Clinical and Epidemiologic Research

The Association between Ocular Biometry and Retinal Vascular Caliber Is Comparable from Early Childhood to Adolescence

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Purpose. We aimed to establish whether the change in retinal microvascular structure observed cross-sectionally with axial elongation and larger corneal curvature is comparable from early childhood to adolescence.

Methods. In all, 1077 Sydney Paediatric Eye Study participants (36 to <72 months of age) and 1740, 2353, and 1216 from the Sydney Childhood Eye Study (6, 12, and 17 years of age), respectively, were examined. Quantifiable retinal vascular caliber measurements were obtained using validated computer-based methods. Ocular biometry measurements were performed according to standardized protocols.

Results. After multivariable adjustment, in children 36 to <72 months of age, each 1.0-mm increase in axial length was associated with a 3.67- and 6.53-μm narrowing of mean retinal arteriolar caliber ($P = 0.005$) and venular caliber ($P < 0.0001$), respectively. Each 1.0-mm increase in axial length in children 6, 12, and 17 years of age was associated with a 5.30-, 3.96-, and 4.03-μm decrease in mean retinal arteriolar caliber, respectively. Each 1.0-mm increase in axial length in children 6, 12, and 17 years of age was associated with a 7.12-, 6.72-, and 6.85-μm decrease in retinal venular caliber, respectively. Corneal curvature was inversely associated with retinal vascular caliber among all age groups ($P < 0.001$). Among those without significant refractive error (>0.00 and <2.00 diopters), significant inverse associations were observed between axial length and corneal curvature with retinal vessel caliber among all age groups.

Conclusions. We demonstrate a similar magnitude of retinal vessel narrowing with axial length elongation and increasing corneal curvature from childhood through to adolescence. These data confirm the robustness of the associations between ocular biometric traits and retinal microvascular structural changes during childhood development. (*Invest Ophthalmol Vis Sci.* 2013;54:1501–1508) DOI:10.1167/iovs.12-11036

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Supported by the Sydney Paediatric Eye Disease Study, which is supported by Australian National Health and Medical Research Council (NHMRC) Grant 402425; The Sydney Childhood Eye Study, which is supported by Australian NHMRC Grants 253732 and 512530; the Westmead Millennium Institute, University of Sydney; the Vision Co-operative Research Centre, University of New South Wales, Sydney, Australia; and NHMRC Centre for Clinical Research Excellence Grant 529923 (BG). The authors alone are responsible for the content and writing of this article.

Submitted for publication September 26, 2012; revised November 1 and 29 and December 13, 2012; accepted December 18, 2012.

Disclosure: **B. Gopinath**, None; **J.J. Wang**, None; **A. Kifley**, None; **A.G. Tan**, None; **T.Y. Wong**, None; **P. Mitchell**, None

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The study of the retinal microvasculature has increased in importance since recent reports have demonstrated independent associations between the caliber of retinal arterioles and venules with both ocular and systemic diseases.[1–3] Moreover, there remains scope for the development of retinal vessel caliber measurements as biomarkers for future vascular disease risk assessment in targeted areas and patient subgroups (e.g., patients with diabetes, suspected hypertension, and stroke).[4] It has been hypothesized that a putative association of myopic refraction and longer axial length with retinal vascular caliber could reflect processes fundamental to the pathophysiologic characteristics of myopia.[5–7]

Currently, data on the relationship between axial length and retinal vascular caliber have been mainly provided by adults studies,[7–9] with only two childhood studies[5,10] to have assessed this relationship.[5,7–10] Specifically, two Singaporean studies of young children 48 to 72 months of age ($n = 469$)[10] and 7 to 9 years of age ($n = 767$)[5] have shown that elongated axial length is associated with narrower retinal arteriolar and venular caliber. Likewise, adult studies have shown a significant narrowing of both retinal arteriolar and venular caliber with increasing axial length.[7–9] However, among the three studies of adults and children that took into account ocular magnification,[5,8,9] only Lim et al.[8] showed that this association still persisted. To date, no studies involving Caucasian children and/or adolescents have assessed this association. Adolescents are both an optimal and important population to study because young children, whose eyes are undergoing rapid growth, may not reflect relationships observed in adults eyes. Further, unlike the eyes of older adults, adolescent eyes are still relatively healthy and free from disease processes such as diabetes,[1] which could influence the retinal microvascular structure.

In this study, we aimed to assess the cross-sectional relationship between ocular biometry with retinal vascular caliber in multiple samples, including preschool- to high school–aged children, using data from the Sydney Paediatric Eye Study (SPEDS) of children 36 to <72 months of age, and the Sydney Childhood Eye Study (SCES) of children 6, 12, and 17 years of age. In particular, we aimed to establish whether the magnitude and pattern of change in retinal microvascular structure associated with axial elongation and greater corneal curvature, observed cross-sectionally, is comparable between

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early childhood through to adolescence in a racially heterogeneous community-based study sample.

Methods

Study Population

This report uses data collected from a cross-sectional study (SPEDS) and a longitudinal study (SCES). SPEDS is a population-based study that was conducted during 2007–2009 and recruited children between the ages of 6 and 72 months ($n = 3333$) via door-to-door census in four randomly selected postcodes in metropolitan Sydney, Australia. A total of 2461 children were examined (73.8% response rate; Fig. 1). This report focused on children 36 to <72 months of age, due to the difficulty encountered obtaining retinal photographs from a large proportion of children < 36 months of age. Written informed consent was obtained from parents and all examination protocols were approved by the University of Sydney Human Research Ethics committee and adhered to tenets of the Declaration of Helsinki.

SCES is a population-based survey of eye conditions and other health outcomes in school children living within the Sydney Metropolitan Area, Australia. Study methods have been previously described.[11] Briefly, year 1 students from a stratified random cluster sample of 34 primary schools across Sydney (6–7 years of age, hereafter referred to as the 6-year-old cohort) were eligible to participate. Data for the 6-year-old cohort were collected during 2003–2004 (Fig. 2). Also, students in a stratified random cluster sample of 21 high schools across Sydney (attending School Year 7) were eligible to participate. Data for the 12-year-old cohort (12–13 years of age) were collected during 2004–2005 (Fig. 2). Of the baseline participants 12 years of age, 1216 (51.7%) were resurveyed 5 years later (during 2009–2011), and are here referred to as the 17-year-old cohort (includes children 16–19 years of age; Fig. 2). Only cross-sectional analyses of the 12- and 17-year-old cohorts were performed in the present study. Stratification used socioeconomic status data from the Australian Bureau of Statistics, and 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.[11] We obtained informed written consent from at least one parent of each child, and verbal assent from each child before the survey.

Retinal Photography and Analysis

In SPEDS and SCES, following pupil dilation, multiple digital retinal photographs of the macula and optic disc were obtained for both eyes (Canon 60° Mydriatic Fundus Camera, model CF-60 Uvi; Canon Inc., Tokyo, Japan). The methods used in both studies to measure retinal vessel caliber have been described previously.[7,10] Briefly, a computer imaging analysis program (IVAN; University of Wisconsin-Madison, Madison, WI) was used to measure the caliber of all retinal vessels within 0.5 to 1.0 disc diameter from the optic disc. The grader would choose the photo to be graded based on the sharpness of the image and disc placement. Average retinal arteriolar and venular calibers in SPEDS and SCES were calculated using the Knudtson–Hubbard formula.[12]

In this study, retinal vascular caliber measurements for the right eye of each child were used. Left eye measurements were used only if the photograph of the right eye was ungradable, given that high correlation between the two eyes has been reported previously.[13] Masked grading of all the photos from both SPEDS and SCES were conducted in one center by multiple graders.[12] Intergrader reliability was high with Pearson correlation coefficients for arteriolar caliber between 0.84 and 0.91 and between 0.87 and 0.93 for venular caliber. In SCES, 50 random retinal images were remeasured 2 weeks apart. Intraclass correlation coefficients were consistently >0.85 for arteriolar caliber and were >0.97 for venular caliber, which indicates good to excellent intragrader reproducibility.[14]

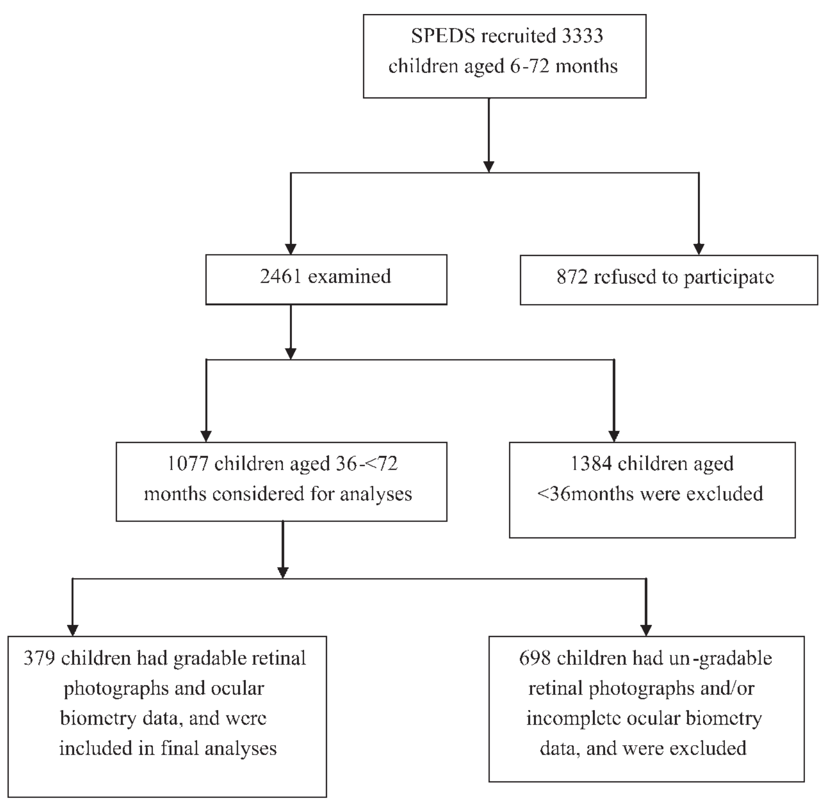

Figure 1. Participant flowchart in the SPEDS study during 2007–2009.

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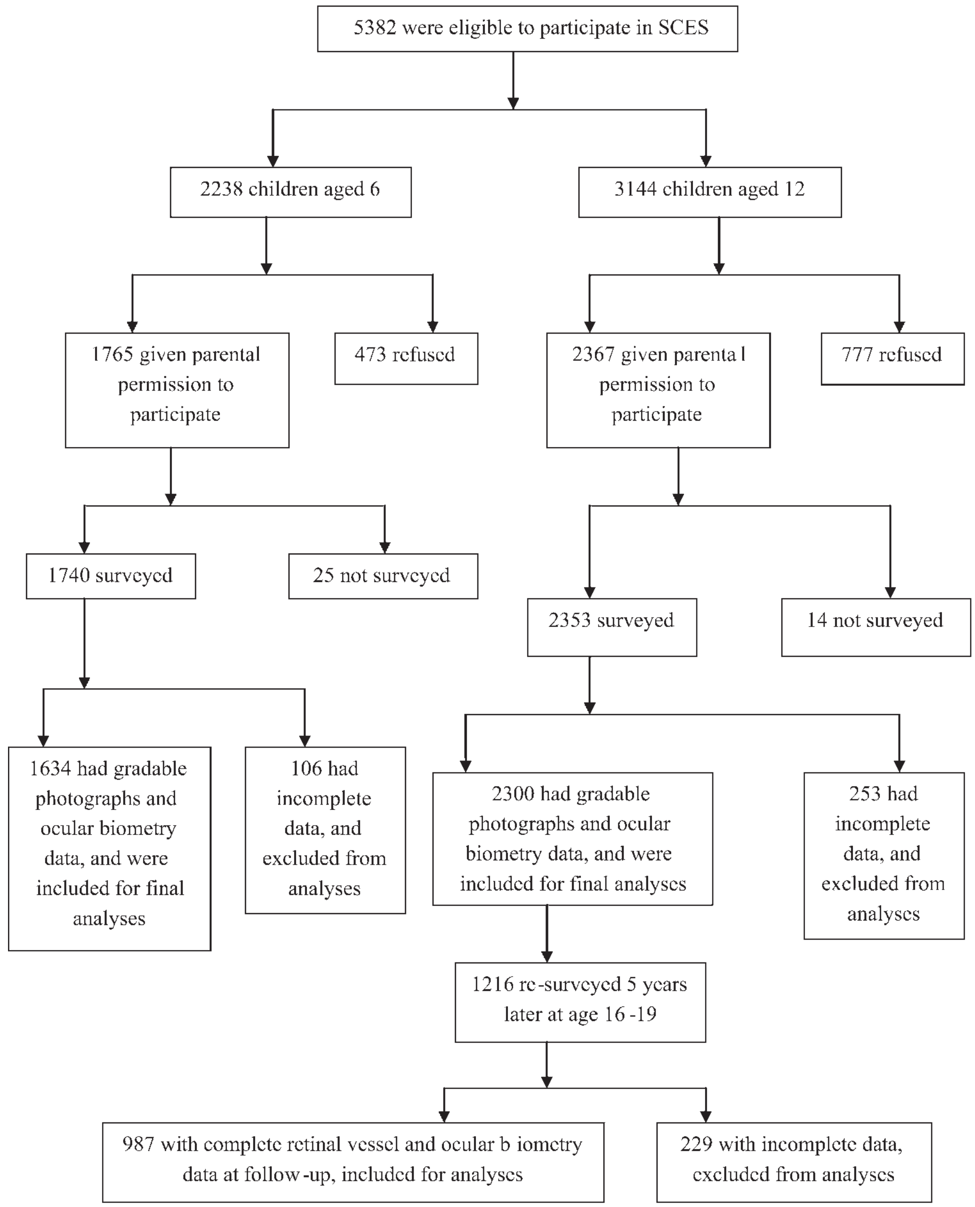

Figure 2. Participant flowchart in the SCES study during 2003–2005 and 2009–2011.

Autorefraction and Ocular Biometry

In SPEDS, the table-mounted autorefractor (Canon RK-F1; Canon Inc.) was attempted on all children $\geq$ 30 months of age after cycloplegia (with pupil diameter $\geq$ 6 mm, not reactive or constricting to light). In SPEDS and SCES, axial length and corneal curvature were measured before cycloplegia with an optical biometer (IOLMaster; Carl Zeiss Meditec, Oberkochen, Germany), using dual-beam partial coherence interferometry.[15] The average of five measurements was used for analyses. Iris color was assessed from the undilated pupil of each eye and graded by the observer as blue, hazel-green, tan-brown, or dark brown. Spherical equivalent refraction was calculated as the sum of spherical power plus ½ cylindrical power.[16]

Assessment of Covariates

In SPEDS, two questionnaires (113-item and 63-item) were completed by the parents of the children in the study. In SCES, parents were asked to complete a comprehensive 193-item questionnaire. Questions from both SPEDS (obtained from the 63-item questionnaire) and SCES covered sociodemographic information including ethnicity, country of birth, education, occupation, and parental age. The parents of all Australian children are provided with a health record booklet at birth ("Blue book") in which health professionals accurately record birth variables, specifically birth weight, birth length, head circumference, gestational age, and mode of delivery. We asked parents to extract this information from their child's health record booklet, as reported elsewhere (in SPEDS this was asked in the 113-item questionnaire).[11,17,18] The distribution of birth weight in the present sample agrees well with published Australian figures for this cohort.[19] Height was measured with children standing, without shoes. Weight in kilograms was measured using a standard portable weighing machine calibrated before and during the study. Body mass index (BMI) was calculated as weight divided by the height squared (kg/m^2).

In both SPEDS and SCES, after 5 minutes resting, systolic and diastolic blood pressures (BPs) and heart rate were measured with a digital automatic BP monitor (Intellisense, model HEM-907; Omron Healthcare, Lake Forest, IL) in a seated position. An average of two readings in SPEDS and three readings in SCES were used for data

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TABLE 1. Study Characteristics of the Preschool-Aged (3–<6 years) and School-Aged (6-, 12-, and 17 years) Children

Characteristic	3 to <6 Years Old* (n = 379)	6 Years Old† (n = 1634)	12 Years Old† (n = 2300)	17 Years Old† (n = 987)
Age, y	4.6 (10.3)	6.7 (0.4)	12.7 (0.4)	17.2 (0.5)
Male sex	200 (52.8)	831 (50.9)	1165 (50.7)	488 (49.4)
Body mass index, kg/m^2	16.0 (1.8)	16.2 (2.1)	20.4 (4.2)	22.7 (4.2)
Ethnicity				
Caucasian	203 (53.4)	1036 (63.4)	1374 (60.0)	628 (63.6)
East Asian	67 (17.7)	278 (17.0)	344 (15.0)	142 (14.4)
Southeast Asian	45 (11.9)	38 (2.3)	126 (5.5)	63 (6.4)
Middle Eastern	27 (7.1)	78 (4.8)	163 (7.1)	56 (5.7)
Mixed/others	37 (9.8)	204 (12.5)	285 (12.4)	93 (9.9)
Systolic blood pressure, mm Hg	93.2 (9.9)	99.7 (10.6)	112.7 (10.9)	121.5 (12.8)
Diastolic blood pressure, mm Hg	56.5 (10.0)	60.0 (10.4)	65.1 (8.5)	68.6 (9.3)

Data are presented as mean (SD) or proportions, n (%).
* Children from the SPEDS study.
† Children from the SCES study.

analyses. We used a cuff appropriate to the size of the child's upper right arm and followed general recommendations on selecting cuff size to ensure that the bladder length was approximately 80% and width was ≥40% of the arm circumference, and covered the upper arm but did not obscure the antecubital fossa.[20,21] BP and BMI were measured on school premises for the SCES and at the site of a study clinic for the SPEDS.

Statistical Analyses

Statistical analyses were performed using a commercial software program (SAS v9.2; SAS Institute, Cary, NC). Retinal vascular caliber was the dependent variable and axial length and corneal curvature were the independent variables. Within each cross-sectional cohort, multiple linear regression models were used to analyze a possible linear relationship between axial length and corneal curvature (i.e., per unit increase) with retinal vessel diameter. We first adjusted for age and sex, and then further adjusted for ethnicity, birth weight, BMI, and systolic BP. We also conducted supplementary analyses, by analyzing data from children without significant refractive error (defined as spherical equivalent refraction > 0.00 and <2.00 diopters [D]) to evaluate if magnification had an effect on the relationship between retinal vessel caliber, axial length, and corneal curvature.[16]

RESULTS

Table 1 shows the study characteristics of children/adolescents from SPEDS and SCES included for analyses. Among 3 to <6-, 6-, 12-, and 17-year-old children 53%, 63%, 60%, and 64% were Caucasian, respectively. Mean BMI (SD) in 3 to <6-, 6-, 12-, and 17-year-old children was: 16.0 (1.8), 16.2 (2.1), 20.4 (4.2), and 22.7 (4.2), respectively.

Association between Axial Length and Retinal Vascular Caliber

For the current analyses, we included 379 children between 36 and <72 months of age (35% of participants examined in SPEDS; Fig. 1). After multivariable adjustment, each unit (1-mm) increase in axial length was associated with 3.67- and 6.53-μm narrowing of retinal arteriolar caliber ($P = 0.005$) and venular caliber ($P < 0.0001$), respectively (Table 2).

In the 6-year-old cohort, 1634 were included for analyses (Fig. 2). Table 2 shows that each 1.0-mm increase in axial length was associated with a 5.30- and 7.12-μm narrowing of retinal arteriolar caliber ($P < 0.0001$) and venular caliber ($P < 0.0001$), respectively. In the 12-year-old sample, 2300 had quality retinal photographs and data on axial length and corneal curvature (Fig. 2). In this sample, each 1.0-mm increase in axial length was associated with a 3.96- and 6.72-μm narrowing of retinal arteriolar caliber ($P < 0.0001$) and venular caliber ($P < 0.0001$), respectively.

Finally, there were 987 from the 17-year-old cohort included for analyses (Fig. 2). In this age group, after multivariable adjustment, each 1.0-mm increase in axial length was associated with a 4.03- and 6.85-μm narrowing of retinal arteriolar caliber ($P < 0.0001$) and venular caliber ($P < 0.0001$), respectively (Table 2).

Association between Corneal Curvature and Retinal Vascular Caliber

After multivariable adjustment, in the preschool-aged children, each 1.0-mm increase in corneal curvature was associated with a 14.53- and 14.29-μm narrowing of retinal arteriolar caliber (P

TABLE 2. Linear Relationship between Axial Length and Retinal Vascular Caliber among Children from Preschool to High School

	Retinal Arteriolar Caliber, μm				Retinal Venular Caliber, μm			
	Age–Sex Adjusted		Multivariable-Adjusted*		Age–Sex Adjusted		Multivariable-Adjusted*	
Per 1.0-mm Increase in Axial Length	β	P	β	P	β	P	β	P
Preschool (n = 379)								
3 to <6 y	−2.96	0.01	−3.67	0.005	−4.40	0.001	−6.53	<0.0001
School aged								
6 y (n = 1634)	−4.57	<0.0001	−5.30	<0.0001	−6.13	<0.0001	−7.12	<0.0001
12 y (n = 2300)	−2.77	<0.0001	−3.96	<0.0001	−3.42	<0.0001	−6.72	<0.0001
16 to 17 y (n = 922)	−3.33	<0.0001	−4.03	<0.0001	−4.64	<0.0001	−6.85	<0.0001

* Further adjusted for ethnicity, iris color, body mass index, systolic blood pressure, and birth weight.

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Table 3. Linear Relationship between Corneal Curvature and Retinal Vascular Caliber among Children from Preschool to High School

	Retinal Arteriolar Caliber, µm				Retinal Venular Caliber, µm			
	Age–Sex Adjusted		Multivariable-Adjusted*		Age–Sex Adjusted		Multivariable-Adjusted*	
Per 1.0-mm Increase in Corneal Curvature	***β***	***P***	***β***	***P***	***β***	***P***	***β***	***P***
Preschool (n = 379)								
3 to <6 y	−12.87	<0.0001	−14.53	<0.0001	−12.59	0.001	−14.29	0.0004
School aged								
6 y (n = 1634)	−8.52	<0.0001	−10.08	<0.0001	−13.74	<0.0001	−14.36	<0.0001
12 y (n = 2300)	−8.30	<0.0001	−9.32	<0.0001	−10.68	<0.0001	−12.92	<0.0001
16 to 17 y (n = 922)	−7.56	<0.0001	−6.77	<0.0001	−11.38	<0.0001	−11.84	<0.0001

* Further adjusted for ethnicity, iris color, body mass index, systolic blood pressure, and birth weight.

< 0.0001) and venular caliber ($P = 0.0004$), respectively (Table 3). In children 6, 12, and 17 years of age, each unit increase in corneal curvature was associated with a 10.08-, 9.32-, and 6.77-µm narrowing of retinal arteriolar narrowing (all values of $P <$ 0.0001), respectively. Similarly, each 1.0-mm increase in corneal curvature in children 6, 12, and 17 years of age was associated with a 14.36-, 12.92-, and 11.84-µm narrowing of retinal venular narrowing (all values of $P < 0.0001$), respectively (Table 3).

Correlation coefficients between axial length and corneal curvature among 3 to <6, 6-, 12-, and 17-year-old children were: 0.69, 0.73, 0.59, and 0.59, respectively (Table 4). Correlation coefficients for axial length and corneal curvature and for retinal arteriolar and venular caliber were significantly larger in the 6-year-old group compared with the 17-year-old group. Given the high correlation between axial length and corneal curvature, we performed supplementary analyses, in which both corneal curvature and axial length were included in the multivariable model. In relation to retinal venular caliber, only axial length remained significantly associated among all age groups (data not shown). Among, 3-, <6-, and 12-year-old children, both axial length and corneal curvature were significantly associated with retinal arteriolar caliber. However, in all other age groups only axial length (and not corneal curvature) was significantly associated with retinal arteriolar caliber (data not shown). Because there was some evidence of collinearity in these models, we have chosen not to adjust for both axial length and corneal curvature in the final, parsimonious model; that is, the primary model used for all analyses includes only the following covariates: age, sex, ethnicity, birth weight, BMI, and systolic BP.

Association between Ocular Biometry and Retinal Vascular Caliber Stratified by Ethnicity

We also examined the association between axial length and corneal curvature with retinal vascular caliber in Caucasian and East Asian children separately (Table 5). In preschool-aged children, significant inverse associations between ocular biometry and retinal vascular caliber were observed only in Caucasian children, but not in East Asian children. However, among all other age groups, similar associations were observed in both ethnic groups (Table 5).

Association between Ocular Biometry and Retinal Vascular Caliber among Those without Significant Refractive Error

To minimize the impact of ocular magnification on the observed associations between axial length and corneal curvature with retinal vessel caliber, we reanalyzed the associations among children without significant refractive error (Table 6). Significant inverse associations were observed between each 1.0-mm increase in axial length and corneal curvature with retinal arteriolar and venular caliber in children of all age groups (Table 6).

Discussion

This unique study examined the association between axial length and corneal curvature with retinal vascular caliber from early childhood to adolescence, after adjusting for a range of potential confounders such as age, sex, ethnicity, iris color, BMI, and BP. A significant narrowing of both retinal arteriolar and venular caliber was observed with axial elongation and greater corneal curvature. These relationships remained among those without significant refractive error.

A similar pattern and magnitude of retinal arteriolar narrowing with axial length elongation were observed from the preschool through to the high school years; that is, a decrease of between 3.7 and 4.0 µm in retinal arteriolar caliber was observed. Likewise, a significant decrease in retinal venule calibers was observed with longer axial length. These concur

Table 4. Correlation Coefficients between Retinal Vessel Caliber, Axial Length, and Corneal Curvature among SPEDS Study and SCES Study Participants

Age Group	Axial Length and Corneal Curvature	Axial Length and Retinal Arteriolar Caliber	Axial Length and Retinal Venular Caliber	Corneal Curvature and Retinal Arteriolar Caliber	Corneal Curvature and Retinal Venular Caliber	Retinal Arteriolar Caliber and Retinal Venular Caliber
3 to <6 y	0.69	−0.19	−0.20	−0.26	−0.22	0.57
6 y	0.73	−0.24	−0.24	−0.17	−0.20	0.61
12 y	0.59	−0.21	−0.16	−0.19	−0.15	0.55
17 y	0.59*	−0.26	−0.23	−0.18	−0.17	0.50*

* $P < 0.05$ compared with the 6-year-old age group.

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Table 5. Linear Relationship between Axial Length and Corneal Curvature with Retinal Vascular Caliber Stratified by Ethnicity among Children from Preschool to High School

Age Group	Caucasian				East Asian			
	Retinal Arteriolar Caliber*		Retinal Venular Caliber*		Retinal Arteriolar Caliber*		Retinal Venular Caliber*	
	β	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Per 1.0-mm increase in axial length								
3 to <6 y	−4.55	0.03	−6.23	0.002	−0.88	0.76	−3.37	0.39
6 y	−5.66	<0.0001	−6.94	<0.0001	−8.00	<0.0001	−11.01	<0.0001
12 y	−4.52	<0.0001	−7.77	<0.0001	−3.36	<0.0001	−5.84	<0.0001
17 y	−4.87	<0.0001	−7.22	<0.0001	−3.26	0.002	−5.30	0.0002
Per 1.0-mm increase in corneal curvature								
3 to <6 y	−20.89	0.0002	−17.45	0.0002	−13.88	0.16	−21.58	0.09
6 y	−10.48	<0.0001	−14.93	<0.0001	−13.98	0.001	−21.42	<0.0001
12 y	−8.86	<0.0001	−14.35	<0.0001	−9.60	0.002	−12.27	0.0
17 y	−6.24	0.002	−11.62	<0.0001	−10.51	0.02	−8.55	0.18

* Adjusted for age, sex, iris color, body mass index, systolic blood pressure, and birth weight.

with published findings of two prior Singaporean childhood studies that reported a narrowing of 3.2 and 3.5 μm in retinal arteriolar diameter with increasing axial length, respectively.[5,10] Similarly, these childhood studies reported a narrowing of retinal venular caliber with axial elongation within the range of 5.6 and 4.6 μm.[5,10]

The pattern and magnitude of the association between corneal curvature and retinal vascular structural changes were also consistent from early childhood through to adolescence. A significant narrowing of retinal arterioles and venules was observed with greater corneal curvature during early and middle childhood, and adolescence. A study of Singaporean Chinese preschoolers[10] observed an association between corneal curvature and retinal venular caliber, but not with arteriolar caliber.[10]

Previously, we had shown that refractive error $\geq$ 2.00 D contributes to variation in measurements in retinal vessels in children.[16] Refractive error and axial length may affect the magnification and apparent dimensions of retinal structures on fundus photography.[5] In the Blue Mountains Eye Study, retinal vessel diameter was observed to be smaller in adults with myopic compared with hyperopic refraction.[9] Also, in the Beaver Dam Eye Study of older adults, myopic refraction was found to be associated with smaller retinal vascular caliber.[7] Thus, we reanalyzed associations between ocular biometry and retinal vascular caliber among children without significant refractive error. We observed that significant, inverse linear associations between axial length and corneal curvature with retinal vascular caliber measures still persisted in children without significant refractive error. This contrasts with the findings of a Singapore childhood study,[5] which showed that the association between axial length and retinal vascular caliber did not persist after correcting for ocular magnification. However, we caution that if the impact of magnification error on retinal vessel measures is continuous, these analyses might still not distinguish between the true impacts of axial length and magnification error on retinal vessel diameter.

Because the association between axial length and corneal curvature with retinal vascular caliber persisted in children without significant refractive error, alternate mechanisms other than magnification effects are likely to be involved. Previous studies that have shown a decrease in ocular pulse and retinal blood flow with increasing myopia[22–24] support a direct biological relation between longer axial length and narrower retinal vascular caliber.[8] Moreover, increased axial elongation in myopic eyes could lead to mechanical stretching and

Table 6. Linear Relationship between Axial Length and Corneal Curvature with Retinal Vascular Caliber among Children without Significant Refractive Error (>0.00–<2.00 Diopters)

Age Group	Retinal Vascular Caliber, μm*			
	Retinal Arteriolar Caliber		Retinal Venular Caliber	
	β	*P*	*β*	*P*
Per 1.0-mm increase in axial length				
3 to <6 y (*n* = 297)	−4.50	0.01	−6.27	0.001
6 y (*n* = 1408)	−5.95	<0.0001	−8.02	<0.0001
12 y (*n* = 1773)	−4.90	<0.0001	−7.80	<0.0001
17 y (*n* = 578)	−5.82	<0.0001	−8.26	<0.0001
Per 1.0-mm increase in corneal curvature				
3 to <6 y (*n* = 297)	−14.64	0.0003	−13.07	0.003
6 y (*n* = 1408)	−10.17	<0.0001	−14.51	<0.0001
12 y (*n* = 1773)	−9.79	<0.0001	−13.39	<0.0001
17 y (*n* = 578)	−8.02	0.0002	−15.00	<0.0001

* Adjusted for age, sex, ethnicity, iris color, body mass index, systolic blood pressure, and birth weight.

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thinning of the choroid and retinal pigment epithelium.[10,25–28] Thus, this pathologic increase in ocular dimensions could result in stretching and elongation of the retinal vasculature, leading to a concomitant reduction in the width of retinal arterioles and venules.[10] Our findings could thus help understand important clinical observations. For instance, it was shown that myopic eyes are less likely to have diabetic retinopathy, possibly due to reduced blood flow, which may mitigate proliferation of the disease.[29–31] In contrast, longer axial length and reduced ocular blood flow could be contributing factors to damage in glaucomatous eyes.[8,32]

The underlying mechanisms for the association between greater corneal curvature and narrowing of the retinal vessels, however, are less clear. Corneal curvature might share the same viscoelastic properties of lamina cribrosa as central corneal thickness (CCT).[33] Larger corneal curvature might share the same mechanism as that of the thinner CCT, which is related to a thinner lamina cribrosa and the reduced mechanical support for blood vessel passing through would in turn result in the compression of retinal vessel walls.[10,33] It is possible that the observed association between corneal curvature and retinal vascular caliber could be due to axial length and corneal curvature being interrelated. Further studies are warranted to delineate the pathophysiologic pathways that mediate the inverse relationship between corneal curvature and retinal vascular caliber.

Given that all population-based data on the association between ocular biometry and retinal vascular structural changes to date have been provided by Asian childhood studies,[5,10] we aimed to establish whether axial length and corneal curvature are related to retinal vascular caliber in Caucasian children and adolescents. We found that the effect of axial length and corneal curvature on retinal vascular structure was similar in Caucasian and East Asian children 6 years of age and older, which suggests that ethnicity does not modify the association between ocular biometry and retinal vessel calibers. However, in children 6 years of age and younger, associations between ocular biometry and retinal vascular caliber were present only in Caucasian and not in East Asian children. We speculate that this is likely due to the small number of East Asian children with gradable photographs in SPEDS ($n = 67$).

Strengths of our study include its relatively large, racially heterogeneous sample of children and adolescents, high reproducibility in retinal vessel measures, standardized assessment of ocular biometry, and the availability of detailed information on a large number of potential confounders. Study limitations also deserve discussion. We cannot rule out the possibility of residual confounding from unmeasured or unknown factors, which could have influenced observed associations. Second, the possibility of selection bias cannot be disregarded, given that subsets of children without quality retinal photographs were excluded from analyses in this study. Finally, this report presents only cross-sectional data; we are unable to provide longitudinal comparisons of retinal vessel caliber measures from 12 to 17 years of age, because the cameras used to obtain digital retinal photographs at baseline and follow-up in the SCES had differing magnification, and currently there is no correction factor available to account for this magnification difference.

In conclusion, this racially heterogeneous study sample showed a consistent pattern and magnitude of retinal arteriolar and venular caliber narrowing with axial elongation and greater corneal curvature, from early childhood through to adolescence, and among children without significant refractive error. Our data provide a better understanding of how changes to ocular biometric traits are related to changes in retinal microvascular structure during childhood and adolescence.

References

1. Samarawickrama C, Huynh SC, Wang JJ, et al. Relationship between retinal structures and retinal vessel caliber in normal adolescents. *Invest Ophthalmol Vis Sci*. 2009;50:5619–5624.
2. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. *Surv Ophthalmol*. 2009;54:74–95.
3. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004;351:2310–2317.
4. Ikram MK, Ong YT, Cheung CY, Wong TY. Retinal vascular caliber measurements: clinical significance, current knowledge and future perspectives [published online ahead of print September 20, 2012]. *Ophthalmologica*. doi:10.1159/000342158.
5. Cheung N, Tikellis G, Saw SM, et al. Relationship of axial length and retinal vascular caliber in children. *Am J Ophthalmol*. 2007;144:658–662.
6. Patton N, Maini R, MacGillivary T, et al. Effect of axial length on retinal vascular network geometry. *Am J Ophthalmol*. 2005;140:648–653.
7. Wong TY, Knudtson MD, Klein R, et al. Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. *Ophthalmology*. 2004;111:1183–1190.
8. Lim LS, Cheung CY, Lin X, et al. Influence of refractive error and axial length on retinal vessel geometric characteristics. *Invest Ophthalmol Vis Sci*. 2011;52:669–678.
9. Wong TY, Wang JJ, Rochtchina E, Klein R, Mitchell P. Does refractive error influence the association of blood pressure and retinal vessel diameters? The Blue Mountains Eye Study. *Am J Ophthalmol*. 2004;137:1050–1055.
10. Li LJ, Cheung CY, Gazzard G, et al. Relationship of ocular biometry and retinal vascular caliber in preschoolers. *Invest Ophthalmol Vis Sci*. 2011;52:9561–9566.
11. Ojaimi E, Rose KA, Smith W, et al. Methods for a population-based study of myopia and other eye conditions in school children: the Sydney Myopia Study. *Ophthalmic Epidemiol*. 2005;12:59–69.
12. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27:143–149.
13. Leung H, Wang JJ, Rochtchina E, et al. Computer-assisted retinal vessel measurement in an older population: correlation between right and left eyes. *Clin Exp Ophthalmol*. 2003;31:326–330.
14. Mitchell P, Liew G, Rochtchina E, et al. Evidence of arteriolar narrowing in low-birth-weight children. *Circulation*. 2008;118:518–524.
15. Hitzenberger CK. Optical measurement of the axial eye length by laser Doppler interferometry. *Invest Ophthalmol Vis Sci*. 1991;32:616–624.
16. Joachim N, Rochtchina E, Tan AG, et al. Right and left correlation of retinal vessel caliber measurements in anisometropic children: effect of refractive error. *Invest Ophthalmol Vis Sci*. 2012;53:5227–5230.
17. Robaei D, Rose K, Ojaimi E, et al. Visual acuity and the causes of visual loss in a population-based sample of 6-year old Australian children. *Ophthalmology*. 2005;112:1275–1282.
18. Gopinath B, Baur LA, Garnett S, et al. Body mass index and waist circumference are associated with blood pressure in preschool-aged children. *Ann Epidemiol*. 2011;21:351–357.
19. Robaei D, Kifley A, Gole GA, Mitchell P. The impact of modest prematurity on visual function at age 6 years: findings from a population-based study. *Arch Ophthalmol*. 2006;124:871–877.
20. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental

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animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension*. 2005;45:142–161.

21. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(suppl 2):555–576.
22. Perkins ES. The ocular pulse. *Curr Eye Res*. 1981;1:19–23.
23. Avetisov ES, Savitskaya NF. Some features of ocular microcirculation in myopia. *Ann Ophthalmol*. 1977;9:1261–1264.
24. Benavente-Perez A, Hosking SL, Logan NS, Broadway DC. Ocular blood flow measurements in healthy human myopic eyes. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:1587–1594.
25. Lim LS, Yang X, Gazzard G, et al. Variations in eye volume, surface area, and shape with refractive error in young children by magnetic resonance imaging analysis. *Invest Ophthalmol Vis Sci*. 2011;52:8878–8883.
26. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt*. 2005;25:381–391.
27. Nishida Y, Fujiwara T, Imamura Y, et al. Choroidal thickness and visual acuity in highly myopic eyes. *Retina*. 2012;32:1229–1236.
28. Ikuno Y, Tano Y. Retinal and choroidal biometry in highly myopic eyes with spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2009;50:3876–3880.
29. Lim LS, Lamoureux E, Saw SM, et al. Are myopic eyes less likely to have diabetic retinopathy? *Ophthalmology*. 2010;117:524–530.
30. Quigley M, Cohen S. A new pressure attenuation index to evaluate retinal circulation. A link to protective factors in diabetic retinopathy. *Arch Ophthalmol*. 1999;117:84–89.
31. Cunha Vaz JG, Fonseca JR, de Abreu JR, Lima JJ. Studies on retinal blood flow. II. Diabetic retinopathy. *Arch Ophthalmol*. 1978;96:809–811.
32. Nemeth J, Michelson G, Harazny J. Retinal microcirculation correlates with ocular wall thickness, axial eye length, and refraction in glaucoma patients. *J Glaucoma*. 2001;10:390–395.
33. Lesk MR, Hafez AS, Descovich D. Relationship between central corneal thickness and changes of optic nerve head topography and blood flow after intraocular pressure reduction in open-angle glaucoma and ocular hypertension. *Arch Ophthalmol*. 2006;124:1568–1572.

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