Relationship between Retinal Structures and Retinal Vessel Caliber in Normal Adolescents

Chameen Samarawickrama,[1] *Son C. Huynh,*[1] *Jie Jin Wang,*[1,2] *Amy Pai,*[1] *Nichole Joachim,*[1] *George Burlutsky,*[1] *Tien Y. Wong,*[2,3] *and Paul Mitchell*[1]

Purpose. To describe the normal physiological relationship between retinal arteriolar and venular caliber and retinal nerve fiber layer (RNFL), macular, and optic nerve head parameters.

Methods. The Sydney Childhood Eye Study assessed 2038 adolescents aged 12 years. Retinal vessel calibers were measured from digital fundus photographs using standardized protocols. Optical coherence tomography measurements of RNFL, macular, and optic nerve head parameters were obtained with the Fast-scan protocol of the Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA). Mixed model analyses were performed.

Results. After adjustment for covariates, each micrometer increase in RNFL thickness was associated with a 0.22-μm (0.15%, $P < 0.0001$) and 0.49-μm (0.23%, $P < 0.0001$) increase in mean arteriolar and venular caliber, respectively. This positive association existed across all RNFL quadrants (0.07%–0.24%, $P \leq 0.002$). Each micrometer increase in macular thickness (inner/outer) and cubic millimeter increase in macular volume was associated with a 0.12/0.15-μm (0.08%–0.10%, $P < 0.0001$) and 5.31-μm (3.53%, $P < 0.0001$) increase in mean arteriolar caliber and a 0.22/0.31-μm (0.10%–0.15%, $P < 0.0001$) and 10.95-μm (5.08%, $P < 0.0001$) increase in mean venular caliber, respectively. Finally, each millimeter increase in vertical optic disc diameter and each square millimeter increase in optic disc area was associated with a 2.83-μm (1.88%, $P = 0.02$) and 2.02-μm (1.35%, $P = 0.01$) increase in mean retinal arteriolar caliber and a 5.73-μm (2.66%, $P = 0.001$) and 5.02-μm (2.33%, $P < 0.0001$) increase in mean retinal venular diameter, respectively.

Conclusions. In normal adolescent retinas, thicker RNFL and macula parameters and larger optic discs correlate with larger retinal vascular caliber. Understanding these normal anatomic relationships is essential for determining their significance in studying the vascular etiology of ocular and systemic diseases. (*Invest Ophthalmol Vis Sci.* 2009;50:5619–5624) DOI:10.1167/iovs.09-3878

From the [1]Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia; [2]Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia; and [3]Singapore Eye Research Institute, National University of Singapore, Singapore.

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Corresponding author: Paul Mitchell, Centre for Vision Research, Department of Ophthalmology, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia; paul_mitchell@wmi.usyd.edu.au.

The study of retinal vessel caliber has increased in importance since recent reports have shown strong associations between the caliber of the retinal arterioles and venules and both ocular and systemic diseases. As such, vascular processes are implicated in many diseases involving the optic nerve (e.g., glaucoma, anterior ischemic optic neuropathy)[1,2] and the retina (e.g., age-related macular degeneration)[3–5] within the eye, as well as cardiovascular and cerebrovascular diseases.[6–23] However, not all reports have demonstrated significant associations.[13,24,25] Nonetheless, the evidence indicates that retinal vessel caliber may be a potent biomarker for some systemic conditions, as well as for many ocular diseases.

This vascular involvement was inferred after population-based studies in adults demonstrated that ocular anatomic structure and ocular disease prevalence were associated with changes in retinal vessel caliber, and increasingly, longitudinal data are validating this hypothesis. However, studies in adult populations are influenced by the disease process being examined, as well as by unavoidable ocular (e.g., cataract) and systemic (e.g., diabetes) confounders present with increasing age. Studies in young children are free of such confounders and have already provided some useful information; however, the eye in young children is undergoing rapid growth and may not reflect the relationships seen in adult eyes. Thus, the optimal population to examine is one in which the eye has reached adult size but is still free of common confounders. Such a situation is found in the eyes of adolescents.

The purpose of this study was therefore to document normative associations between retinal nerve fiber layer (RNFL), macular and optic nerve head parameters with retinal arteriolar and venular caliber in a large population-based sample of adolescents from Sydney, Australia, who are generally free of common ocular and systemic confounders and would be likely to reflect the normal physiological state in adult eyes.

Methods

Study Population

The Sydney Childhood Eye Study, incorporating the Sydney Myopia Study, examined a population-based sample of primary and secondary school students in Sydney. The study was approved by the Human Research Ethics Committee, University of Sydney, the Department of Education and Training, and the Catholic Education Office, New South Wales, Australia, and adhered to the tenets of the Declaration of Helsinki. Detailed study methods have been published elsewhere.[26–29] In brief, year-7 students (median age 12 years) were examined in 21 secondary schools across the metropolitan area of Sydney, Australia, from 2003 to 2005. The schools were selected by random cluster sampling and a proportional mix of public and private or religious schools were included and stratified according to socioeconomic data from the Australian Bureau of Statistics. All year-7 students in these schools were invited to participate. Informed written consent was obtained from at least one parent of each child, coupled with the verbal assent of all children. Examinations were performed on 2353 (75.3%) of 3144 eligible year-7 students from 2004 to 2005. Children with amblyopia, other retinal diseases, or poor or incomplete OCT

measurements or digital photographs were excluded from the analyses.

Questionnaire Data

Parents completed a comprehensive 193-item questionnaire from which each child's demographic and ocular history data were drawn. Parents of all Australian children are provided with a health record booklet at birth (the Blue Book) in which health professionals accurately record birth variables. As reported previously, we asked parents to extract this information from their child's Blue Book.[26,27]

Examinations

A thorough ocular examination was performed on all children. Monocular distance visual acuity (VA) was tested at 8 feet (244 cm) using a logarithm of the minimum angle of resolution (logMAR) chart. Presenting VA was assessed without and with spectacle correction, if worn, and was recorded as the number of letters read correctly from 0 to 70 (Snellen acuity, <20/200–20/10). The Beaver Dam Eye Study modification of the Early Treatment Diabetic Retinopathy Study protocol[30] was used to perform subjective refraction in children whose presenting VA was <0.02 logMAR units (<54 letters or <20/20). Axial length and keratometry were measured before cycloplegia with an optical biometer (IOLMaster; Carl Zeiss Meditec, Jena, Germany),[26,27] where the average of five measurements was used in analyses. Standing height, in meters, was measured for each child without shoes, while weight, in kilograms, was measured using a standard, calibrated, portable weighing machine. Body mass index (BMI) was calculated as weight divided by height squared (kilograms/square meters). Blood pressure was measured three times with an automated machine (model HEM-907; Omron Health Care, Singapore) with the average of the three measurements used for analyses.

Cycloplegia was induced with cyclopentolate 1% and tropicamide 1% (1 drop each), after instillation of amethocaine 1% (1 drop). Autorefraction was performed with an autorefractor (RK-F1; Canon, Tokyo, Japan) approximately 25 minutes after the last drop.

Retinal Vessel Measurements

Digital retinal photographs centered on each optic disc were obtained through dilated pupils using standardized settings from a nontelecentric fundus camera (CF-60UVi fundus camera, CF-DA camera adapter, EOS-10D digital camera; Canon).[27] Methods used to measure retinal arteriolar and venular calibers from digital fundus photographs have been described in detail elsewhere.[31,32] In brief, a computerized program was used to measure the caliber of all retinal vessels 0.5 to 1 disc diameter from the optic disc margin from digital fundus photographs centered on the optic disc. The vascular caliber measurements, measured in pixels and converted to micrometers, were summarized as average indices according to previously described formulas.[31–33] The central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) are hypothesized summary measurements of the average arteriolar and venular calibers of that eye. Retinal vessel caliber measured from only right eyes was used in this study, as a high correlation between calibers of the two eyes has been reported.[32,34] Four graders, masked to all participant characteristics, performed the retinal vessel caliber measurements for this study. One grader performed the majority (64%) of the measurements.

Optical Coherence Tomography

Optical coherence tomography (Stratus OCT, software ver. 4.0.4; Carl Zeiss Meditec, Dublin, CA) was performed through dilated pupils to obtain cross-sectional measurements of the retina and optic discs. The Stratus OCT utilizes partial coherence interferometry technology to obtain optical A-scans of the retina. This instrument has an axial resolution of approximately 10 μm,[35] as well as good intraobserver and interobserver reproducibility.[36,37]

Average peripapillary RNFL thickness was measured with the Fast RNFL thickness scanning protocol, consisting of 256 A-scans along a circular path with radius of 1.73 mm. Three RNFL fast scans were performed without making any changes to the scan placement and were averaged before analysis. The macular region was also imaged. Macular parameters were measured using the fast macular thickness mapping protocol, which acquires six 6-mm radial lines, consisting of 128 A-scans per line, passing through the foveal center in 1.92 seconds. An average of three scans was used for analysis. Finally, optic nerve head parameters were measured with the fast optic disc scanning protocol that acquires a full scan in the same period and consists of six 4-mm-long line scans arranged radially and centered on the optic disc, totaling 768 A-scans per optic nerve head. The average of three scans was used for analysis. A single experienced operator performed >90% of the scans. An internal fixation target was used for all scans, and the location of each scan on the retina was monitored with an infrared-sensitive video camera. The scans were performed assuming standard axial length (24.46 mm) and refraction (0 D) for consistency with usual clinical practice and were only accepted if they were free of artifacts, showed complete cross-sectional images, and had signal strengths of at least 5. Ocular magnification was corrected for this instrument with the appropriate formulas.[38]

Statistical Analysis

χ^2 was used to compare participants with nonparticipants in our sample for characteristics including sex and ethnicity. Student's *t*-test was used for comparing differences in age, BMI, birth weight, birth length, mean arterial blood pressure (MABP), and axial length. We constructed mixed models, with schools being the random effect, to adjust for the influence of age, sex, ethnicity, BMI, birth weight, axial length, and MABP. The model was first created with RNFL parameters as the independent variable and retinal arteriolar caliber as the dependent variable. A second model was then created with retinal venular caliber as the dependent variable, such that together the set of models described the associations between RNFL and arteriolar and venular caliber. Similar sets of mixed models were further created with macular parameters and optic nerve head parameters as independent variables (all analyses were performed with SAS software; ver. 9.1.3; SAS Institute, Cary, NC).

Results

Table 1 compares the characteristics of the adolescents included and excluded from our analyses. Those excluded were

Table 1. Characteristics of the Included and Excluded Children

	Excluded Children (n = 315)		Included Children (n = 2038)		
	n	**%**	***n***	**%**	***P***
Sex (boys)	135	42.9	1055	51.8	0.003
Ethnicity					
Caucasian	174	55.2	1232	60.5	
East Asian	56	17.8	296	14.5	
South Asian	26	8.3	103	5.1	
Middle Eastern	22	7.0	144	7.1	
Other	37	11.8	263	12.9	0.07
	Mean	**SD**	**Mean**	**SD**	***P***
Age, y	12.7	0.4	12.7	0.4	0.3
BMI, kg/m^2	20.0	4.0	20.5	4.2	0.08
Birth weight, kg	3.34	0.55	3.35	0.56	0.8
Birth length, cm	50.5	3.2	50.7	3.0	0.6
MABP, mm Hg	80.6	8.4	81.0	8.4	0.4
Axial length, mm	23.37	1.06	23.39	0.81	0.8

TABLE 2. Relationship of Retinal Vessel Caliber to Each Unit Increase in RNFL and Macular Parameters

RNFL/Macular Parameters	Retinal Arteriolar Diameter (μm)			Retinal Venular Diameter (μm)		
	Adjusted Mean (CI)	%	*P*	Adjusted Mean (CI)	%	*P*
RNFL Parameters						
RNFL (EI), mm^2	21.43 (16.12 to 26.73)	14.27	<0.0001	47.60 (40.12 to 55.09)	22.10	<0.0001
RNFL, μm	0.22 (0.17 to 0.28)	0.15	<0.0001	0.49 (0.41 to 0.57)	0.23	<0.0001
Quadrants of retinal thickness						
Superior, μm	0.10 (0.07 to 0.14)	0.07	<0.0001	0.24 (0.20 to 0.29)	0.11	<0.0001
Inferior, μm	0.10 (0.07 to 0.13)	0.07	<0.0001	0.20 (0.16 to 0.25)	0.09	<0.0001
Temporal, μm	0.07 (0.03 to 0.12)	0.05	0.002	0.15 (0.08 to 0.22)	0.07	<0.0001
Nasal, μm	0.08 (0.04 to 0.11)	0.05	<0.0001	0.20 (0.14 to 0.25)	0.09	<0.0001
Macular Parameters						
Foveal minimal thickness, μm	0.004 (−0.03 to 0.04)	0.002	0.8	0.01 (−0.03 to 0.06)	0.01	0.6
Central macular thickness, μm	0.02 (−0.01 to 0.06)	0.01	0.2	0.06 (0.01 to 0.11)	0.03	0.02
Central fovea average thickness						
Inner macular thickness, μm	0.12 (0.07 to 0.16)	0.08	<0.0001	0.22 (0.16 to 0.28)	0.10	<0.0001
Outer macular thickness, μm	0.15 (0.10 to 0.19)	0.10	<0.0001	0.31 (0.25 to 0.38)	0.15	<0.0001
Macular volume, mm^3	5.31 (3.66 to 6.96)	3.53	<0.0001	10.95 (8.58 to 13.31)	5.08	<0.0001

Data are the mean, 95% confidence interval (CI), and percent change (%) from mean vessel diameter, adjusted for age, sex, ethnicity, axial length, BMI, birth weight, and MABP. RNFL (EI), RNFL estimated integral.

similar in all characteristics except for sex, where they were more likely to be female. Retinal vessel caliber was measured by four graders and demonstrated a very high intergrader reliability, with intergrader correlation coefficients for CRAE varying from 0.82 to 0.88 and for CRVE varying from 0.93 to 0.95. Table 2 demonstrates the relationship between RNFL and macular parameters with retinal arteriolar and venular caliber. After adjustment for age, sex, ethnicity, BMI, birth weight, axial length, and MABP, each micrometer increase in RNFL was associated with a 0.22-μm (0.15%, $P < 0.0001$) increase in mean arteriolar caliber and a 0.49-μm (0.23%, $P < 0.0001$) increase in mean venular caliber. This strong relationship existed before adjustment, as shown in Figure 1. This positive relationship was present across all RNFL quadrants when analyzed individually, with each micrometer increase in mean RNFL thickness by quadrant associated with a 0.07- to 0.10-μm (0.05%–0.07%, $P \leq 0.002$) increase in mean arteriolar caliber and a 0.15- to 0.24-μm (0.07%–0.11%, $P < 0.0001$) increase in mean venular caliber. Each square millimeter increase in the estimated RNFL integral was associated with a 21.43-μm (14.27%, $P < 0.0001$) and 47.60-μm (22.10%, $P < 0.0001$) increase in mean arteriolar and venular caliber, respectively.

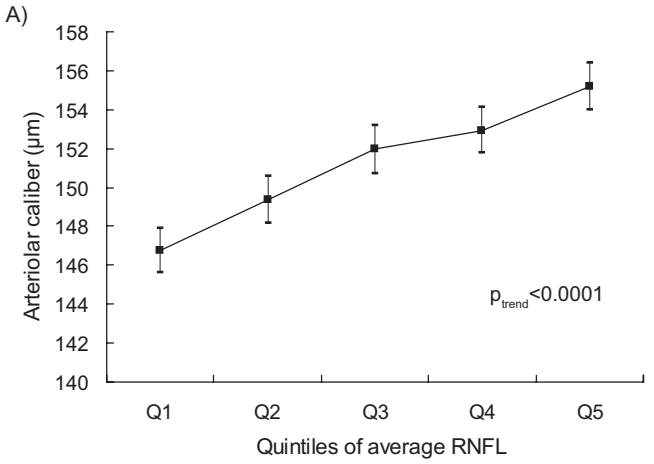
Table 2 also demonstrates the relationship between macular parameters and retinal arteriolar and venular caliber. Each micrometer increase in inner and outer macular thickness was associated with a 0.12- and 0.15-μm (0.08% and 0.10% change from mean arteriolar caliber) increase in mean arteriolar caliber and a 0.22- and 0.31-μm (0.10% and 0.15% change from mean venular caliber) increase in mean venular caliber, respectively. Each cubic millimeter increase in macular volume was associated with a 5.31-μm (3.53%, $P < 0.0001$) increase in mean arteriolar diameter and a 10.95-μm (5.08%, $P < 0.0001$) increase in mean venular diameter. Central macular thickness was not associated with retinal arteriolar caliber, although a weak positive association was found with venular caliber ($P = 0.02$).

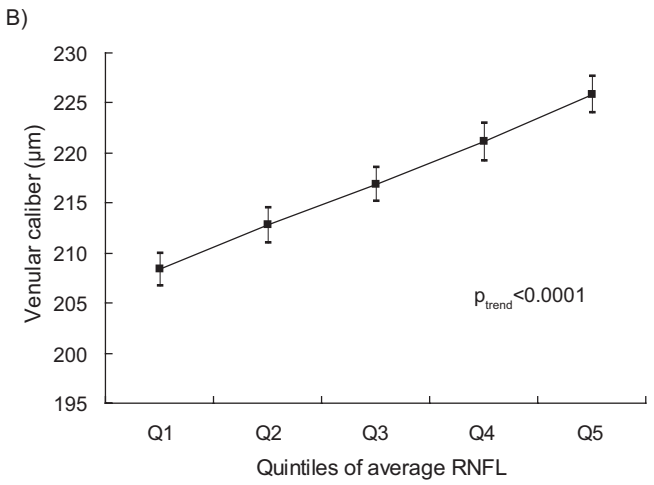
Table 3 demonstrates the relationship between optic nerve head parameters and retinal arteriolar and venular caliber. In multivariate-adjusted analyses, each millimeter increase in vertical disc diameter was associated with a 2.83-μm (1.88%, $P = 0.02$) and 5.73-μm (2.66%, $P = 0.001$) increase in mean arteriolar and venular caliber, respectively, and each square millimeter increase in optic disc area was associated with a 2.02-μm (1.35%, $P = 0.01$) and 5.02-μm (2.33%, $P < 0.0001$) increase in mean arteriolar and venular caliber, independent of the covariates. Larger optic disc area was associated with wider retinal venular caliber, but no significant association with retinal arteriolar caliber was seen in analyses before adjustment (Fig. 2). After adjusting for age, sex, ethnicity, BMI, birth weight, axial length, and MABP, neuroretinal rim area was also positively associated with retinal vessel caliber, with each square millimeter increase in neuroretinal rim area associated with a 1.81-μm (1.21%, $P = 0.01$) and 2.90-μm (1.35%, $P = 0.005$) increase in mean arteriolar and venular caliber, respectively. Horizontal cup diameter, cup area and volume, and the average nerve width were also positively associated with retinal venular caliber, but not with retinal arteriolar caliber (Table 3).

DISCUSSION

In this large population-based study of healthy adolescents, we show that eyes with thicker RNFL, thicker macula, and larger optic discs have wider retinal arteriolar and venular caliber, independent of age, sex, ethnicity, BMI, birth weight, axial length and MABP. This information can be used as reference data for future studies exploring the etiology of ocular as well as systemic diseases.

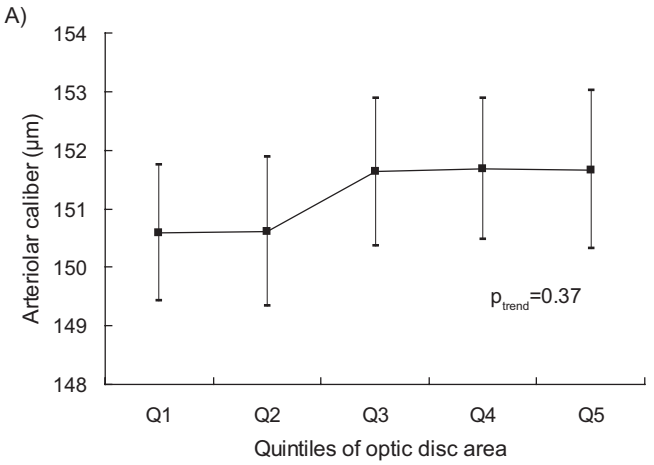
Previous studies conducted in adults[1] and young children[2,39] have demonstrated positive associations between optic disc diameter and both retinal arteriolar and venular caliber. This association has been one of the foundations for the hypothesis of a vascular pathogenesis for nonarteritic anterior ischemic optic neuropathy (NAION).[1,2,4,40,41] It is thought that crowding at the lamina cribrosa in eyes with small optic discs may lead to compression of the retinal vessels at the disc and predispose the eye to NAION. A recent hypothesis by Levin et al.[42] suggests that rather than being an arterial disease, NAION may be primarily a venous occlusive disease. The authors theorized that occlusion of the central retinal vein tributaries within the anterior optic nerve would cause venous congestion with subsequent cytotoxic and vasogenic edema, leading to secondary constriction of the small arterioles via the venoarteriolar response. Our findings in normal healthy eyes also demonstrate this positive association between optic disc diameter and disc area with both arteriolar and venular caliber, suggest-

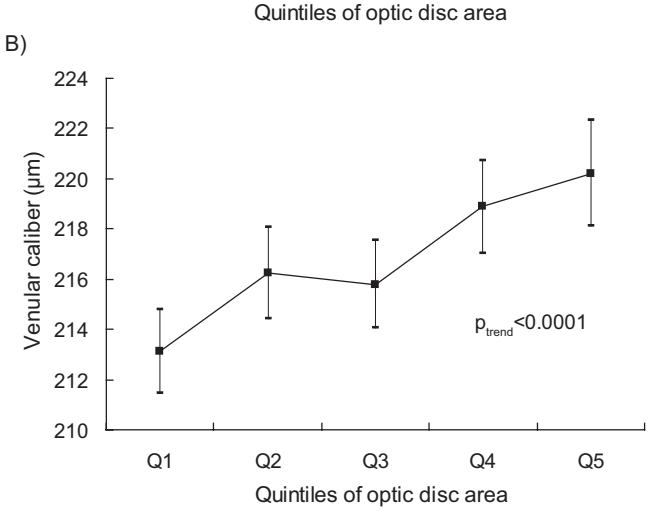




Quintiles of RNFL (μm)
Q1 56.61 – 95.17
Q2 95.17 – 101.26
Q3 101.27 – 106.15
Q4 106.17 – 112.47
Q5 112.49 – 165.08

Figure 1. Relationship between quintiles of RNFL thickness and (**A**) retinal arteriolar caliber and (**B**) retinal venular caliber before adjustment.





Quintiles of optic disc area (mm^2)
Q1 1.18 – 2.00
Q2 2.00 – 2.20
Q3 2.20 – 2.40
Q4 2.40 – 2.67
Q5 2.67 – 4.67

Figure 2. Relationship between quintiles of optic disc area and (**A**) retinal arteriolar caliber and (**B**) retinal venular caliber before adjustment.

Table 3. Relationship of Retinal Vessel Caliber to Each Unit Increase in Optic Nerve Head Parameters

	Retinal Arteriolar Diameter (μm)			Retinal Venular Diameter (μm)		
Optic Disc Parameters	**Adjusted Mean (CI)**	**%**	***P***	**Adjusted Mean (CI)**	**%**	***P***
Vertical disc diameter, mm	2.83 (0.50 to 5.16)	1.88	0.02	5.73 (2.38 to 9.08)	2.66	0.001
Vertical cup diameter, mm	−0.36 (−2.20 to 1.49)	−0.24	0.7	2.17 (−0.48 to 4.82)	1.01	0.1
Vertical cup/disc ratio	−1.46 (−5.05 to 2.12)	−0.97	0.4	2.17 (−2.99 to 7.32)	1.01	0.4
Horizontal disc diameter, mm	0.65 (−2.40 to 3.70)	0.43	0.7	3.95 (−0.43 to 8.34)	1.84	0.08
Horizontal cup diameter, mm	0.13 (−1.76 to 2.02)	0.09	0.9	3.02 (0.30 to 5.74)	1.40	0.03
Horizontal cup/disc ratio	−0.33 (−3.55 to 2.89)	−0.22	0.8	3.57 (−1.06 to 8.21)	1.66	0.1
Disc area, mm^2	2.02 (0.53 to 3.52)	1.35	0.01	5.02 (2.87 to 7.17)	2.33	<0.0001
Cup area, mm^2	−0.001 (−1.90 to 1.90)	−0.0004	1.00	2.85 (0.12 to 5.58)	1.32	0.04
Area cup/disc ratio	−1.65 (−5.77 to 2.46)	−1.10	0.4	0.85 (−5.07 to 6.78)	0.40	0.8
Cup volume, mm^3	4.48 (−4.58 to 13.54)	2.98	0.3	16.52 (3.49 to 29.54)	7.67	0.01
Rim area, mm^2	1.81 (0.40 to 3.23)	1.21	0.01	2.90 (0.86 to 4.95)	1.35	0.005
Average nerve width, μm	12.99 (−1.04 to 27.02)	8.65	0.07	21.09 (0.89 to 41.29)	9.79	0.04

Data are the mean, 95% CI, and percent change (%) from mean vessel diameter, adjusted for age, sex, ethnicity, axial length, BMI, birth weight, and MABP.

ing that deviations outside this association may be abnormal. If the theory put forth by Levin et al. held true, we would expect to find larger venules associated with smaller optic discs in eye predisposed to, or having NAION. We have provided a measured normative association between these parameters for future studies to use in exploring this theory further. Our current findings also demonstrate that eyes with larger macula (inner/outer) thickness and volume and thicker RNFL are associated with wider retinal vessel parameters, consistent with our previous findings reported in young children aged 6 years.[2] Eyes with thicker macula and RNFL may have a higher metabolic level, and hence higher vascular demand, leading to wider retinal vessel caliber.

Many studies have demonstrated that there is a strong association between systemic diseases and the caliber of the retinal vasculature. In the case of coronary heart disease, narrower arteriolar caliber is associated with a higher risk of death,[10,14] supporting the hypothesis that microvascular changes are involved in macrovascular events. However, the associations between retinal structures and systemic diseases have not been explored. There is no rationale for an association between coronary artery disease and thinner RNFL, thinner maculas, or smaller optic discs, but there is a good rationale for the association between retinal neural tissue and cerebral neural conditions.

In some cases, the structures of the eye may be used as proxy markers of disease activity when exploring this relatively new paradigm of a vascular etiology for many systemic diseases. Recent evidence has now shown that vascular processes thought to cause cerebral disease may also alter the vascular architecture of the eye.[21,22,43] Many degenerative cerebral diseases (e.g., multiple sclerosis, Alzheimer's disease) are marked by a loss of cerebral nerve fibers, and studies have shown that cerebral neural loss is mirrored by neural loss manifest as RNFL thinning[19,44–46] measured by OCT. This evidence indicates that RNFL thickness may be a novel marker of major degenerative cerebral diseases. Taken together, vascular diseases affecting the brain also appear to affect the eye, whereas cerebral degenerative diseases also appear to cause RNFL thickness changes that are readily detectable by OCT. Thus, it is possible to study the influence of vascular disease processes on the brain by modeling RNFL thickness changes as a proxy marker for neural loss, as the same vascular processes appear to be occurring in the eye as occur in the brain. Our study provides data on the normal anatomic relationship between common retinal structures and the retinal vasculature including the RNFL and optic disc to aid in the differentiation between pathology and physiology.

Our study has several strengths, including its large population-based, random cluster sample with high response (75.3%) and objective technique of quantitatively measuring the optic nerve head, macular, and RNFL parameters while statistically correcting for important confounders such as axial length, ethnicity, and MABP. Another strength of our study is the use of a healthy adolescent sample with little burden of adult ocular and systemic disease. However, this was determined from both the parent and student questionnaires without validating these self-reported data. Although this is a potential limitation, given the young age of our sample and their level of health awareness, if there are any children with undiagnosed conditions, the number would be very low.

In summary, this population-based study of healthy adolescents documents the positive association between wider retinal vascular caliber with thicker RNFL and macula parameters and larger optic discs, independent of age, sex, ethnicity, BMI, birth weight, axial length, and MABP. Given that adolescent eyes are similar in dimension to adult eyes without the influence of ocular or systemic diseases common in adulthood, our findings may reflect normal anatomic relationships in the adult eye. We have provided normative data that can be used in future research to explore disease etiology in detail.

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