Relationships of Retinal Vessel Diameters with Optic Disc, Macular and Retinal Nerve Fiber Layer Parameters in 6-Year-Old Children

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Purpose. To describe the normal anatomic relationships of retinal vessel diameters with optic disc, macula, and retinal nerve fiber layer parameters in young children.

Methods. This was a population-based, cross-sectional study of 1204 healthy children 6 years of age who were participating in the Sydney Childhood Eye Study. Retinal arteriolar and venular diameters were measured from fundus photographs using standardized computer-based methods. Optical coherence tomography was performed to obtain measurements of the optic disc, macula, and retinal nerve fiber layer parameters.

Results. In multivariate analyses, each standard deviation (SD) decrease in optic disc area was associated with a 0.14-pixel decrease ($P = 0.05$) in arteriolar diameter and a 0.31-pixel decrease ($P < 0.01$) in venular diameter. Each SD decrease in optic cup area was associated with a 0.15-pixel decrease ($P = 0.05$) in arteriolar diameter and a 0.43-pixel decrease ($P < 0.01$) in venular diameter. Each SD decrease in macular (inner/outer) thickness or volume was associated with a 0.25- to 0.39-pixel decrease ($P < 0.01$) in arteriolar diameter and a 0.36- to 0.71-pixel decrease ($P < 0.01$) in venular diameter, and each SD decrease in retinal nerve fiber layer thickness was associated with a 0.62-pixel decrease ($P < 0.01$) in arteriolar diameter and a 0.99-pixel decrease ($P < 0.01$) in venular diameter.

Conclusions. Children's eyes with a smaller optic disc, thinner macula, and thinner retinal nerve fiber layer have narrower retinal vessels. These anatomic relationships may provide new insights into the vascular etiology of various ocular diseases. (*Invest Ophthalmol Vis Sci.* 2008;49:2403–2408) DOI: 10.1167/iovs.07-1313

Many diseases affecting the retina (e.g., age-related macular degeneration, diabetic retinopathy) and optic nerve (e.g., glaucoma, ischemic optic neuropathy) are leading causes of vision loss in adults. Studies suggest that these ocular conditions may have a vascular etiology.[1–4] Supporting this notion are findings from recent population-based studies demonstrating that changes in retinal vessel diameter are associated with or may predict the long-term risk of retinopathy,[5–9] glaucoma,[10] and retinal and macular degenerative abnormalities.[11,12] Not all studies, however, have reported significant associations.[11,13–16] Reasons for these inconsistencies are not apparent, but a better understanding of the normal anatomic relationships of retinal vessel diameter with the relevant retinal and optic disc parameters would clearly be useful. In addition, identifying the ocular factors that may affect retinal vessel diameter also has relevance for studies that examine the use of retinal vessel diameter as a novel biomarker of systemic vascular disease risk.[17–21]

In the Beaver Dam Eye Study, which examined persons 43 years of age and older, narrower retinal vessels were related to smaller optic discs, a sign linked to the pathogenesis of nonarteritic ischemic optic neuropathy and retinal vascular disease.[22] These findings were replicated in a subsequent study of young children in Singapore.[23] Pediatric studies are most ideal to address this type of research question, because the confounding effects of systemic factors (e.g., diabetes, smoking, medication use) and ocular disease processes (e.g., diabetic retinopathy, glaucoma) on retinal vessel measurements are of less concern in young children,[24] allowing more precise evaluation of the normal anatomic relationships of retinal vessel diameter to other ocular parameters.

In this study, we sought to examine the relationships of retinal vessel diameter not only with optic disc features, but also macular and retinal nerve fiber layer (RNFL) parameters, as measured with optical coherence tomography (OCT), in a population-based sample of children in Australia.

Methods

Study Population

Detailed description of the Sydney Childhood Eye Study (also termed Sydney Myopia Study) has been reported elsewhere.[25–28] In brief, 34 primary schools in Sydney were identified through random stratified sampling. Stratification of the city was based on socioeconomic status data from the Australian Bureau of Statistics 2001 national census. Examinations were conducted from 2003 through 2004. The study was approved by the Human Research Ethics Committee, University of Sydney and the Department of Education and Training, New South Wales, Australia. It was conducted in accordance with the tenets of the Declaration of Helsinki. We obtained written informed consent from at least one parent of each child and verbal assent from the children. There were initially 2238 eligible children; 1765 (78.9%) consented to the study. Of these, 25 children were absent from school during the examination period, 431 had OCT scans of inadequate quality, and 105 had retinal photographs that were of inadequate quality for retinal vessel measurement, leaving 1204 (68.2%) children for the analysis. All children attended school (year 1) and were mostly (71%) 6 years of age.

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OCT Measurements

Optic disc parameters were measured through dilated pupils with a Stratus OCT (software ver. 4.0.4; Carl Zeiss Meditec, Dublin, CA), by using a standardized protocol described previously.[25–27] Measurements were performed with the fast optic disc scanning protocol, which acquired full scans in 1.92 seconds.[27] Three fast optic disc scans were performed successively without making changes to scan placement, and the measurements were averaged before analysis. The average thicknesses of the macula and peripapillary RNFL were also measured.[25,26] Similarly, the fast RNFL thickness scanning protocol was used, and measurements used in the analysis were based on average results of three scans. More than 90% of scans were performed by a single experienced operator. Scans were accepted only if they were complete, were free of artifacts, and had signal strengths of at least 5.

All OCT variables used in our analysis, including their reproducibility data, have been described elsewhere.[25–27,29] The transverse dimensions of the optic disc measurements (e.g., disc diameter) were corrected for magnification using the formula: $b = b_0/[1 + (0.018 \times D_{axial}) + (0.002 \times D_{refraction})]$, where b_0 and b are uncorrected and corrected transverse lengths, respectively. The same correction was used for areas with one axial dimension. For transverse areas and for volumes, the denominator was squared. D_{axial} and $D_{refraction}$ are changes in magnification due to differences from default values of axial length (L) and refraction (D_{error}), respectively, where $D_{axial} = (24.46 - L)/0.42$ and $D_{refraction} = (D_{error} - D_{axial})$.[27] Ocular magnification had minimal impact on the thickness measures (e.g., macular, RNFL).[29]

Retinal Photography and Retinal Vessel Measurements

Children had dilated 60° digital photographs taken of the optic disc and macula of both eyes with a fundus camera (60UVi-D10; Canon, Tokyo, Japan), according to standardized procedures.[25–28] Methods used to measure and summarize retinal vessel diameter from digitized photographs after standardized protocols are detailed elsewhere.[30,31] Briefly, a computer-based program was used to measure the diameter of all retinal vessels located 0.5 to 1 disc diameter from the optic disc margin in retinal photographs. Individual retinal vascular caliber measurements from an eye were summarized as average indices according to formulas described previously.[30–32] These indices, the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), represented the hypothesized summary measures of the average arteriolar and venular diameters of that eye. One grader (BT) masked to participant identity and characteristics performed all retinal vessel measurements for this study.[28] Retinal vessel diameters in the right eye were measured, and left eye measurements were used when photographs of the right eye were ungradable. Previous studies have shown high intra- and intergrader reproducibility of the retinal vascular caliber measurements obtained from this computer-based program (intraclass correlation coefficients > 0.85).[23,24,30,31,33–35] Retinal vessel measurements were expressed in pixels and corrected for ocular magnification by using the Bengtsson formula ($1 - 0.017 \times$ spherical equivalent refraction).[33,36]

Collection of Other Information

Anthropometric factors were measured at the school premises. Body mass index (BMI) was calculated as the weight (in kilograms) divided by the square of the height (in meters).[28] Blood pressure was measured according to a standardized protocol.[37] Mean arterial blood pressure (MABP) was calculated as one third of the systolic plus two thirds of the diastolic blood pressure. Cycloplegic autorefraction and keratometry were also performed.[38] Axial length was measured using optical biometry.[28] Information about the child's birth, such as birth weight, was sought in a questionnaire completed by the parents.[28]

Statistical Analysis

We compared characteristics of children included and excluded from our analysis. Results were reported as means or proportions, with differences tested using analysis of variance or χ^2 tests, respectively. Analyses of covariance and linear regression models were used to determine the association between OCT parameters and retinal vessel diameters. We used multiple linear regression models to estimate the differences in arteriolar and venular diameters for each standard deviation (SD) change in OCT parameters, adjusted for age, sex, ethnicity, BMI, birth weight, and MABP. All probabilities quoted are two-sided, and all statistical analyses were undertaken (SPSS ver. 12.0.1; SPSS, Chicago, IL).

Results

Table 1 shows that, compared with the excluded children, children included in our study were slightly more likely to be European Caucasian (white) and to have a lower MABP. Other characteristics were similar.

Figure 1 shows that smaller optic cups were associated with smaller retinal vessel diameters. In multivariate analyses, each SD decrease in optic disc and cup size was also associated with narrower retinal arteriolar and venular diameters (Table 2). The associations of retinal arteriolar and venular diameters with optic cup measures appear to be stronger than those with optic disc measures, and the difference in vessel diameters were more marked in venules than in arterioles. Optic disc rim area was not associated with retinal vessel diameter.

Figures 2 and 3 show that a smaller macular area and thinner RNFL were associated with smaller retinal vessel diameters. In multivariate analyses, a decrease in inner and outer macular thickness and macular volume was associated with narrower retinal arterioles and venules, independent of adjusted covariates (Table 3). Each SD decrease in macular (inner/outer) thickness or volume was associated with a 0.25- to 0.39-pixel ($P < 0.01$) decrease in arteriolar diameter and a 0.36- to 0.71-pixel ($P < 0.01$) decrease in venular diameter. Central macular thickness was not associated with retinal vessel diameters. Further, each SD decrease in RNFL was associated with a 0.62-pixel ($P < 0.01$) decrease in arteriolar diameter and a 0.99-pixel ($P < 0.01$) decrease in venular diameter (Table 3). These associations were similar to retinal thickness in different quadrants of the retina.

Table 1. Characteristics of Children Included and Excluded in the Study

	Excluded Children $n = 531$		Included Children $n = 1204$		
	n	**%**	***n***	**%**	***P***
Sex, boys	259	48.8	600	49.8	0.69
Ethnicity					
European Caucasian	302	56.9	802	66.6	
East Asian	118	22.2	180	15.0	
Middle Eastern	40	7.5	43	3.6	<0.001
	Mean	**SD**	**Mean**	**SD**	
Age (y)	6.71	0.42	6.70	0.43	0.67
BMI (kg/m^2)	16.2	2.2	16.2	2.1	0.93
Birth length (cm)	50.4	3.8	50.8	5.1	0.09
Birth weight (g)	3363	610	3385	575	0.49
MABP (mm Hg)	74.3	9.9	72.9	9.3	0.006
Axial length (mm)	22.5	0.69	22.6	0.69	0.74

Data are numbers and percentages or the mean and SD; probabilities are based on χ^2 (categorical) and independent sample t-test (continuous).

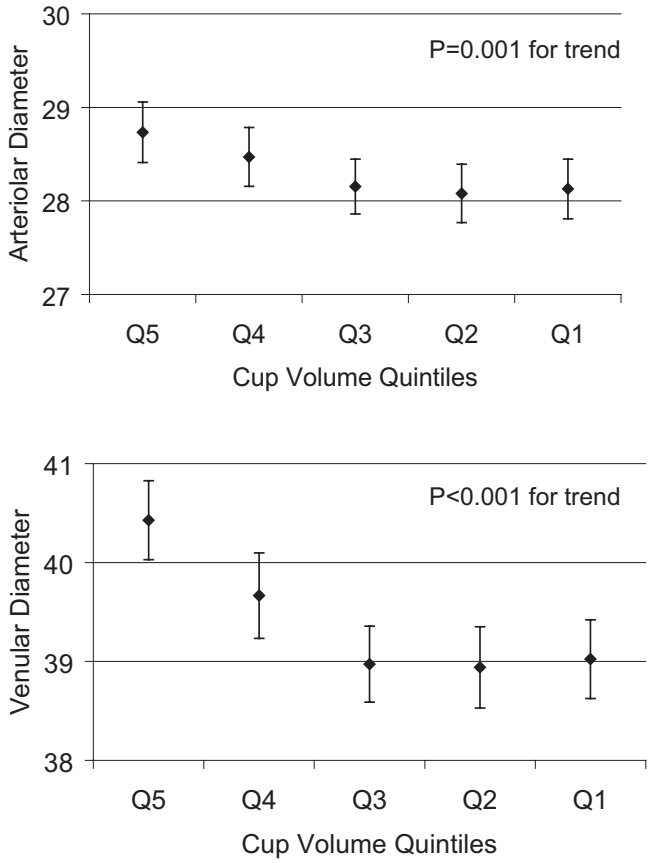

Figure 1. Relationship of retinal arteriolar and venular diameters (in pixels) and optic cup volume (in cubic millimeters).

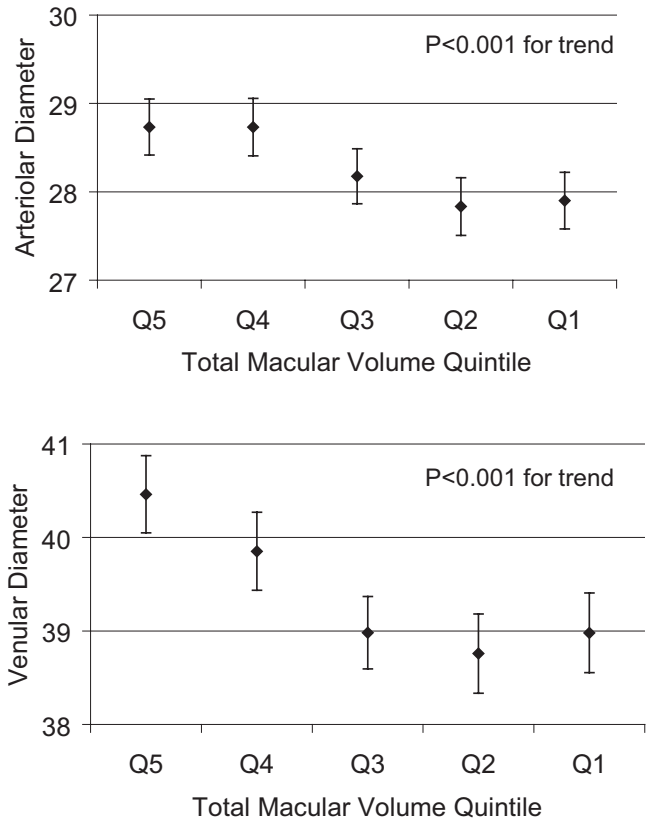

Figure 2. Relationship of retinal arteriolar and venular diameters (pixel) and macular volume (in cubic millimeters).

Table 2. Relationship of Optic Disc Parameters to Retinal Vessel Diameter

Optic Disc Parameters (per SD decrease)	Retinal Arteriolar Diameter (Pixels)				Retinal Venular Diameter (Pixels)			
	Unadjusted Mean (95% CI)*	*P*	Adjusted Mean (95% CI)*	*P*	Unadjusted Mean (95% CI)	*P*	Adjusted Mean (95% CI)	*P*
Vertical disc diameter, 0.27 mm	−0.08 (−0.22, 0.07)	0.29	−0.11 (−0.25, 0.04)	0.15	−0.16 (−0.35, 0.02)	0.09	−0.25 (−0.44, 0.06)	0.01
Vertical cup diameter, 0.32 mm	−0.24 (−0.38, −0.09)	<0.01	−0.15 (−0.30, 0.01)	0.06	−0.52 (−0.70, −0.33)	<0.01	−0.37 (−0.57, −0.17)	<0.01
Vertical cup-to-disc ratio, 0.18	−0.21 (−0.35, −0.07)	<0.01	−0.13 (−0.28, 0.03)	0.10	−0.46 (−0.64, −0.27)	<0.01	−0.30 (−0.47, −0.10)	<0.01
Horizontal disc diameter, 0.21 mm	−0.04 (−0.18, 0.09)	0.53	−0.09 (−0.23, 0.06)	0.22	−0.15 (−0.33, 0.03)	0.10	−0.13 (−0.32, 0.06)	0.17
Horizontal cup diameter, 0.32 mm	−0.22 (−0.36, −0.08)	<0.01	−0.16 (−0.31, −0.01)	0.04	−0.51 (−0.69, −0.33)	<0.01	−0.37 (−0.57, −0.18)	<0.01
Horizontal cup-to-disc ratio, 0.19	−0.21 (−0.35, −0.07)	<0.01	−0.13 (−0.27, 0.02)	0.09	−0.46 (−0.64, −0.28)	<0.01	−0.33 (−0.52, −0.14)	<0.01
Disc area, 0.38 mm^2	−0.12 (−0.26, −0.02)	0.09	−0.14 (−0.29, 0.00)	0.05	−0.29 (−0.47, −0.11)	<0.01	−0.31 (−0.50, −0.12)	<0.01
Cup area, 0.33 mm^2	−0.22 (−0.36, −0.08)	<0.01	−0.15 (−0.30, 0.00)	0.05	−0.54 (−0.72, −0.36)	<0.01	−0.43 (−0.62, −0.23)	<0.01
Cup volume, 0.07 mm^3	−0.20 (−0.34, −0.06)	<0.01	−0.17 (−0.32, −0.02)	0.03	−0.58 (−0.76, −0.39)	<0.01	−0.49 (−0.69, −0.29)	<0.01
Rim area, 0.43 mm^2	0.06 (−0.08, 0.20)	0.41	−0.02 (−0.17, 0.12)	0.30	0.15 (−0.03, 0.34)	0.10	0.03 (−0.17, 0.22)	0.79
Average nerve width, 0.04 mm	0.22 (0.09, 0.34)	<0.01	0.15 (0.01, 0.29)	0.03	0.31 (0.14, 0.48)	<0.01	0.18 (0.00, 0.35)	0.05

* Mean (95% CI) difference in retinal vessel diameter adjusted for age, sex, ethnicity, body mass index, birth weight, and MABP.

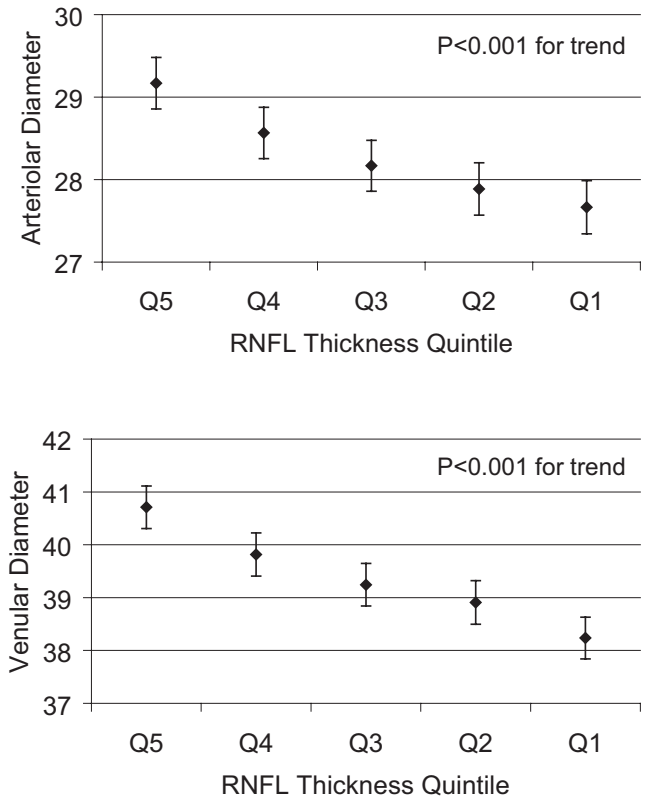

FIGURE 3. Relationship of retinal arteriolar and venular diameters (in pixels) and RNFL thickness (in micrometers).

In supplementary analyses, these associations remained unchanged after additional adjustment for body weight and height.

DISCUSSION

Recent advances in retinal vascular image analysis have permitted reliable quantitative measurement of retinal vessel diameter, providing a means to determine, in epidemiologic studies, the associations of retinal vascular processes with major eye and systemic diseases. Using these techniques, studies in adults have associated retinal vessel diameter with a range of important ocular diseases affecting the optic disc, macula, and retina.[5–11] However, further insights into potential pathophysiological mechanisms of these associations are limited until there is a better understanding of the normal anatomic relationships between retinal vessel diameter and other structural parameters in the retina. Our present study in a population-based sample of young and healthy children provides new data on normal anatomic relationships between retinal vessel diameter and optic disc, macular, and RNFL parameters. In the study, eyes with smaller optic discs, thinner macula, and thinner RNFL, as measured by OCT, had narrower retinal arterioles and venules.

To the best of our knowledge, this is the first study to correlate OCT parameters with retinal vessel diameters. Two previous studies, the Beaver Dam Eye Study in adults and the Singapore Cohort Study of Risk Factors for Myopia in children, which estimated optic disc size from retinal photographs, similarly found narrower retinal vessels in eyes with smaller optic discs.[22,23] As proposed previously, this association could explain the potential mechanistic pathways involved in the pathogenesis of nonarteritic ischemic optic neuropathy.[22,23]

TABLE 3. Relationship of Macular and RNFL Parameters to Retinal Vessel Diameter

Macular/Retinal Parameters (per SD decrease)	Retinal Arteriolar Diameter (Pixel)				Retinal Venular Diameter (Pixel)			
	Unadjusted Mean (95% CI)	*P*	Adjusted Mean (95% CI)*	*P*	Unadjusted Mean (95% CI)	*P*	Adjusted Mean (95% CI)*	*P*
Central macular thickness, 17.7 μm	0.18 (0.04, 0.33)	0.01	0.03 (−0.13, 0.19)	0.69	0.32 (0.13, 0.51)	<0.01	0.15 (−0.07, 0.34)	0.21
Center fovea average thickness								
Inner macular thickness, 16.2 μm	−0.21 (−0.36, −0.07)	<0.01	−0.25 (−0.40, −0.10)	<0.01	−0.23 (−0.42, −0.05)	0.02	−0.36 (−0.56, −0.17)	<0.01
Outer macular thickness, 14.4 μm	−0.41 (−0.55, −0.27)	<0.01	−0.39 (−0.54, −0.24)	<0.01	−0.63 (−0.81, −0.44)	<0.01	−0.71 (−0.90, −0.52)	<0.01
Macular volume								
Total, 0.40 mm^3	−0.36 (−0.50, −0.22)	<0.01	−0.36 (−0.51, −0.21)	<0.01	−0.53 (−0.71, −0.34)	<0.01	−0.62 (−0.81, −0.43)	<0.01
Central, 0.01 mm^3	0.13 (0.03, 0.23)	0.01	0.02 (−0.09, 0.13)	0.69	0.23 (0.09, 0.36)	<0.01	0.09 (0.05, 0.24)	0.21
RNFL (EI), 0.11 mm^2	−0.59 (−0.74, −0.45)	<0.01	−0.59 (−0.75, −0.43)	<0.01	−0.97 (−1.16, −0.78)	<0.01	−0.97 (−1.17, −0.77)	<0.01
RNFL, 11.3 μm	−0.64 (−0.78, −0.50)	<0.01	−0.62 (−0.76, −0.47)	<0.01	−1.02 (−1.20, −0.84)	<0.01	−0.99 (−1.18, −0.80)	<0.01
Quadrants of retinal thickness								
Superior, 20.0 μm	−0.52 (−0.66, −0.38)	<0.01	−0.51 (−0.66, −0.36)	<0.01	−0.78 (−0.96, −0.60)	<0.01	−0.74 (−0.93, −0.55)	<0.01
Inferior, 20.3 μm	−0.52 (−0.66, −0.38)	<0.01	−0.44 (−0.59, −0.29)	<0.01	−0.83 (−1.01, −0.65)	<0.01	−0.78 (−0.97, −0.59)	<0.01
Temporal, 14.4 μm	−0.20 (−0.35, −0.06)	<0.01	−0.21 (−0.36, −0.06)	<0.01	−0.32 (−0.51, −0.14)	<0.01	−0.32 (−0.51, −0.12)	<0.01
Nasal, 19.7 μm	−0.25 (−0.39, −0.10)	<0.01	−0.25 (−0.40, −0.10)	<0.01	−0.44 (−0.62, −0.25)	<0.01	−0.43 (−0.62, −0.23)	<0.01

RNFL (EI), retinal nerve fiber layer (estimated integral).

* Mean (95% CI) difference in retinal vessel diameter adjusted for age, sex, ethnicity, body mass index, birth weight, and MABP.

It is possible that the crowding at the lamina cribrosa in eyes with small optic discs leads to the compression of retinal vessels at the disc and could thereby predispose eyes to nonarteritic anterior ischemic optic neuropathy (NAION).[39,40] Of interest, the magnitude of the association of retinal vessel diameters was stronger for the optic cup than for the optic disc in our study, suggesting that crowding of nerve fibers, hypothesized in the pathogenesis of NAION, as they pass through the lamina cribrosa could be more pronounced within the optic cup.[39,41] Also in keeping with this hypothesis is our finding of narrower retinal vessels in eyes with smaller optic cup-to-disc ratio, a well-known risk factor for NAION.[39,40] Although we do not anticipate NAION to be present in our sample of young children, this intriguing relationship may provide support to the vascular etiology of NAION in adults.[1,42]

Furthermore, our study showed that eyes with a thinner macula and RNFL had narrower retinal vessels. There are no directly comparable studies. Although the biological mechanisms for these findings remain uncertain, it is possible that narrower retinal vessels represent lower metabolic, and thus vascular, demand from eyes with a thinner macula and RNFL. Alternatively, our findings could be a reflection of proportional changes related to retinal vessel diameters and the fundus parameters examined, but this is unlikely to be the case for two reasons. First, we adjusted for anthropometric factors (BMI, height, and weight, separately) in our analyses. Second, not all ocular parameters (e.g., central macular thickness and volume) were shown to change proportionally with retinal vessel diameters. The lack of association between central macular parameters and retinal vessel diameters may reflect the fact that the central part of the macula normally does not have retinal vessels. Additional studies would clearly be useful to elucidate further the mechanistic pathways that may underlie the association of narrower retinal vessels with a thinner macula and RNFL seen in our study.

Another noteworthy observation is the possibility of nonlinearity in the association of retinal vessel diameters with optic disc and macular volumes (Figs. 1, 2). Unlike the relationship with the RNFL (Fig. 3), there appears to be a point at which retinal vessels cease to narrow (below the third quartile of optic disc and macular volumes). The significance of this finding remains unclear.

Strengths of our study include its large population-based sample of healthy 6-year-old children, in whom the confounding effects of systemic conditions (e.g., diabetes, smoking) and ocular disease processes (e.g., diabetic retinopathy, glaucoma) would be minimal by comparison with older adult populations, the standardized assessment of retinal vessel diameters, and use of OCT to precisely determine optic disc, macular, and retinal parameters. However, several potential limitations should be noted. First, the cross-sectional design of the study limits our ability to determine causality. Any biological mechanisms proposed herein should therefore be interpreted with caution and require validation by other studies. Second, despite adjustments for anthropometric and ocular magnification, we cannot totally exclude the possibility that our findings can, at least in part, be explained by a difference in the size of the eye in children growing at various rates. Finally, other limitations regarding the OCT measurements performed in our study, that have been described in detail elsewhere,[25–27] should also be taken into consideration.

In summary, in this study of a population-based sample of predominantly healthy 6-year-old children, we document anatomic relationships between retinal vessel diameters and optic disc, macula, and RNFL parameters. We found that eyes with a smaller optic disc, thinner macula, and thinner RNFL tend to have narrower retinal arterioles and venules. These data provide additional insights into the expected retinal vascular patterns in relation to fundal morphology and may further our understanding of individual susceptibility to ocular diseases affecting the optic disc, macula, and retina. It remains to be explored whether narrower retinal vascular caliber, detectable in early childhood, can provide prognostic information regarding the risks of ocular diseases in adulthood.

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