Developmental Changes in Retinal Microvasculature in Children: A Quantitative Analysis Using Optical Coherence Tomography Angiography

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• PURPOSE: To quantify the macular microvasculature in healthy children of various ages by using optical coherence tomography angiography (OCTA).
• DESIGN: Prospective cross-sectional study.
• METHODS: A total of 333 normal children from 4 to 16 years old were included. OCTA was performed on a 3- × 3-mm area centered on the macular region. Vascular density, perfusion density, fovea avascular zone (FAZ) area, FAZ perimeter, and FAZ acircularity index (AI) were measured and adjusted for axial length. Differences were compared among various ages.
• RESULTS: Among the different age groups, both macular vascular density and perfusion density increased with age ($P < .0001$ and $P = .0028$, respectively). After adjustments were made for the spherical equivalent (SE) and axial length, macular vascular density was significantly associated with age ($r = 0.183$; $P = .001$) No factors were significantly correlated with the perfusion density after adjustment for the age, SE, or axial length. The FAZ area and FAZ perimeter did not change among groups of different ages. Nevertheless, the AI of FAZ in the 4.00-6.99-year-old group was smaller to that of the 13.00-15.99-year-old group ($P = .03$). Younger children had significantly higher rates of nonconsecutive vessels branched toward the macular center ($P = .0002$) and vascular loops contributing to irregular shapes of FAZ ($P = .024$).
• CONCLUSIONS: Macular vascular density and perfusion density continuously increase with age in children. Despite the fact that FAZ area and perimeter did not change, the microstructure of FAZ pruned and tended to form a smooth and regular avascular area during development. (Am J Ophthalmol 2020;219:231–239.

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BEING RESPONSIBLE FOR FINE VISUAL ACUITY (VA), the development and maturation of the retinal macula is a compelling topic. Changes in morphological criteria such as macular thickness during development have been well studied using immunohistochemical staining. By analyzing foveal morphology and cone density, it was determined that the human fovea reaches maturity before 4 years of age.[1] Recently, Alabduljalil and associates[2] found by handheld optical coherence tomography (OCT) that the thickness of inner retinal layers remains constant after birth and that maturation of the photoreceptor layer becomes complete at approximately 24 months after birth. A comprehensive study performed by Lee and associates[3] modeled the developmental trajectories for each retinal layer and suggested most of the retinal layer matured around 4-years-old. Nevertheless, relatively little is known about the development of vascular circulation in the macular region in human after birth.[4] As VA and other visual functions mature in children and adolescents, the nutrition and oxygen demand of the retina tissue could increase, requiring matched vasculature. A previous study reported mRNA expression of VEGF in young cynomolgus monkeys suggested a potential sustaining modification of retinal microvasculature after birth in primates.[5]

Recent advances in OCT angiography (OCTA) have revolutionized the imaging of retinal vessels without intravenous injection of dye, allowing easy noninvasive visualization and quantification of retinal microvasculature. The noninvasive and high-resolution power of OCTA could be optimal for examining children, which provide valuable information for the retina microvasculature.[6] Nevertheless, to date, the practical application of OCTA is limited in children because of the absence of generally recognized references by different commercially available OCTA devices. Several studies have shown that retina vessel density decreases while the area of the fovea avascular zone (FAZ) increases with age in healthy adults, which may be due to the decreased demand of oxygen and nutrition.[7,8] The changes in macular microvasculature during childhood remain unclear. Previous studies have shown that vessel density in children may increase with age.[9] However, the findings have been inconsistent in several studies, which focused on school-aged children.[10,11]

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Therefore, the purpose of the present study was to establish the normal values in the general pediatric population and to investigate the developmental changes in retina microvasculature and FAZ in healthy children.

SUBJECTS AND METHODS

THIS STUDY WAS A PROSPECTIVE, CROSS-SECTIONAL OBSERvational study conducted in the Zhongshan Ophthalmic Center, Sun Yat-sen University, with the permission of the Institutional Review Board. All investigations followed the tenets of the Declaration of Helsinki. All parents or legal guardians gave written informed consent. From January to March 2019, 333 normal, healthy children 4 to 16 years old, without ocular disease but only refractive errors, were consecutively recruited. Best-corrected VA (BCVA) was measured using the logMAR chart. Refractive status was measured using an autorefractor (KR-800, Topcon Medical Systems, Oakland, New Jersey) and axial length (AL) by using an intraocular lens (IOLMaster 500, Zeiss Medical Technology, Brentwood, Missouri) after complete pupil dilation using 1% cyclopentolate (Cyclogyl; Alcon, Fort Worth, Texas). Slit lamp examination, intraocular pressure assessment and scanning laser ophthalmoscopy were conducted to exclude eye conditions such as cataract and retina diseases. Children with a history of premature delivery; congenital eye disease; family history positive for eye disease; spherical equivalent (SE) $> +5$D or < -5D and/or astigmatism >2D; BCVA ≥ 0.2 logMAR; any systemic condition that might affect VA or retinal structure, such as sickle cell disease, stickler syndrome, or diabetes; and a quality OCTA image score lower than 8 of 10 were excluded.

Before the study, the performance of 3 commercially available OCTA devices were evaluated, including RTVue AngioVue system (Optovue, Fremont, California), Cirrus 5000 AngioPlex system (Zeiss), and Spectralis (Heidelberg Engineering, Heidelberg, German). Fifteen healthy children 5-7 years old were randomly grouped for OCTA evaluation using RTVue AngioVue, Cirrus 5000 AngioPlex, or Spctralis OCT angiography, simultaneously. The time of completion and the quality of the OCTA examinations were measured and compared. Among the 3 OCTA devices, 5 of 5 children in the Zeiss group finished the examination with the median completion time of 7 min 10 s for both eyes. All 5 children completed the examination in 20 minutes with quality scores higher than 8 of 10. High quality OCTA images could not be achieved in 2 of 5 children using the RTVue system after several tests. The other 3 children finished the OCTA examination with the median completion time of 5 min 45 s for both eyes. The Spectralis OCTA demanded higher stable gaze and relatively longer times of concentration. Only 2 of 5 children finished the examination within 20 minutes with good quality images. Therefore, the Cirrus 5000 AngioPlex was used in the current study for the acquisition and measurement of OCTA in children.

The Cirrus 5000 AngioPlex has a 68-kHz axial scan repetition rate with axial and transverse resolution of 5 and 15 μm, respectively. Blood flow information was generated from the OCT signal using the optical microangiography complex algorithm with 245 A-scans in each B-scan. Line-scan ophthalmoscope images were provided for motion tracking. The 3- $\times$ 3-mm OCTA scans centered on the fovea were obtained using the tracing system for both eyes. The quality of the OCTA images was assessed by the quality score (range: 0-10) generated in the software by the examination operator. The OCTA image was retaken if the OCTA quality score was <8 or significant motion artifacts were observed.

Built-in software was used to analyze the vascular density of the macula (the total length of blood vessel from the skeletonized image-to-the total area [in mm^{-1}] ratio), perfusion density of the retina (the area with blood perfusion-to-the total area ratio), the FAZ area (mm^2), the FAZ perimeter (mm), and the acircularity index (AI; i.e., the measured perimeter of FAZ-to-the perimeter of projected circle ratio with the same area as the FAZ, 0 to 1) of FAZ. Only the superficial capillary plexus (SCP) was analyzed in this study because the projection from the SCP generates artifacts to the deep capillary plexus and may confound the results. In order to quantitatively analyze the superficial retinal microvasculature, the SCP was autosegmented by the built-in software for consistency and comparability. The value of FAZ area, the FAZ perimeter, and the vascular density were adjusted based on axial length by a method previously reported.[12]

Statistical analysis was performed using Prism software (GraphPad, LaJolla, California) or SPSS software (SPSS Inc., Chicago, Illinois). Comparisons of continuous variables were performed using one-way analysis of variance (-ANOVA) and multiple comparison for trend. Bivariate correlation and partial correlation analyses were performed to determine the relationships between demographics and ocular variables associated with the macular microvasculature. Analysis of the dichotomous variables was performed using the chi-square test (or the Fisher exact test when appropriate). The level of significance was set at a P value of .05.

RESULTS

A TOTAL OF 638 EYES IN 333 PATIENTS WITH A MEAN AGE 9.98 $\pm$ 3.09 years (range: 4.02-15.89 years) were enrolled. Overall, 168 patients (50.5%) were boys. Children were subdivided into 4 groups based on age: n = 77 (23.12%), n = 90 (27.03%), n = 108 (32.43%), and n = 58 (17.42%) children were 4.00-6.99, 7.00-9.99, 10.00-12.99, and 13.00-

15.99 years old, respectively. The average ± SE refractive error was −1.07 ± 2.26 diopters (D), and the mean axial length was 23.75 ± 1.26 mm. The average logMAR BCVA was 0.013.89 ± 0.083 (Table 1). The correlation of macular vascular metrics of both eyes, including the FAZ area, the FAZ perimeter, the FAZ AI, the full macular vascular density, the vascular density in the central macula (within the 1-mm central circle on the Early Treatment Diabetic Retinopathy Study grid), the vascular density in the paramacular area (the full macular area eliminated the central macular), the full macular perfusion density, the perfusion density in the central macula and perfusion density in paramacular area, are summarized in the Supplemental Table. All metrics including the vascular density, perfusion density, FAZ area, FAZ perimeter, and AI of FAZ showed moderate to high correlation between both eyes (all $P < .0001$). Therefore, only 1 eye from each participant was analyzed in the subsequent study. The OCTA image of the right eye of each child was used for analysis. The OCTA image of the left eye was used only if the image quality of the right eye was not satisfactory.

• **MACULAR VASCULAR DENSITY AND PERFUSION DENSITY IN CHILDREN AT VARIOUS AGES:** The macular vascular density and perfusion density were calculated and compared across various age groups for the full macula, the central macular, and the paramacular areas separately from the OCTA images. Statistical significance was found for vascular density for the full macular area from 20.81 ± 1.56 in the 4.00-6.99-year-old group to 21.57 ± 1.05 in the 7.00-9.99-year- old group, 21.61 ± 1.35 in the 10.00-12.99-year-old group, and 22.01 ± 0.89 in the 13.00-15.99-year-old group ($P < .0001$ by one-way ANOVA, $P < .0001$ by multiple comparison linear trend) (Figure 1, A). The trend remained significant after refining the macular area to the central macular and the paramacular area (central macular: $P = .0015$ by one-way ANOVA; $P = .0002$ by multiple comparison linear trend; para-macular: $P < .0001$ by one-way ANOVA; and $P < .0001$ by multiple comparison linear trend) (Figure 1, B and C). The perfusion density also increased significantly with age in the full macular area from 0.376 ± 0.027 in the 4.00-6.99-year-old group to 0.384 ± 0.017 in the 7.00-9.99-year-old group, 0.384 ± 0.020 in the 10.00-12.99-year-old group, and 0.389 ± 0.014 in the 13.00-15.99-year-old group ($P = .0028$ by one-way ANOVA, $P = .0007$ by multiple comparison linear trend) (Figure 1, D). The increase of perfusion density in macular was mainly from the paramacular area ($P = .0055$ by one-way ANOVA, $P = .0019$ by multiple comparison linear trend) but not in the central macular area ($P = .25$ by one-way ANOVA) (Figure 1, E and F, 2, Table 2).

Bivariate correlation was performed between the age, sex, SE, axial length, and vascular and perfusion density. The age, SE, and axial length were significantly correlated with macular vascular and perfusion density (all $P <$

TABLE 1. Demographic Characteristics of 333 Participants

Variable	Total N = 333 (100%)	4-6 Years Old n = 77 (23.12%)	7-9 Years Old n = 90 (27.03%)	10-12 Years Old n = 108 (32.43%)	13-15 Years Old n = 58 (17.42%)
Right/left eye	293/40	52/25	80/10	104/4	57/1
Mean ± SD age (median: range), y	9.98 ± 3.09 (10.05: 4.02-15.89)	5.61 ± 0.83 (5.75: 4.02-6.73)	8.67 ± 0.83 (8.72: 7.04-9.99)	11.40 ± 0.87 (11.27: 10.06-12.96)	14.37 ± 0.87 (14.20: 13.06-15.89)
Males/females	168/165	38/39	43/47	58/50	29/29
Mean ± SD SE (median: range), D	−1.03 ± 2.26 (−1.13: −5.00 to 5.00)	1.11 ± 1.33 (1.00: −3.63 to 5.00)	−0.68 ± 2.22 (−0.75: −5.00 to 5.00)	−1.93 ± 1.61 (−1.63: −5.00 to 4.63)	−2.61 ± 2.10 (−2.25: −5.00 to 1.25)
Mean ± SD axial length (median: range), mm	23.73 ± 1.25 (23.86:19.83-26.00)	22.35 ± 0.95 (22.30:19.83-24.85)	23.61 ± 1.07 (23.60:20.11-25.97)	24.39 ± 0.82 (24.44: 21.78-25.89)	24.53 ± 0.92 (24.51:22.33-26.00)
Mean ± SD logMAR visual acuity (median: range)	0.011 ± 0.057 (0.00: −0.079 to 0.15)	0.062 ± 0.077 (0.00:0.00 to 0.15)	0.0053 ± 0.047 (0.00: −0.079 to 0.15)	−0.0035 ± 0.028 (0.00: −0.079 to 0.15)	−0.017 ± 0.043 (0.00: −0.079 to 0.097)

D = diopter; SE = spherical equivalent.

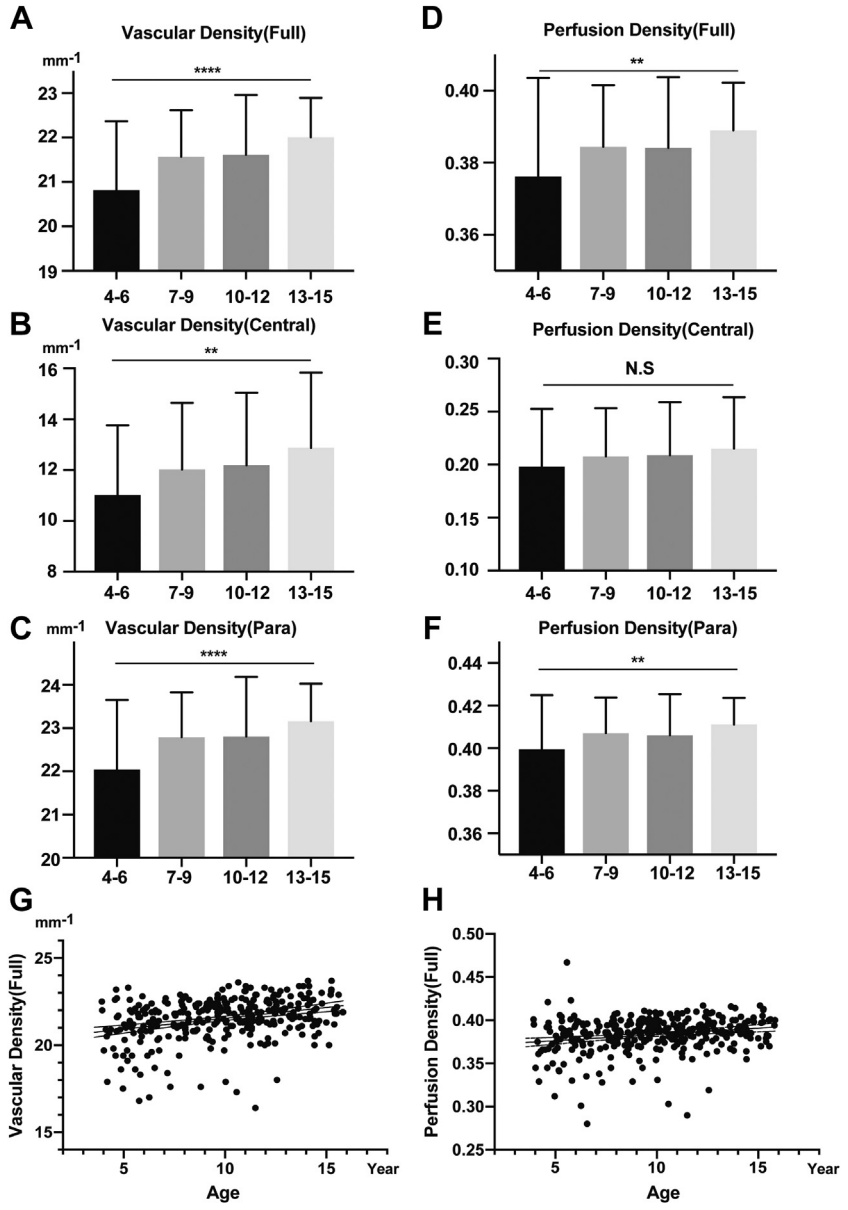

FIGURE 1. Macular vascular density and perfusion density in children of various ages. Statistical analysis showed that vascular density increased with age in the full macular area (A), central macular area (B), and paramacular area (C). (D) Perfusion density was also higher in older children at the full macular area. (E) In the central macular, the perfusion density did not change dramatically with age. (F) Statistical increase was found for vascular density in the paramacular area in older children. (G) A linear regression model of vascular density in full macular area with age is shown. (H) Linear regression model of perfusion density in full macular area with age. *P < .05; **P < .01; ***P < .001; **** P < .0001; N.S No significance.

.0001). In addition, after adjusting for SE and AL, age still significantly and positively correlated with vascular density (r = .183; $P = .001$). No statistically significant correlation was detected between age and perfusion density after adjustment for SE and axial length (r = 0.097; $P = .081$) (Table 3, Figure 1, G and H).

• **CHARACTERISTICS OF FAZ IN CHILDREN AT VARIOUS AGES:** The FAZ area and FAZ perimeter did not change significantly between groups at different ages (FAZ area, $P = .19$ by one-way ANOVA test; FAZ perimeter, $P = .46$ by Kruskal-Wallis test). Nevertheless, the FAZ tended to become regular with increasing age according to the AI. The AI in the 4.00-6.99-year-old group was 0.68 ± 0.09, which is significantly less than that in the 13.00-15.99-year-old group (0.72 ± 0.08; $P = 0.03$ by the Kruskal-Wallis test; $P = .037$ by the Dunn multiple comparisons test) (Table 4, Figure 3, A to C).

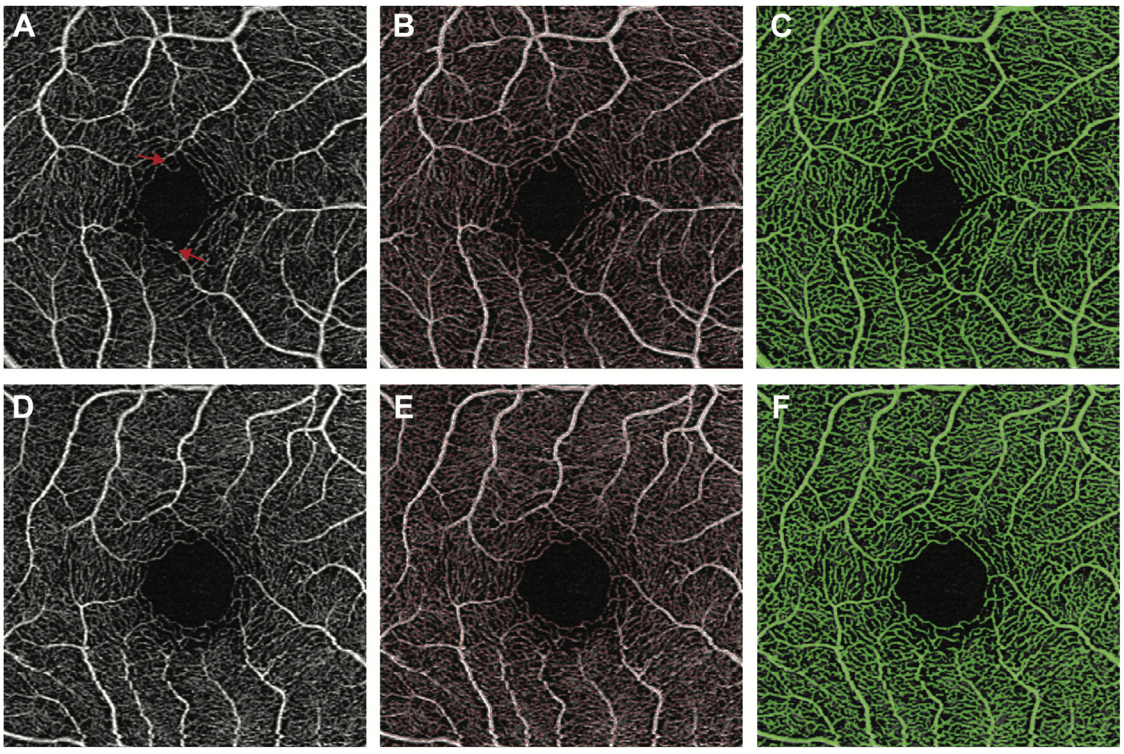

FIGURE 2. Representative cases of retina superficial capillary plexus by optical coherence tomography angiography (OCTA). (A-C) Images showing the retina superficial capillary plexus by OCTA in a healthy 6-year-old girl with AL as 22.1 mm, spherical equivalent (SE) as +1.75D and LogMAR BCVA as 0.1. The shape of fovea avascular zone was irregular with the presence of loop-like structure (red arrow). (D-F) Images showing the retina superficial capillary plexus by OCTA of a healthy 14-year-old boy with AL as 24.56 mm, SE as −3.0D, and LogMAR best-corrected visual acuity as −0.1. The microvasculature in the 14-year-old boy was more complicated and compacted than with images of the 6-year-old girl. (B and E) Skeletonized images generated by the built-in software for the vascular density measurement. (C and F) Binarized images generated by the built-in software for the perfusion density measurement.

Also, several signs that could be associated with the maturity of FAZ were quantified, including the nonconsecutive vessel branches toward the macular center and the vascular loops contributing to the irregular shape of FAZ (Figure 2, D through I). In children 4.00-6.99 years old, more than one-fourth of the children (25.94%) presented with nonconsecutive vessels branched toward the macular center, and 36.36% children showed vascular loops contributing to the irregular shape. The percentages decreased to 20% and 32.22% in children 7.00-9.99 years old (11.11%) and 27.78 in children 10.00-12.99 years old (5.17%) and 18.97% in children 13.00-15.99 years old, respectively. Children at younger ages had significantly higher rates to present nonconsecutive vessel branches and vascular loops contributing to the irregular shape of FAZ ($P = .0002$ and $P = .024$ by chi-square test for trend, respectively) (Table 5).

DISCUSSION

OCTA HAS RAPIDLY EVOLVED AS A NOVEL, NONINVASIVE imaging technique that provides images of the retina microvasculature in seconds. Unlike fundus fluorescein angiography, OCTA discriminates retinal blood flow without dye and avoids the risk of allergic reactions. Considering these advantages, OCTA appears to be an excellent tool for examination of retina microvasculature in children.[13]

OCTA separates the retina capillary networks into superficial and deep vascular plexi. The superficial vascular plexus supplies the ganglion cell layer and the inner plexiform where a decrease in blood flow and macular vessel density with aging has been demonstrated.[7,14,15] These changes may be caused by decreased demands for oxygen and nutrients. Nevertheless, it remains unknown whether the blood supply and vessel density of the retinal superficial vascular plexus continues to develop in children accompanied by an increased demand of oxygen and nutrient. Zhang and associates[10] reported that the superficial capillary plexus was not related to age in a study of 75 eyes in children 8-16 years of age. In addition to the small sample size, no distribution data of age were provided. Recently, Hsu and associates[9] reported that the superficial vascular density and deep vascular density were increased with age in children 9 weeks-17 years of age. Nevertheless, these

TABLE 2. Macular Vascular Density and Perfusion Density in Children at Different Ages

Variables	4-6 Years Old (n = 77)	7-9 Years Old (n = 90)	10-12 Years Old (n = 108)	13-15 Years Old (n = 58)	*P* (One-Way ANOVA)	*P* (Multiple Comparison Linear Trend)
Mean ± SD vascular density (median), mm^{-1}						
Full macular	20.81 ± 1.56 (21.10)	21.57 ± 1.05 (21.80)	21.61 ± 1.35 (21.90)	22.01 ± 0.89 (21.90)	<.0001	<.0001
Central macular	11.02 ± 2.74 (10.70)	12.02 ± 2.62 (12.10)	12.19 ± 2.86 (12.50)	12.88 ± 2.96 (12.65)	.0015	.0002
Para-macular	22.04 ± 1.61 (22.40)	22.79 ± 1.04 (22.84)	22.81 ± 1.38 (23.00)	23.16 ± 0.87 (23.25)	<.0001	<.0001
Mean ± SD perfusion density (median)						
Full macular	0.376 ± 0.027 (0.380)	0.384 ± 0.017 (0.387)	0.384 ± 0.020 (0.387)	0.389 ± 0.014 (0.389)	.0028	.0007
Central macular	0.198 ± 0.054 (0.191)	0.208 ± 0.045 (0.211)	0.209 ± 0.050 (0.210)	0.215 ± 0.048 (0.214)	.25	NA
Para-macular	0.399 ± 0.026 (0.402)	0.407 ± 0.017 (0.409)	0.406 ± 0.019 (0.411)	0.411 ± 0.013 (0.413)	.0055	.0019

NA = not applicable.

TABLE 3. Relationships Among Age, Sex, SE, Axial Length, and Vascular Density/Perfusion Density

	Vascular Density (Full Macular)				Perfusion Density (Full Macular)			
	Bivariate Correlation		Partial Correlation (Adjusted by the Rest of Significant Characters)		Bivariate Correlation		Partial Correlation (Adjusted by the Rest of Significant Characters)	
Variables	r	*P*	r	*P*	r	*P*	r	*P*
Age, y	0.303	<.0001	0.183	.001	0.221	<0.0001	0.097	.081
Sex	−0.047	.389[a]	–	–	−0.029	.59[a]	–	–
SE, D	−0.228	<.0001	−0.010	.863	−0.593	<.0001	0.021	.701
Axial length, mm	0.266	<.0001	0.056	.311	0.655	<.0001	0.006	.913

SE = spherical equivaent.
[a]Spearman correlation.

TABLE 4. FAZ Characters in Children at Different Ages

Variables	4-6 Years Old (n = 77)	7-9 Years Old (n = 90)	10-12 Years Old (n = 108)	13-15 Years Old (n = 58)	*P*	*P* (Multiple Comparison)
Mean ± SD FAZ area (median), mm^2	0.22 ± 0.084 (0.22)	0.24 ± 0.085 (0.23)	0.24 ± 0.093 (0.24)	0.25 ± 0.089 (0.25)	.19	NA
Mean ± SD FAZ perimeter (median), mm^{-1}	1.97 ± 0.41 (2.02)	2.06 ± 0.36 (2.05)	2.03 ± 0.42 (2.09)	2.07 ± 0.36 (2.12)	.46[a]	NA
Mean ± SD FAZ AI (median)	0.68 ± 0.09 (0.69)	0.69 ± 0.07 (0.69)	0.70 ± 0.08 (0.70)	0.72 ± 0.08 (0.73)	.03[a]	.037 (4-6 vs. 13-15)[b]

AI = acircularity index; FAZ = fovea avascular zone.
[a]Kruskal-Wallis test.
[b]Dunn's multiple comparisons test.

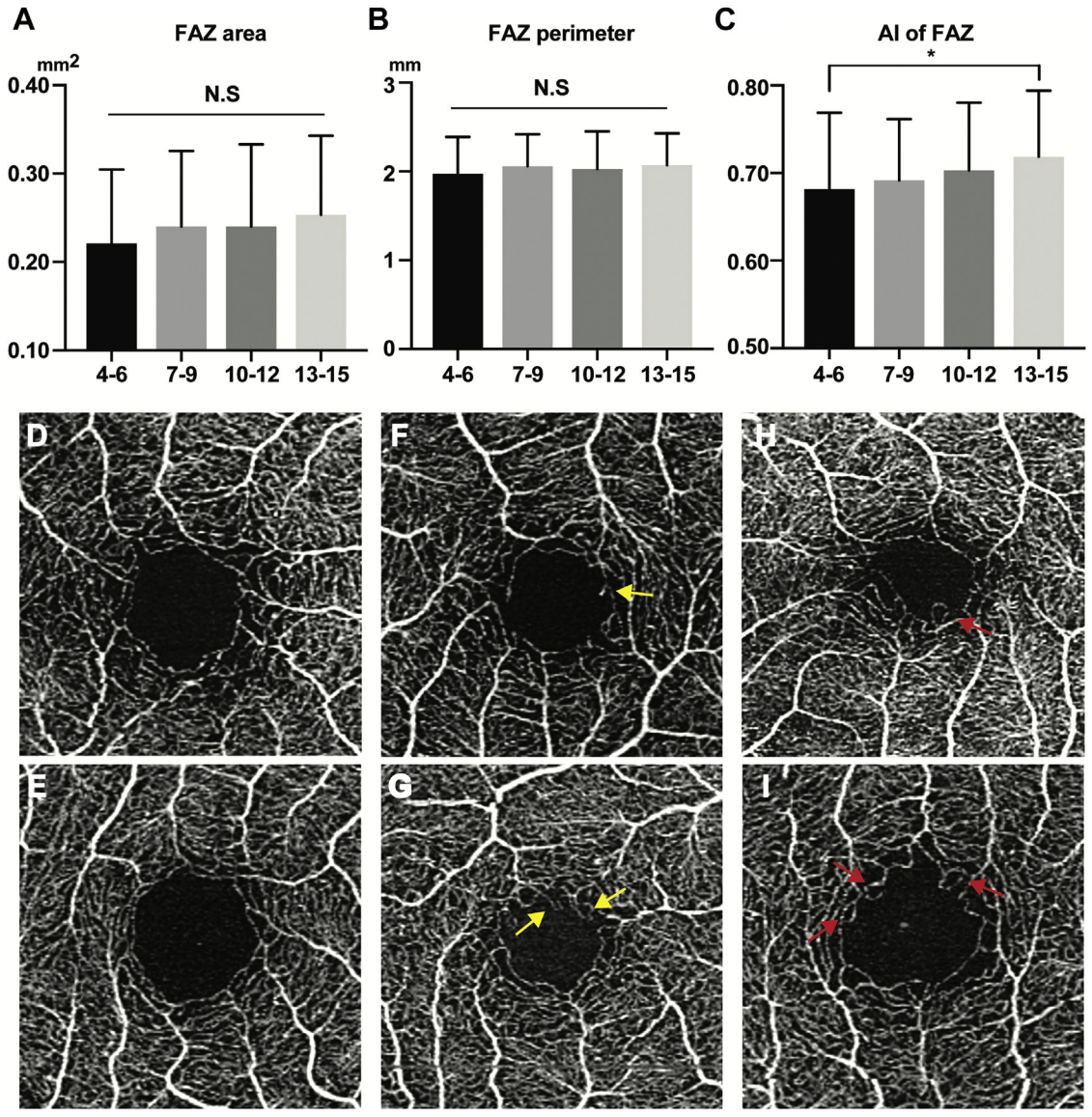

FIGURE 3. Morphological characters of FAZ in children at different ages. The fovea avascular zone (FAZ) areas (A) and FAZ perimeters (B) were comparable in children of different ages. However, the acircularity index (AI) of FAZ (C) in older children was statistically higher than in younger children. (D-E) Two examples are shown of regularly shaped FAZ with smooth edges and continuous vessels from a normal 13-year-old boy (D) and a 15-year-old girl (E). (F-G) Two examples are shown of the nonconsecutive vessel branches toward the macular center (yellow arrow) from a normal 7-year-old boy (F) and a 4-year-old boy (G). (H-I) Two examples are shown of the vascular loops contributing to the irregular shape of FAZ (red arrow) from a normal 6-year-old girl (H) and a 5-year-old boy (I). *$P < .05$; NS = no significance.

data were not adjusted for the AL. Considering the wide range of AL in children, the conclusions still need to be verified. In this study, first the continuous development of the microvasculature was demonstrated in terms of increased vessel density and perfusion density with age after adjusting for the AL.

Although most studies have reported that development of the macula should be completed at approximately 4 years of age. Recently, Lee and associates[3] showed a continuous development of the retinal layers in adolescents and even younger adults by handheld OCT, yet at a much slower rate. In the para- and perifovea, the ganglion cell layer increased slightly in thickness even after the child's fourth year. The development of the outer retina layer could last until 10 years of age. These data suggested an ignored fine adjustment of the macular structure, which could be the possible basis of the continuous development of the macular microvasculature.

The foveal avascular zone is an area devoid of both superficial and deep plexi. The FAZ is thought to remain avascular throughout ocular development and is the most important organization related to macular acuity.[16] The

TABLE 5. Percentage of Children with Nonconsecutive Vessel Branches and Vascular Loops in FAZ

	4-6 Years Old (n = 77)	7-9 Years Old (n = 90)	10-12 Years Old (n = 108)	13-15 Years Old (n = 58)	*P*
Nonconsecutive vessel branches, n/N	20/77 (25.94%)	18/90 (20%)	12/108 (11.11%)	3/58 (5.17%)	.0002
Vascular loops, n/N	28/77 (36.36%)	29/90 (32.22%)	30/108 (27.78%)	11/58 (18.97%)	.024

FAZ = fovea avascular zone.

discontinuous vessel loop of FAZ is considered a topographic biomarker of pathological conditions of the retina vessels.[17-19] Nevertheless, to date, it remains unknown when and how the FAZ forms and matures. The present study found that, although the area and perimeter of FAZ remain unchanged from the age of 4, FAZ microstructural development continues even until 13-16 years of age. The FAZ becomes more regular, smoother, and continuous with age. The number of nonconsecutive vessel branches toward the macular center and vessel loops decreased dramatically in older children. Our study first proposed 2 microvascular indicators, the nonconsecutive vessel branches and vascular loops contributing to the irregular shape of FAZ could be associated with the maturity of FAZ. These results also suggest a continuous pruning process of FAZ during development. In future studies, it will be compelling to determine whether the pruning processing are the physiological basis for macular development and whether it is induced by increased demand for oxygen and nutrition.

In children, the quantitative analysis of retinal blood flow and FAZ is necessary for evaluation of macular perfusion status in several congenital and acquired retinopathies, including retinopathy of prematurity, familial exudative vitreoretinopathy, coats, and others. These results present a normative database of the macular microvasculature, including vascular density, perfusion density, and FAZ by OCTA in more than 300 children 4-16 years of age, which fill in gaps in normative values as well as the status of retinal microvasculature maturation.

The present study included a large population of healthy children with a relatively equal age distribution and analyzed a large amount of information regarding the macular microvasculature. Nevertheless, several limitations remain. First, as a hospital-based study, despite the fact that critical exclusion criteria were used, the study may not entirely represent a normal population. In addition, this study was conducted solely in Chinese children. As race and ethnicity could affect the foveal shape and may influence FAZ development, the generalizability of these data still needs further confirmation in other races. Furthermore, as a cross-sectional study, trends of maturation in macular vasculature and FAZ were shown between children and adolescents. Nevertheless, a longitudinal study remains warranted to demonstrate continuous changes of macular vessels during development. Finally, even though eye movement was traced and decreased using software, the artifacts introduced by eye motion could not be totally removed. Although image quality was assessed by both quality score and assessment by an experienced investigator, the artifacts were more common in young children.

In conclusion, the microcirculation database was expanded in children from 4 to 16 years old using OCTA. Our results suggest that macular vascular density and perfusion density increase with age. Although FAZ area and perimeter did not change, the microstructure of FAZ pruned and tended to form smooth and regular avascular areas during development. Further studies are needed to determine the mechanisms and clinical significance of these changes.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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