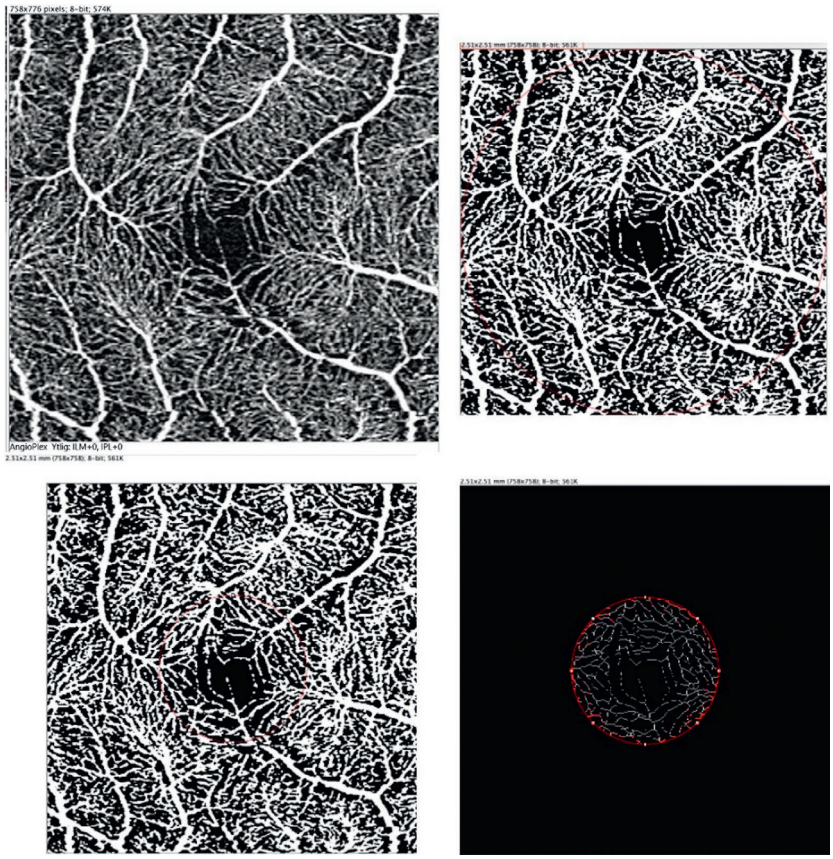

FIGURE 1 Panel showing some stages of the image processing for case ID 163 with axial length 20.97 mm. Top-left: original uncorrected image with 758 × 777 pixels and presumed 3 × 3 mm. Top-right: the image was cropped to remove the extra vertical pixels resulting in 758 × 758 pixels, and then the size of the scan was corrected resulting in a real size of 2.51 × 2.51 mm. The image was then "binarized" using the Fiji software; the red circle shows the total area where measurements of perfusion and vessel density were taken. It must be noted that the diameter of the total area was different for each participant, in this case 2.51 mm. Bottom-Left: The image shows the central 1 mm diameter circle where central measurements of perfusion and vessel density were taken. Bottom-Right: example of the measurement of vessel density in the central 1 mm. For this measurement images were "skeletonised" using the Fiji software resulting in fine lines corresponding to the length of the capillaries as shown in the image. The diameter of the central circle was 1 mm for all participants.

TABLE 1 Summary of measurements performed at the macula.

	Scan size[a] (mm)	AFAZ (mm^2)	PER central (%)	PER total (%)	VD central (1/mm)	VD total (1/mm)	Foveal Thickness (μm)	Macular Thickness (μm)	Fovea-to-Macula ratio
N	86	86	86	86	86	86	86	86	86
Mean	2.80	0.20	19.61	38.66	12.42	23.11	206.67	320.94	0.65
Std. Deviation	0.11	0.09	4.80	3.83	2.78	2.09	20.08	15.57	0.07
Std. Error of Mean	0.01	0.01	0.52	0.41	0.30	0.23	2.17	1.68	0.01
Median	2.80	0.19	19.45	39.17	12.51	23.26	202.00	321.00	0.63
Percentiles									
25	2.72	0.14	16.51	36.57	10.74	21.54	192.25	312.00	0.60
50	2.80	0.19	19.45	39.17	12.51	23.26	202.00	321.00	0.63
75	2.88	0.25	21.79	40.98	13.82	24.36	217.00	333.00	0.68

Abbreviations: AFAZ. Area of the foveal avascular zone, PER, perfusion, VD, vessel density.

[a]Scans are square shaped and this value quantifies the size of one side of the square.

the same scan, to maintain spatial correspondence between these measures. The Supplementary Information methods file provides detailed descriptions of the segmentation and structural measurements.

RESULTS

The final sample included 86 participants, 35 males (41%) and 51 females (59%). The mean age of the participants was

TABLE 2 Spearman correlations between microvascular measurements (VD, vessel density; PER, perfusion), structural (Foveal and Macular Thickness) and FMTR (Fovea-to-Macula Thickness Ratio) and functional measure (BCVA, best corrected visual acuity), (AFAZ, area of the foveal avascular zone).

		AFAZ (mm^2)	VD central (1/mm)	PER central (%)	VD total (1/mm)	PER total (%)	Foveal Thickness (μm)	Macular Thickness (μm)	FMTR	Age (years)
VD central (1/mm)	Correlation	**−0.64****								
	Sig. (2-tailed)	**<0.001**								
	N	**86**								
PER central (%)	Correlation	**−0.62****	0.93**							
	Sig. (2-tailed)	**<0.001**	<0.001							
	N	**86**	86							
VD total (1/mm)	Correlation	0.00	0.55**	0.50**						
	Sig. (2-tailed)	1.00	<0.001	<0.001						
	N	86	86	86						
PER total (%)	Correlation	−0.01	0.46**	0.40**	0.86**					
	Sig. (2-tailed)	0.94	<0.001	<0.001	<0.001					
	N	86	86	86	86					
Foveal Thickness (μm)	Correlation	**−.069****	**0.39****	**0.43****	0.01	0.02				
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**	0.91	0.84				
	N	**86**	**86**	**86**	86	86				
Macular Thickness (μm)	Correlation	0.004	0.08	0.06	**0.23***	**0.30****	0.16			
	Sig. (2-tailed)	0.97	0.49	0.56	**0.04**	**0.01**	0.13			
	N	86	86	86	**86**	**86**	86			
FMTR	Correlation	**−0.62****	**0.28****	**0.32****	−0.17	−0.17	0.84**	−0.34**		
	Sig. (2-tailed)	**<0.001**	**0.01**	**0.003**	0.12	0.12	<0.001	0.001		
	N	**86**	**86**	**86**	86	86	86	86		
Age (years)	Correlation	0.15	*−0.21*	*−0.20*	−0.14	−0.04	**−0.25***	0.03	−0.18	
	Sig. (2-tailed)	0.18	*0.06*	*0.07*	0.21	0.72	**0.02**	0.80	0.10	
	N	86	*86*	*86*	86	86	**86**	86	86	
BCVA (logMAR)	Correlation	*−0.20*	0.15	0.17	0.10	0.05	0.18	−0.21	0.20	**−0.29****
	Sig. (2-tailed)	*0.06*	0.17	0.12	0.39	0.62	0.10	0.05	0.06	**0.007**
	N	*86*	86	86	86	86	86	86	86	**86**

Note: Relevant correlations are given in bold, italic correlations show trends that failed to reach statistical significance. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

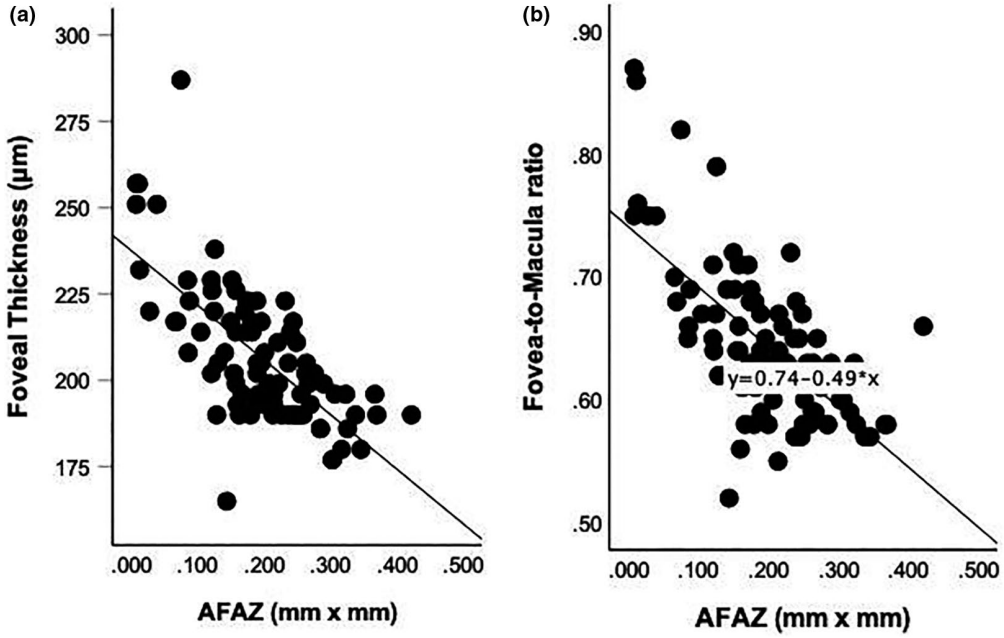

FIGURE 2 Relationships between the area of the foveal avascular zone (AFAZ) and structural measures of the macular area. (a) shows the negative correlation between foveal thickness (*y*-axis) and area of the FAZ (*x*-axis). (b) shows the negative correlation between the fovea-to-macula thickness ratio (*y*-axis) and the area of the FAZ (*x*-axis). A more marked change in fovea-to-macula ratio is expected for FAZ with smaller areas (left side of the graph b) but that is not captured by the linear regression line.

12.4 years (SD = 2.5); ethnicities were Caucasian (n = 68), East Asian (n = 4), West Asian (n = 12) and African (n = 2). The mean axial length was 23.1 mm (SD = 0.86), mean intraocular pressure (IOP) was 16.1 mmHg (SD = 3.7) and mean best-corrected acuity was −0.10 logMAR (SD = 0.09). The mean spherical equivalent refractive error was +0.59 D (SD = 1.3). Table 1 summarises the OCTA results for the 3 × 3 mm scan at the macula.

The correlations between AFAZ and other structural and microvascular measures are summarised in Table 2. Figure 2 shows two scatter plots with the relationships between the area of the FAZ (AFAZ) and structural measures at the fovea and at the macula. Representative examples of structural and microvasculature images are given in Figure 3. Some trends in Table 2 failed to materialise into significant correlations. One is the negative trend between AFAZ and best corrected visual acuity (BCVA), suggesting that smaller AFAZ tends to be associated with worse acuity. The negative trends between age and vessel density, and age and perfusion, in the central 1 mm suggest that these variables might reduce during this period of life.

Macular thickness was higher in the eyes of Caucasians (mean = 324 µm, SD = 14) than in non-Caucasian participants (mean = 310 µm, SD = 16), $t(3.5) = 85$ ($p < 0.001$). Total vessel density was higher in non-Caucasian eyes (Caucasian: median = 22.6 mm^{-1}, IQR = 0.9; non-Caucasian: median = 23.62 mm^{-1}, IQR = 2.54; Mann-Whitney U test, MW = 333, Z = –2.96 (p = 0.003)). Total macular perfusion was significantly higher in Caucasians (median = 39.39, IQR = 3.65) than non-Caucasians (median = 36.66, IQR = 4.94; Mann-Whitney U Test, MW = 360, Z = –2.67 (p = 0.007)).

DISCUSSION

In line with the initial hypothesis, the current study found significant relationships between structural and microvasculature measures obtained with OCTA at the macula in healthy eyes of healthy children. The most important finding was the relationship between the area of the FAZ (AFAZ) and the fovea-to-macula thickness ratio.[21] Thicker foveae were associated with increased vascular density and perfusion.

In line with other studies, microvasculature measures in the central 1 mm and the AFAZ were correlated with foveal thickness.[3,11,16,35,36] However, assessing only the foveal thickness gives incomplete information if, for example, the foveal pit is poorly defined as in cases of fovea plana. The fovea-to-macula thickness ratio (FMTR) has been used in a previous study investigating the relationship between the severity of cystoid macular oedema and severity of ROP.[21] In the current study we observed that children with higher FMTR (shallower pits) have smaller AFAZ. To discuss these findings, it is necessary to recap the mechanism of formation of FAZ.

There are currently two different models trying to explain the development of the FAZ. The first is based on ischemia causing the foveal pit: towards the end of gestation, the choriocapillaris meshwork in the fovea regresses by apoptosis.[3,19] Due to metabolic stress, neurons in the

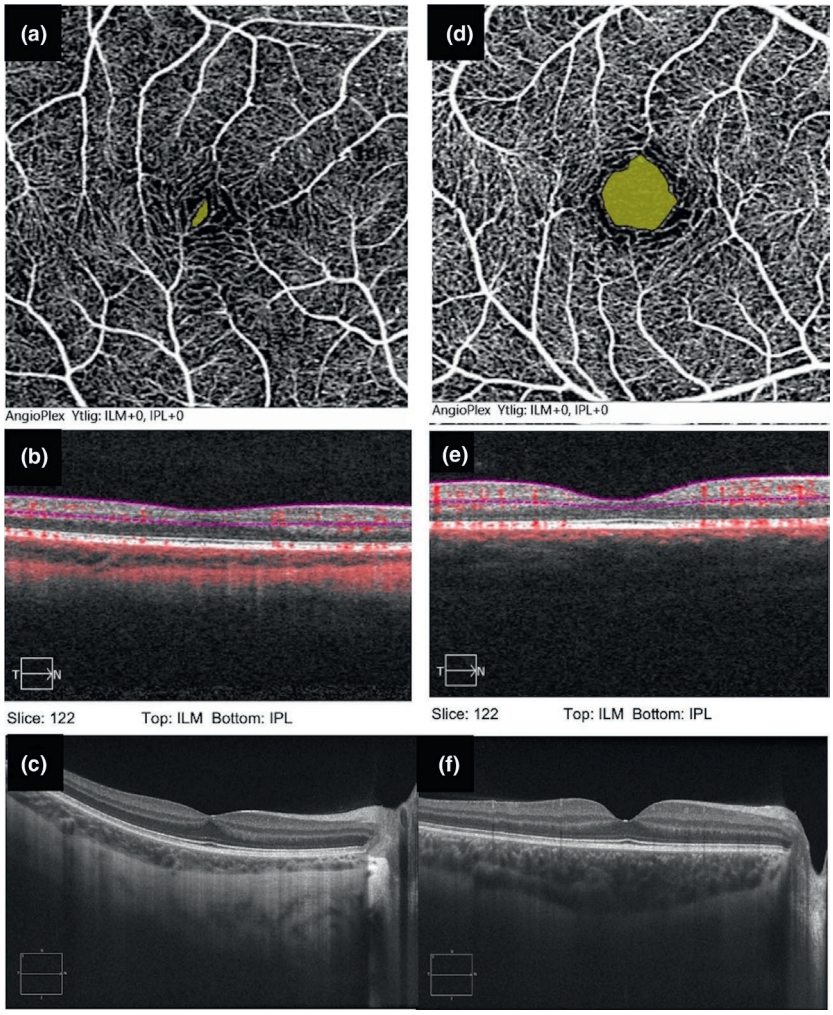

FIGURE 3 Example of images from two participants, one with a fovea-to-macula thickness ratio of 0.86 (a, b, c, ID 119) and one with a ratio of 0.56 (d, e, f, ID 140); both were male and born in 2010. The top images A and D shows the en-face image of the superficial capillary plexus, the avascular zone in a) is extremely small compared to d). In d), the foveal avascular zone was fitted automatically by the instrument; however, in (a), it was fitted manually because the instrument was unable to find the foveal avascular zone. Images b) and e) show the slab used by the AngioPlex software to compute the superficial capillary plexus statistics. Images c) and f) show a high-resolution picture of the macular structure. In the "normal FAZ" shown in d) (fovea-to-macula thickness ratio 0.56) the corresponding structural image f) shows a large cleavage of the inner retinal layers at the foveola. In contrast, in the reduced FAZ given in a) (fovea-to-macula thickness ratio 0.86) the corresponding structural image c) shows a continuity of inner nuclear layer and ganglion cell layer over the foveolar centre.[8,35] FAZ, foveal avascular zone.

fovea die or migrate from that region of the retina leading to formation of the foveal pit.[11,37] When regression of the microvasculature fails the FAZ never develops, as in individuals with retinopathy of prematurity. The persisting vasculature contributes to a thicker central fovea and, therefore, affects the typical foveal anatomy. An alternative mechanism for development of the foveal pit and the FAZ is the effect of IOP. In this process the foveal pit develops progressively under the effect of IOP, and there is a migration of inner retinal layers away from the fovea and migration of cone photoreceptors into the fovea.[18,35] It is likely that these two processes are complementary rather than mutually exclusive. According to these models a shallow pit, corresponding to high FMTR, and vascularised foveae are likely to be the result of an underdeveloped fovea. In the current study we failed to find a significant association between high FMTR and changes in acuity, but we observed a trend in which a smaller AFAZ seem to be associated with poorer visual acuity. These results show that persistence microvasculature in the fovea may have subtle functional disadvantages.

Samara and colleagues noted that, in adults, differences in the FAZ were associated with incomplete cleavage of the inner retinal layers at the foveola,[35] which leads to a higher fovea-to-macula thickness ratio. It remains unclear if the microvasculature (which can now be measured with OCTA) leads to the persistence of these neurons or the other way around. Springer and Hendrickson proposed that the presence of retinal vasculature inhibits the formation of a foveal pit for reasons that remain unclear.[19] As shown in Figure 3, our findings show incomplete lateral displacement of the inner retinal layers, particularly of the inner nuclear and ganglion cell layers. It is important to emphasise that in the present study none of the participants

had reduced vision or gestational age, yet reduced AFAZ and FMTR were observed in some cases. Our findings add to the evidence that the microvasculature and structural configurations of the macula in full-term and healthy children revealed by OCTA can vary substantially.[11,12,38] This variability needs to be considered when examining the retina, not only in children but also in adults.

In the current study we also found differences in macular measures between ethnicities, in line with previous investigations.[39,40] Few of our participants were non-Caucasian so limited conclusions can be drawn from these data.

A strength of the current study was the use of the same scan for structural and microvascular measures, with all manual segmentations being performed by the same researcher (NH, with quality checks performed by AFM). Using corrected scaled images was also a strength but introduced a possible limitation. Changing the area of the scans meant that the statistics for the microvasculature computed by the Angioplex software were partially inaccurate because they assumed an incorrect area of measurement. Manual computation of the microvasculature statistics using the ImageJ/Fiji software might limit the comparisons between our values and those of other studies using a different algorithm such as the Angioplex software.

CONCLUSIONS

Children with higher fovea-to-macula thickness ratios have shallower pits and smaller AFAZ. The fovea-to-macula thickness ratio seems a reliable way to quantify the structural development of the fovea and can be used to investigate cross-sectional or longitudinal correlations with foveal microvasculature.

According to the current theories of development of the FAZ and foveal pit, high FMTR with small AFAZ may correspond to more incomplete development of the fovea. Clinicians need to be aware of this variability of the fovea in both children and adults when making management decisions. The reasons for, and implications of incomplete foveal development remain to be investigated.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Pelsin Demir: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Validation (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead). **Nathaniel Hovespian:** Data curation (equal); Formal analysis (equal); Investigation (equal); Writing – original draft (equal). **Peter Pagels:** Conceptualization (supporting); Resources (supporting); Visualization (supporting); Writing – review & editing (supporting). **Vanja Petersson:** Investigation (supporting); Methodology (supporting); Supervision (supporting); Writing – review & editing (supporting). **Karthikeyan Baskaran:** Methodology (supporting); Project administration (supporting); Supervision (supporting); Writing – original draft (equal); Writing – review & editing (equal). **Antonio Filipe Macedo:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (equal); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing – original draft (supporting); Writing – review & editing (supporting).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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