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The Relationship between Changes in Body Mass Index and Retinal Vascular Caliber in Children

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Objective To examine the longitudinal relationship between changes in childhood body mass index (BMI) and retinal vascular caliber.

Study design A prospective study of 421 healthy children aged 7-9 years in 2001 who returned for follow-up in 2006. At both visits, retinal photographs and anthropometric measurements were taken following standardized protocols. Retinal arteriolar and venular calibers were measured using a computer-based program and summarized as central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE).

Results At follow-up, mean weight, height, and BMI increased significantly ($P < .001$). Mean CRVE increased by 3.4 μm ($P < .001$) but mean CRAE did not alter significantly ($P = .340$). On multivariate analysis, greater BMI was cross-sectionally associated with narrower CRAE ($P < .01$) and wider CRVE ($P < .01$). On longitudinal analysis, increasing BMI was associated with increasing CRVE ($P = .04$) over the 5-year period. Baseline BMI was associated with increased venular caliber and decreased arteriolar caliber at follow-up, and vice versa ($P < .05$).

Conclusions Increasing BMI is associated with increasing retinal venular caliber over time in children, and baseline retinal vascular caliber changes increase the risk of higher BMI at follow-up. As both widened retinal venular caliber and greater BMI are associated with risk of cardiovascular events in adults, progressive retinal venular widening could be a manifestation of an adverse microvascular effect of obesity early in life. *(J Pediatr 2014;165:1166-71)*.

Childhood overweight and obesity have become a major public health concern worldwide. Epidemiologic studies suggest that close to 50% of children are overweight in some developed countries.[1,2] More importantly, childhood obesity is associated with early-onset diabetes, dyslipidemia, and hypertension,[3] and future risk of cardiovascular disease and mortality.[4] Although studies have linked childhood obesity or its measures with large-vessel disease, the effect of obesity on the microvasculature is less well documented. This is, at least in part, because of the difficulty in noninvasively studying subtle changes in the microcirculation.

Recent technological advances have allowed precise and reliable quantitative measurements of retinal vascular caliber from retinal photographs. Wider retinal veins and narrower retinal arteries have been associated with measures of obesity in a wide range of studies in children[5-9] and adults.[10,11] Similar associations have been observed between these variations in retinal vascular caliber and other cardiovascular risk factors (diabetes, hypertension).[11-13] In addition, narrowed retinal arterioles and widened retinal venules have also been linked to future cardiovascular events (stroke, coronary heart disease), independent of traditional risk factors.[14-16] Therefore, variations in retinal vascular caliber may represent a useful marker of microvascular changes that precede development of overt cardiovascular disease.[15]

A few cross-sectional studies have shown associations between retinal vascular caliber and measures of obesity in children.[5-9] Although it has been proposed that these findings may reflect early adverse microvascular effects of obesity in early life, there is a lack of longitudinal data. The purpose of this study was to examine the relationship between changes in body mass index (BMI) and changes in retinal vascular caliber over time in young children and adolescents.

Methods

The Singapore Cohort Study of Risk Factors for Myopia is a school-based study of children aged 7-9 years at baseline in Singapore. Details of the study population have been described elsewhere.[17] In brief, permission to conduct the study was obtained from the Ministry of Education of Singapore. The study was supported by the principals and teachers of the 2 schools. To sample children from schools with different overall academic performance, 2 elementary schools were selected based on prior National Examination results of their students. One school in the Eastern part of Singapore ranked among the top 20 schools in the country, and

BMI	Body mass index
CRAE	Central retinal artery equivalent
CRVE	Central retinal vein equivalent
WHO	World Health Organization

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the other school in the Northern part of Singapore ranked among the bottom 20 schools. A third school (Western province) was enrolled in 2001. Initially, 2913 children were recruited for the study with a participation rate of 67.9% (1979 participants). Children from grades 1 and 2 from an eastern school (n = 660) and children from grades 1, 2, and 3 from a northern school (n = 1023) were invited to participate in November 1999, and children from grades 1, 2, and 3 from a western school (n = 1230) were enrolled in May 2001. Children with medical conditions (n = 94), such as heart disorders, syndrome-associated myopia, or eye disorders, such as cataracts, were excluded from the study. In 2006, 1251 participants attended a follow-up examination. After excluding participants with missing BMI measurements or without gradable retinal photographs at either visit (n = 65), a total of 421 participants were left for analysis.

The Ethics Committee of the Singapore Eye Research Institute approved the study, and the conduct of the study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all parents after the nature of the study was explained.

All participants were examined on the school premises by a team of ophthalmologists, optometrists, and research assistants on both visits. After pupil dilatation with cyclopentolate 1%, digital retinal photographs centered on the optic disc were taken of both eyes using a Canon CR6-45NM nonmydriatic camera (Tochigiken, Japan).

The methods used to measure and summarize retinal vascular caliber from digitized photographs after standardized protocols have been described.[18,19] Briefly, a computer-based program was used to measure the caliber of all retinal vessels located 0.5-1 disc diameter from the optic disc margin in the digitized retinal photographs. Before measurement, an image conversion factor was derived from 50 randomly selected images, calculated as a standard vertical optic disc diameter (assumed to be 1800 μm) divided by optic disc diameter in pixels. The conversion factor in this study was 7.67 μm per pixel. Individual retinal vascular caliber measurements from an eye were summarized as an average index according to formulae described elsewhere.[20] These indices, the central retinal artery and vein equivalents (CRAE and CRVE), represent the average arteriolar and venular caliber of that eye.

Trained graders, masked to participant identity and characteristics, performed the retinal vascular caliber measurements for both visits. Retinal vascular caliber in the right eye was measured. Left eye measurements were performed when photographs of the right eye were ungradable. Remeasurement of 50 retinal images 2 weeks apart showed high reproducibility, with intraclass correlation coefficients of 0.873 for CRAE and 0.928 for CRVE.

Height, weight, and blood pressure measurements were performed on school premises using standardized protocols.[21] Height was measured with students standing and without shoes. Weight was measured using a standard portable weighing machine calibrated before the beginning of the study. BMI was calculated as the weight divided by the square of the height (kg/m^2). Sex- and age-specific BMI SDS or Z-scores were calculated using the World Health Organization (WHO) AnthroPlus software (2009), which used the 2007 WHO reference growth charts for ages 5-19 years.[22]

Blood pressure was measured in the seated position after 5 minutes of rest using an automated sphygmomanometer (Omron HEM 705 LP; Omron Healthcare, Inc, Bannockburn, Illinois) with the appropriate cuff size. The cuff size was selected to ensure that the bladder spanned the circumference of the arm and covered at least 75% of the upper arm without obscuring the antecubital fossa. The average of 3 separate measurements of systolic blood pressure and diastolic blood pressure was used for analysis. Mean arterial blood pressure was calculated as one-third of the systolic blood pressure plus two-thirds of the diastolic blood pressure. Blood pressure measurement methods did not differ between the 2 visits.

Cycloplegic refraction was obtained using calibrated autorefractometers (RK5; Canon, Inc Ltd, Tochigiken, Japan). Axial length was obtained using a biometry ultrasound unit (probe frequency, 10 mHz; Echoscan US-800; Nidek Co. Ltd, Tokyo, Japan). One drop of 0.5% proparacaine was instilled into each eye before ultrasound biometry measurements were made. The average of 6 values was taken with the SD of the 6 measurements <0.12 mm.

Statistical Analyses

We compared characteristics of included and excluded participants using the Student *t* test. Participant characteristics at the 2001 and the 2006 visits had their means and SD compared for differences using paired *t* tests. Linear regression models were used to analyze the association between BMI and retinal vessel caliber, initially adjusted for age and sex (model 1), and then additionally adjusted for race, spherical equivalent, birth weight, and fellow retinal vessel caliber (model 2). Beta coefficients and 95% CIs are reported. The associations between changes in retinal vascular caliber and BMI across the 5-year interval were compared using ANOVA across 3 ordinal categories of BMI change. All statistical analyses used SPSS v 17 (SPSS Inc, Chicago, Illinois).

Results

Out of 421 participants, 49.2% were male and 50.8% were female; 81.9% were Chinese, 12.6% Malay, 5.0% Indian, and 0.5% of other ethnicities. Compared with participants excluded from the analysis because of incomplete BMI data or ungradable images (n = 65), included participants were slightly older (7.93 vs 7.76; P = .001) and had more myopic spherical equivalent refraction (−1.59 D vs 0.34 D; $P < .001$) but were similar in other characteristics.

The changes in characteristics between the 2 visits are outlined in Table I. Weight, height, BMI, and BMI Z-score significantly increased between the 2001 and 2006 visits. BMI increased from an average of 17.0-19.3 kg/m^2 ($P < .001$), and BMI Z-score from 0.35-0.44 (P = .048).