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ORIGINAL RESEARCH

Independent and Synergistic Effects of High Blood Pressure and Obesity on Retinal Vasculature in Young Children: The Hong Kong Children Eye Study

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BACKGROUND: High blood pressure (BP) and obesity are becoming increasingly prevalent among children globally. Although prior studies have shown their adverse impacts on macrovascular health, less is known about their effects on microvascular heath. This study aims to evaluate the independent and synergistic effects of hypertensive BP and obesity on retinal vasculature in young children.

METHOD AND RESULTS: 1006 children aged 6 to 8 years were recruited from the Hong Kong Children Eye Study. Quantitative retinal vascular parameters, including central retinal arteriolar and venular equivalents and retinal arteriolar and venular fractal dimensions, were measured from retinal photographs following a standardized protocol. BP and body mass index were categorized according to reference values from American Academy of Pediatrics and International Obesity Task Force guidelines respectively. Children with hypertensive systolic BP had the narrowest central retinal arteriolar equivalents compared with children with either elevated or normotensive systolic BP (162.4, 164.6, and 167.1 μm; *P*-trend <0.001). Increased standardized systolic BP was associated with narrower central retinal arteriolar equivalents (β=−2.276 μm, *P*<0.001), wider central retinal venular equivalents (1.177, *P*=0.007), and decreased arteriolar fractal dimensions (β=−0.004, *P*=0.034). Children with obesity had the smallest arteriolar fractal dimensions compared with children with overweightness and normal weight (1.211, 1.234, and 1.240; *P*-trend=0.004). Children with both hypertensive BP and either overweightness or obesity had the narrowest central retinal arteriolar equivalents and smallest arteriolar D_f (*P*-trend<0.001 and *P*-trend=0.007).

CONCLUSIONS: Our findings demonstrate the potential synergistic or additive effects for both hypertensive BP and obesity on retinal vasculature in children.

Key Words: high blood pressure ■ hypertension ■ obesity ■ optical imaging

Hypertension and obesity are two of the most important cardiovascular risk factors globally. Over the past few decades, the prevalence of both childhood hypertension and obesity have been increasing worldwide in relation to a paradigm shift in health-related behaviors, including reduced physical activity levels, a more sedentary lifestyle, increased screen time, and less healthy dietary patterns.[1–3] In some countries, nearly 1 in 4 children is overweight or obese.[4] Given the increase in evidence suggesting

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CLINICAL PERSPECTIVE

What Is New?

- In this population-based study, our results showed that narrower retinal arteriolar caliber and smaller arteriolar fractal dimension were associated with elevated blood pressure, hypertensive blood pressure, and obesity.
- Children with both hypertensive blood pressure and either overweightness or obesity had the narrowest retinal arterioles and smallest arteriolar fractal dimension, suggesting the potential additive or synergistic effect of categorical hypertensive blood pressure and overweightness or obesity on retinal vasculature in children.

What Are the Clinical Implications?

- Our findings offer insights into the microvascular effects of cardiovascular risk factors on children, as well as add further clinical value to the pediatric clinical guidelines.
- More proactive interventional approaches should be implemented in children with cardiovascular risk factors to prevent the development of microvascular impairments.

Nonstandard Abbreviations and Acronyms

CRAE	central retinal arteriolar equivalent
CRVE	central retinal venular equivalent
DBP	diastolic blood pressure
D_f	fractal dimension
SBP	systolic blood pressure
WHtR	waist-to-height ratio

that hypertension and obesity in childhood track through adulthood[5,6] and predict the future development of adverse cardiovascular events,[7,8] it is essential to understand the early and potentially reversible effects of high blood pressure (BP) and obesity on vascular health in children. Although there have been many prior studies concerning the adverse impacts of hypertension and obesity on large vessel structures (ie, the macrovascular level),[9–11] there are fewer such studies concerning their effects on the health of smaller vessels (ie, the microvascular level).[12]

Retinal arterioles and venules, measuring 100 to 300 μm in size, are the only visible and optically accessible small blood vessels in the human body. In the past 2 decades, advances in retinal vascular imaging have provided a possible window for accessing the human microvasculature using noninvasive techniques.[13,14] Numerous population-based studies of older adults have shown alternations in retinal vasculature (eg, retinal arteriolar narrowing and retinal venular widening) among individuals with hypertension[15,16] and obesity.[17] A few studies among children have also shown that similar alterations, particularly retinal arteriolar narrowing, are associated with increased BP and body mass index (BMI),[18–21] suggesting that preclinical changes in the microvascular network may commence in early life. Yet such studies may have overlooked the effect of fat distribution on retinal vasculature. Some evidence suggests that waist-to-height ratio (WHtR), a marker of central obesity, is a better predictor for cardiovascular risk factors in children than BMI.[22,23] Nevertheless, the baseline association of WHtR with retinal vasculature in children remains unclear. Evaluating such an association may add to understandings of the underlying pathophysiological pathway between the two. Moreover, not much is known about any independent and potentially synergistic effects of childhood BP and obesity on retinal vasculature. Identifying such relationships may have clinical implications for interventional approaches.

In this study, we investigated the independent and synergistic effects of childhood BP, BMI, and WHtR on quantitative retinal vascular parameters in a population-based sample of school-aged children. Findings from our study will offer insights into the microvascular effects of cardiovascular risk factors on children, as well as add further clinical value to pediatric clinical guidelines.

METHODS

Materials supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

This current study was a substudy of the HKCES (Hong Kong Children Eye Study), an ongoing population-based cohort study of eye conditions in more than 4000 children (n=4257) from grades 1 to 3 (aged about 6–8 years) among primary schools in Hong Kong.[24–26] In brief, the HKCES was designed to observe the development of children's eyes. Sample selection was based on a stratified and clustered randomized sampling frame. Invitations to join the cohort were sent to primary schools registered in the Education Bureau based on ranking numbers generated randomly by computer. Data for this study were collected from participants recruited consecutively from January 2016 to July 2017. Except refractive errors, children with ocular diseases were excluded from the analysis. All participants underwent a full ophthalmic examination,

a physical examination, and a standardized interview. The study adhered to the Declaration of Helsinki, with the study protocol being approved by the Ethics Committee Board of Prince of Wales Hospital and the Chinese University of Hong Kong. The parents of all participating children were asked to sign a declaration of informed consent.

Retinal Photography

Retinal photographs were taken using a digital fundus camera (TRC-50DX; Tropcon, Tokyo, Japan) after pupil dilation with 1% cyclopentolate (Alcon, Belgium) and 1% tropicamide (Santen, Japan) under standardized settings. Two retinal photographs, centered at the optic disc and fovea respectively, were obtained from each eye. The photograph centered at the optic disc of the right eye of each participant was used in our analysis; in the case the photograph for the right eye was ungradable, measurements were performed on that for the left eye.

Quantitative Measurements of the Retinal Vessel Calibers

Retinal photographs were analyzed quantitatively using a semiautomated computer-assisted program (Singapore I Vessel Assessment, version 4.0, National University of Singapore, Singapore).[27] For each retinal photograph, a trained grader, masked to the participants' demographics, measured retinal vascular parameters following a standardized protocol. Photographs with suboptimal qualities (eg, those out of focus or with cutoffs of the measured region) for grading were excluded from the analysis.

Retinal vessel calibers were calculated and summarized as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) values using the Knudtson-Parr-Hubbard formula.[28] Fractional dimension (D_f) was measured in terms of both the whole vascular network and the arteriolar and venular networks separately, based on skeletonized line tracings using the box counting method:[29] a smaller D_f value reflects a simpler vascular network, whereas a larger value indicates a more complex and denser vascular network. In this study, arteriolar (arteriolar D_f) and venular networks (venular D_f) were analyzed for a more specific reflection of changes in the 2 vascular systems.

Anthropometrics

BP was measured in the seated position after 5 minutes of rest using a digital autonomic blood pressure monitor (Vital Signs Monitor, Heal Force Bio-Meditech Holdings Group, Shanghai, China), with an appropriate cuff size for accurate measurements. Three measurements were taken for each subject, with the average result being used for further analysis. Both systolic (SBP) and diastolic blood pressure (DBP) values were classified into three groups using the age-, sex-, and height-specific BP cutoff values according to American Academy of Pediatrics guidelines.[30] Children with BP values within the 90th percentile were classified as normotensive, between the 90th and 95th percentile as elevated BP, and above the 95th percentile as hypertensive BP rather than hypertension because of the inconclusiveness of a one-time visit. Body height and weight were measured using a professional integrated set (seca, Hamburg, Germany); height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI was then calculated by dividing weight (in kg) by the square of height (in meters). Children were categorized as normal weight, overweight, and obese using the age- and sex-specific BMI cutoff values from International Obesity Task Force guidelines.[31] Lastly, waist circumference was measured using a flexible tape wrapped horizontally around the navel. WHtR was then calculated by dividing the waist circumference (in cm) by height (in cm).

Statistical Analysis

The characteristics of children included in our study were reported as means, SDs, and interquartile ranges. Independent *t* test or chi-square test was performed to compare the characteristics of the recruited population in this substudy versus that of the nonrecruited population in HKCES. In the primary analysis, we aimed to determine the associations between the clinical BP and BMI categories, as defined by the current clinical guidelines, with retinal vascular parameters. In the secondary analysis, we aimed to correlate the *Z* scores for SBP, DBP, BMI, and WHtR derived from the original HKCES with retinal vascular parameters.

In the primary analysis, an ANCOVA was performed (95% CI; level of significance, $P<0.05$) to estimate the means of retinal vascular parameters, including CRAE, CRVE, arteriolar D_f, and venular D_f, according to the clinical BP and BMI categories. Three models were performed. Model 1 was unadjusted (crude) and performed on all retinal vascular parameters. Model 2 was a multivariate model performed on CRAE and CRVE outcomes. Model 3 was a multivariate model performed on arteriolar and venular D_f outcomes. Variables were entered into the models under main effect. We tested for trends by treating the clinical BP and BMI categories as continuous ordinal variables, namely normotensive BP, elevated BP, hypertensive BP; normal weight, overweight, and obese. Multiple comparisons were performed using the Bonferroni's method to test for any differences between the groups. The Bonferroni alpha level was

0.05. To examine the presence of any additive effects between hypertension and obesity on retinal vessel parameters, we categorized our study subjects into four groups: (1) children with normal weight and normotensive BP; (2) children with overweightness/obesity and normotensive BP; (3) children with normal weight and hypertensive BP; and (4) children overweightness/obesity and with hypertensive BP. We also included a cross-product interaction term as independent variable in the ANCOVA (ie, yes/no hypertensive BP and yes/no overweight/obese) to test for potential effect modifications.

In the secondary analysis, *Z* scores for SBP and DBP were calculated using the age-, sex-, and height-specific means and SDs; *Z* scores for BMI and WHtR were calculated using the age- and sex-specific means and SDs derived from the reference population (n=4257) of the HKCES.[24] Multiple linear regression analysis was performed to correlate retinal vascular parameters with the *Z* scores for SBP, DBP, BMI, and WHtR. Potential effect modifiers were tested by including SBP×BMI *Z* scores, DBP×BMI *Z* scores, SBP×WHtR *Z* scores, and DBP×WHtR *Z* scores as interaction terms in the multiple linear regression analysis. A significant *P* value was defined as <0.05. All statistical analysis was performed using SPSS (version 23, SPSS, Inc., Chicago, IL).

RESULTS

We recruited 1050 children, excluding 8 because of suboptimal retinal images for grading and 36 with incomplete data on anthropometric or BP or axial length measurements. 1006 children were recruited for the final analysis. The mean age was 7.6 years; 50.8% were female and 49.2% were male. Table 1 summarizes the participant demographics. Table S1 compares the characteristics of the recruited population in this substudy (n=1006) versus that of the nonrecruited population (n=3251) from HKCES, showing no significant difference between the 2 groups. Based on American Academy of Pediatrics guidelines, 73% (n=739) and 71% (n=715) of children were classified as having normotensive SBP and DBP, 10% (n=102) and 11% (n=110) as having elevated SBP and DBP, and 17% (n=165) and 18% (n=181) as having hypertensive SBP and DBP respectively. In our cohort, 8% children (n=80) had both hypertensive SBP and DBP. Based on International Obesity Task Force guidelines, 87% children (n=874) were classified as normal weight, 10% (n=96) as overweight, and 3% (n=36) as obese.

Table 2 shows the relationships between retinal vascular parameters and SBP categories. Narrower CRAE was associated with higher SBP categories in Models 1 and 2 (all *P*-trend<0.001). In the multivariable Model 2, children with hypertensive SBP had narrower CRAE than those with normotensive SBP (162.4 µm versus 167.1 µm, *P*<0.001); the difference was insignificant when comparing children with hypertensive SBP and those with elevated SBP (162.4 µm versus 164.6 µm, *P*=0.191). Children with elevated SBP had

Table 1. Baseline Characteristics of the Study Population (n=1006)

Parameter	No.	Mean	SD	Interquartile Range
Subject age, y	1006	7.6	1.0	6.8 to 8.4
Sex				
Female	511			
Male	495			
Height, cm	1006	124.7	7.9	119.0 to 130.0
Weight, kg	1006	25.0	5.7	21.1 to 27.6
Normal weight	874			
Overweight	96			
Obese	36			
Head circumference, cm	1006	51.9	2.4	51.0 to 53.0
Waist circumference, cm	1006	57.8	6.6	53.0 to 60.5
Waist circumference *Z* score	1006	−0.045	0.841	−0.600 to 0.305
Waist-to-height ratio *Z* score	1006	−0.002	0.960	−0.592 to 0.520
Body mass index, kg/m^2	1006	16.0	2.4	14.4 to 16.9
Body mass index *Z* score	1006	−0.076	0.806	−0.601 to 0.254
Heart rate, bpm	1006	79.6	10.7	72.0 to 86.0
Systolic blood pressure, mm Hg	1006	101.4	10.8	94.0 to 108.5
Normotensive SBP	739			
Elevated SBP	102			
Hypertensive SBP	165			
Systolic blood pressure *Z* score	1006	−0.065	0.991	−0.729 to 0.613
Diastolic blood pressure, mm Hg	1006	65.1	8.4	59.0 to 70.5
Normotensive DBP	715			
Elevated DBP	110			
Hypertensive DBP	181			
Diastolic blood pressure *Z* score	1006	0.029	0.989	−0.682 to 0.640
Mean arterial blood pressure, mm Hg	1006	77.2	8.4	71.5 to 82.7
Central retinal arteriolar equivalent, µm	1006	166.1	12.0	157.8 to 174.1
Central retinal venular equivalent, µm	1006	232.4	16.1	221.8 to 243.3
Arteriolar D_f	1006	1.238	0.051	1.205 to 1.275
Venular D_f	1006	1.221	0.049	1.189 to 1.254
Axial length, mm	1006	23.2	1.0	22.5 to 23.7
Spherical equivalence, diopter	1006	0.11	1.6	−0.5 to 1.0

DBP indicates diastolic blood pressure; D_f, fractal dimension; and SBP, systolic blood pressure.

Table 2. Analysis of Covariance of Retinal Vascular Parameters in Relation to Clinical Systolic Blood Pressure Categories

Parameters	Model	Adjusted Mean (95% CI)			*P*-Trend*	*P* Value†	*P* Value‡	*P* Value§
		Normotensive SBP (n=739)	Elevated SBP (n=102)	Hypertensive SBP (n=165)				
CRAE, µm	1	167.3 (166.5–168.2)	164.4 (162.1–166.7)	161.8 (160.0–163.6)	<0.001	0.065	<0.001	0.234
	2	167.1 (166.5–167.8)	164.6 (162.8–166.5)	162.4 (160.9–163.9)	<0.001	0.037	<0.001	0.191
CRVE, µm	1	232.7 (231.5–233.8)	232.9 (229.8–236.0)	230.8 (228.4–233.3)	0.394	>0.9	0.561	>0.9
	2	231.9 (230.9–232.8)	234.5 (232.0–237.0)	233.4 (231.3–235.4)	0.100	0.162	0.617	>0.9
Arteriolar D_f	1	1.241 (1.238–1.245)	1.232 (1.222–1.242)	1.229 (1.221–1.237)	0.011	0.293	0.019	>0.9
	3	1.240 (1.237–1.244)	1.232 (1.222–1.242)	1.233 (1.225–1.241)	0.139	0.394	0.369	>0.9
Venular D_f	1	1.221 (1.218–1.225)	1.223 (1.213–1.232)	1.220 (1.213–1.228)	>0.9	>0.9	>0.9	>0.9
	3	1.222 (1.218–1.225)	1.221 (1.211–1.230)	1.220 (1.212–1.227)	0.887	>0.9	>0.9	>0.9

Model 1: not adjusted. Model 2: adjusted for axial length and fellow vessel caliber, BMI. Model 3: adjusted for axial length, CRAE, CRVE, and BMI. BMI indicates body mass index; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; D_f, fractal dimension; and SBP, systolic blood pressure.

*P-trend across normotensive, elevated SBP, and hypertensive SBP groups.

†P value between normotensive and elevated SBP groups after Bonferroni correction.

‡P value between normotensive and hypertensive SBP groups after Bonferroni correction.

§P-value between elevated SBP and hypertensive SBP groups after Bonferroni correction.

narrower CRAE (164.6 µm versus 167.1 µm, *P*=0.037), compared with children who were normotensive after adjusting for axial length, CRVE and BMI. A similar inverse relationship was observed between arteriolar D_f and SBP categories in Model 1 (*P*-trend=0.011). As illustrated in Model 1, smaller arteriolar D_f was observed among children with hypertensive SBP compared with the normotensive SBP group (1.229 versus 1.241, *P*=0.019). However, the trend was attenuated after further adjusting for axial length or CRVE or BMI. No significant associations were found between SBP categories versus CRVE and venular D_f respectively. Similar significant inverse correlations were observed between DBP categories and CRAE (Table S2).

Table 3 shows the relationships between clinical BMI categories and retinal vascular parameters. Model 1 shows that clinical BMI categories were associated with CRAE (*P*-trend=0.033), with children with obesity having narrower CRAE compared with children with normal weight (161.2 µm versus 166.4 µm, *P*=0.032); however, this trend became attenuated after further adjusting for axial length or CRVE or mean arterial blood pressure. In the multivariate Model 3, children with obesity had the smallest arteriolar D_f compared with children with overweightness and normal weight (1.211, 1.234, 1.240, *P*=0.004) independent of axial length, CRAE, CRVE, and mean arterial blood pressure. No significant associations were found between BMI categories versus CRVE and venular D_f respectively.

Table 4 shows the relationships between the combination of BP and BMI categories with retinal vascular parameters. Children with both hypertensive BP and either overweightness or obesity had the narrowest CRAE (Figure 1) and smallest arteriolar D_f (Figure 2) in both the univariable and multivariable analysis (all *P*-trend<0.05). No significant interaction effect between BMI and BP categories was found in relation to CRAE (*P*-interaction=0.272; Figure 1) and arteriolar D_f (*P*-interaction=0.956; Figure 2). Likewise, no significant relationship was found between BMI and BP categories with CRVE and venular D_f.

Table 5 shows the multiple linear regression analysis between the *Z* scores of SBP, DBP, BMI, and WHtR and retinal vascular parameters. In the multivariable analysis, a higher SBP *Z* score was significantly associated with narrower CRAE (–2.276 µm, *P*<0.001), wider CRVE (1.177 µm, *P*=0.007), and smaller arteriolar D_f (–0.004, *P*=0.034). Similar patterns were observed between DBP *Z* scores and retinal vascular parameters. In the multivariable analysis, a higher BMI *Z* score was associated with smaller arteriolar D_f (–0.004, *P*=0.046). A higher WHtR *Z* score was significantly related with smaller arteriolar D_f only in the unadjusted Model 1 (–0.005, *P*=0.020). WHtR *Z* score was not associated with the vascular parameters in the multivariate adjusted model. There were no significant interaction effects between SBP×BMI *Z* scores, DBP×BMI- *Z* scores, SBP×WHtR *Z* scores, and DBP×WHtR *Z* scores on retinal vascular parameters.

DISCUSSION

We demonstrated the impact of categorical hypertensive BP and obesity, as defined by contemporary pediatric clinical guidelines, on retinal vasculature in children aged 6 to 8 years old. Unlike adult hypertension and obesity, which are defined based on certain cutoff values, childhood BP and BMI categories are age, sex, and height specific, thus, the need to take into account their respective normally distributed data.[30,31] We also showed

Table 3. Analysis of Covariance of Retinal Vascular Parameters in Relation to Clinical Body Mass Index Categories

Parameters	Model	Adjusted Mean (95% CI)			*P*-Trend*	*P* Value†	*P* Value‡	*P* Value§
		Normal Weight (n=874)	Overweight (n=96)	Obese (n=36)				
CRAE, µm	1	166.4 (165.6–167.2)	165.5 (163.1–167.9)	161.2 (157.3–165.1)	0.033	>0.9	0.032	0.197
	2	166.2 (165.6–166.8)	165.9 (164.0–167.8)	165.3 (162.2–168.4)	0.839	>0.9	>0.9	>0.9
CRVE, µm	1	232.3 (231.2–233.4)	234.3 (231.0–237.5)	229.5 (224.2–234.7)	0.288	0.773	0.914	0.389
	2	232.2 (231.4–233.0)	234.0 (231.4–236.5)	232.7 (228.5–237.0)	0.442	0.609	>0.9	>0.9
Arteriolar D_f	1	1.240 (1.237–1.244)	1.233 (1.222–1.243)	1.209 (1.192–1.225)	<0.001	0.494	<0.001	0.049
	3	1.240 (1.237–1.243)	1.234 (1.224–1.245)	1.211 (1.194–1.228)	0.004	0.905	0.004	0.069
Venular D_f	1	1.221 (1.218–1.225)	1.220 (1.210–1.230)	1.220 (1.204–1.236)	0.954	1.000	1.000	1.000
	3	1.222 (1.218–1.225)	1.219 (1.209–1.229)	1.219 (1.203–1.235)	0.862	>0.9	>0.9	>0.9

Model 1: not adjusted. Model 2: adjusted for axial length and fellow vessel caliber, MABP. Model 3: adjusted for axial length, CRAE, CRVE, and MABP. CRAE indicates central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; D_f, fractal dimension; and MABP, mean arterial blood pressure.

*P-trend across normal weight, overweight, and obese groups.

†P value between normal weight and overweight groups after Bonferroni correction.

‡P value between normal weight and obese groups after Bonferroni correction.

§P value between overweight and obese groups after Bonferroni correction.

that standardized BP and BMI—analyzed as continuous variables—were associated with retinal vascular parameters. Specifically, narrower retinal arteriolar caliber and smaller arteriolar D_f were significantly associated with elevated or hypertensive BP and obesity. Our findings add to the growing evidence that microvascular alterations, particularly in the arteriolar network, owing to childhood hypertension and obesity occur early in life before the manifestation of cardiovascular diseases.

Notably, our results demonstrated that retinal arteriolar narrowing was already observable in children with elevated BP, revealing possible deleterious impacts of preclinical hypertension on the retinal vasculature. Our results extended previous findings supporting an inverse relationship between BP level and retinal arteriolar caliber for both adults and children.[18–21,32] Among adults, previous studies have shown that both retinal arteriolar narrowing and venular widening predict hypertension,[14–16] in addition to cardiovascular morbidity and mortality,[33,34] independently of traditional risk factors. Similar retinal vascular changes observed in our children could therefore represent preclinical markers for future pathophysiological changes to the cardiovascular system in adulthood. With increasing evidence showing an association between childhood BP levels and higher future risks of hypertension and cardiovascular mortality,[35,36] the early detection of retinal vascular alterations in children with prehypertension and hypertension may have implications for the future development of cardiovascular diseases among them. Longitudinal studies of our cohort would be essential for confirming these predictions.

In our study, we demonstrated an association between smaller arteriolar D_f, and increase BP Z scores in children. Our results extend previous findings from a Singaporean study showing a negative correlation between BP levels and retinal vascular D_f in children.[37] Given that fractal analysis is a quantitative measure of the overall geometry of a retinal vascular system, a smaller arteriolar D_f reflects retinal arteriolar rarefaction. According to Murray's principle, the vascular branching pattern develops to allow efficient blood flow at the least possible expense of energy from shear stress exerted on the vessel wall.[38] Functionally, a sparser vascular network indicates reduced efficiency in blood flow, which is postulated to be associated with a higher risk of microcirculatory damage. Because microvascular rarefaction is hypothesized to be both a primary defect and downstream consequence of long-standing hypertension,[39] examining the retinal vascular D_f may offer us further information on the optimality of the microvasculature. In adults, alterations in retinal vascular D_f are correlated with an increased risk of stroke[40] and other cardiovascular diseases.[41] On the other hand, the long-term complications of reduced arteriolar D_f in children needs to be evaluated through future longitudinal studies.

Our results revealed a new association between smaller arteriolar D_f and childhood obesity, which echoed a recent Australian study demonstrating an inverse correlation between BMI level and arteriolar D_f in children 11 to 12 years old.[42] This is in line with our understanding of microvascular adaptations due to obesity, which itself is associated with retinal endothelial dysfunction and vascular agenesis.[43] Remarkably, these microcirculatory alterations are already evident in children at ages 6 to 8, suggesting that adverse changes may begin even earlier. Similar to the Australian study,[42] we did not find any significant associations with retinal venular D_f; this is inconsistent with a previous Malay study of 166 children aged 6 to 12 years that showed otherwise.[44] Although we do not

Table 4. Analysis of Covariance of Retinal Vascular Parameters in Relation to Clinical Blood Pressure and Body Mass Index Categories

Parameters	Model	Adjusted Mean (95% CI)			*P*-Trend*
		Normal Weight and Normotensive BP (n=676)	Overweight/Obese and Normotensive BP (n=67)	Normal Weight and Hypertensive BP (n=198)	Overweight/Obese and Hypertensive BP (n=65)	
CRAE, µm	1	167.3 (166.4–168.2)	166.8 (164.0–169.7)	163.4 (161.8–165.1)	161.7 (158.8–164.6)	<0.001
	2	167.1 (166.4–167.8)	166.9 (164.7–169.2)	163.9 (162.6–165.2)	161.7 (159.4–164.0)	<0.001
CRVE, µm	1	232.8 (231.6–234.0)	233.0 (229.1–236.8)	230.6 (228.3–232.8)	232.9 (229.0–236.9)	0.364
	2	232.0 (231.0–233.0)	232.9 (229.8–235.9)	232.2 (230.4–234.0)	236.4 (233.3–239.5)	0.072
Arteriolar D_f	1	1.242 (1.238–1.246)	1.230 (1.218–1.242)	1.234 (1.227–1.241)	1.222 (1.210–1.235)	0.005
	3	1.242 (1.238–1.246)	1.229 (1.217–1.241)	1.235 (1.228–1.243)	1.222 (1.210–1.235)	0.007
Venular D_f	1	1.221 (1.218–1.225)	1.219 (1.207–1.231)	1.222 (1.215–1.229)	1.221 (1.209–1.233)	0.987
	3	1.222 (1.218–1.225)	1.218 (1.207–1.230)	1.222 (1.215–1.229)	1.217 (1.206–1.229)	0.851

Model 1: not adjusted. Model 2: adjusted for axial length and fellow vessel caliber. Model 3: adjusted for axial length, CRAE, and CRVE. BP indicates blood pressure; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; and D_f, fractal dimension.
*P across the four groups.

have a definitive explanation for the inconsistency, differences in ethnicity, sample size, and classifications of the study group could be possible reasons.

Our results showed that WHtR, a marker of central obesity, was not associated with retinal vascular parameters in young children. This echoed to a Swiss study that showed no significant relationship between WHtR and retinal vascular diameters.[45] Some evidence previously suggested that compared with BMI, WHtR is more strongly correlated with cardiovascular risk factors in children,[22,23] thus making it a better predictor of cardiovascular disease outcomes in adulthood.[46] Very few studies have investigated the effect of fat distribution on microvasculature in young children. Given the increasing evidence suggesting effect of obesity on microcirculation commences in early life, and a study showing higher WHtR trajectory over the past decade could predict retinal arteriolar narrowing in mid-childhood[47]; we hypothesized that higher WHtR may also correlate with retinal vascular parameters in young children age 6 to 8. However, our results showed that only BMI is associated with alterations in retinal vasculature but not WHtR. This may suggest the effect of central obesity on small vessels is cumulative and the change may be more evident only as it progresses in mid-childhood. The effect of WHtR on microcirculation in the pediatric population has to be further investigated. Longitudinal studies for our children with high WHtR would be crucial to study its long-term implications, as well as to compare the strength of the predictive value and cumulative effect of BMI and WHtR on microcirculation.

Potential synergistic or additive effects of childhood hypertension and obesity on the retinal vasculature were also examined in our analysis. Children with both hypertensive BP and either overweightness or obesity had the narrowest CRAE and smallest D_f among the 4 study groups. Given that numerous studies have already shown that retinal vascular changes have predictive value for systemic diseases, we suggest that for those with already observable microvascular changes at a young age, more proactive interventions (eg, diet control, weight reduction, exercise, and lifestyle modifications) should be encouraged to prevent the development of hazardous diseases and further microvascular impairments. Future follow-up studies could evaluate the validity of retinal imaging as a monitoring tool for interventional responses in this group. Notably, the small sample size of our study group may be prone to bias; further large-scale studies are thus required to examine the additive effect more effectively.

Certain underlying pathophysiological mechanisms may already explain our current observations. Hypertension is associated with the reduced

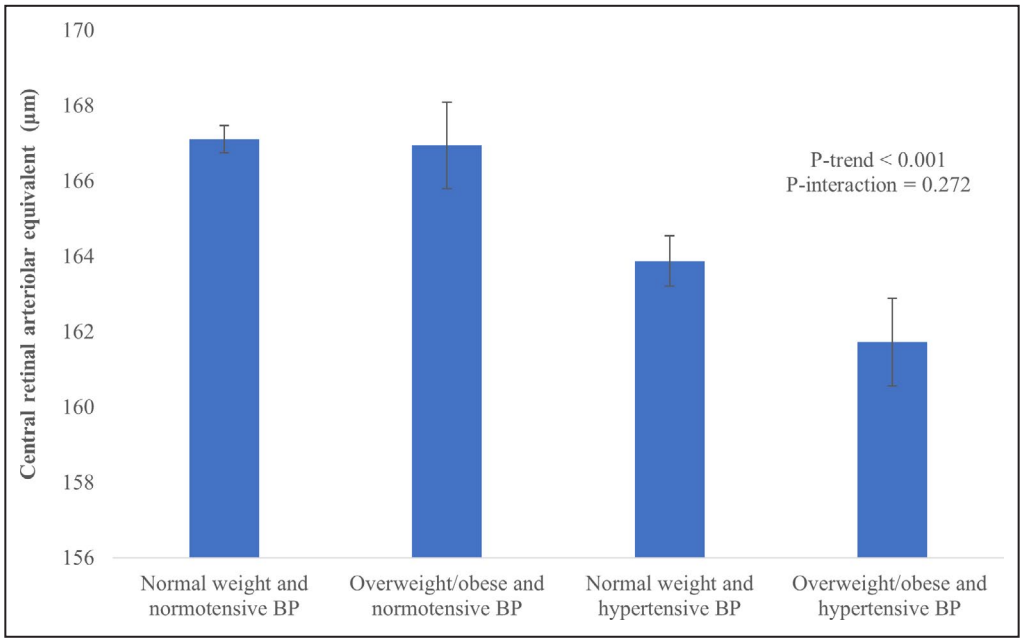

Figure 1. Mean central retinal arteriolar equivalent (CRAE) in relation to clinical blood pressure (BP) and body mass index (BMI) categories, adjusted for axial length and fellow vessel caliber.

bioavailability of nitric oxide (NO), leading to endothelial dysfunction and myogenic vasoconstriction, given that NO is crucial to vasodilation.[39,48] Chronic hypertension may hence lead to an overwhelmed vasoconstrictive response and even complete closure of the vessels. This then results in microvascular rarefaction, which reflects a reduced genomic complexity in the microvascular network resulting from vessel destruction and insufficient angiogenesis.[39] In obese individuals, inflammation and the oxidative stress exerted in the

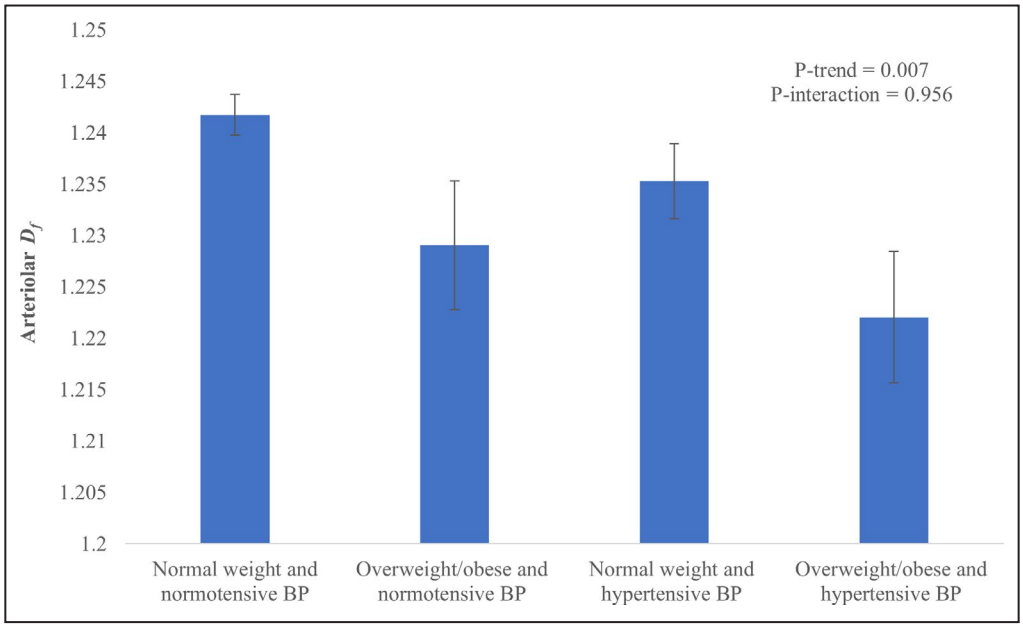

Figure 2. Mean arteriolar fractal dimension (arteriolar D_f) in relation to clinical blood pressure (BP) and body mass index (BMI) categories, adjusted for axial length, central retinal arteriolar equivalent (CRAE), and central retinal venular equivalent (CRVE).

Table 5. Multiple Linear Regression Analysis for *Z* Scores of Systolic Blood Pressure, Diastolic Blood Pressure, Body Mass Index, and Waist-to-Height Ratio With Retinal Vascular Parameters

Parameter	Model	CRAE, μm		CRVE, μm		Arteriolar D_f		Venular D_f	
		B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value
Systolic blood pressure *Z* score	1	−2.379 (−3.115 to −1.643)	<0.001	−0.358 (−1.362 to 0.646)	0.485	−0.005 (−0.008 to −0.002)	0.001	−0.001 (−0.004 to 0.002)	0.473
	2	−2.276 (−2.879 to −1.673)	<0.001	1.177 (0.327 to 2.026)	0.007	−0.004 (−0.007 to <0.001)	0.034	−0.002 (−0.005 to 0.001)	0.199
Diastolic blood pressure *Z* score	1	−2.145 (−2.886 to −1.404)	<0.001	−0.158 (−1.164 to 0.849)	0.758	−0.005 (−0.008 to −0.002)	0.003	−0.001 (−0.004 to 0.002)	0.693
	2	−2.047 (−2.641 to −1.453)	<0.001	1.268 (0.439 to 2.097)	0.003	−0.004 (−0.007 to <0.001)	0.033	−0.002 (−0.005 to 0.001)	0.304
BMI *Z* score	1	−0.860 (−1.782 to 0.062)	0.067	0.316 (−0.919 to 1.552)	0.615	−0.006 (−0.010 to −0.002)	0.005	<0.001 (−0.004 to 0.004)	0.972
	3	−0.121 (−0.866 to 0.625)	0.751	0.464 (−0.558 to 1.486)	0.373	−0.004 (−0.008 to <0.001)	0.046	<0.001 (−0.004 to 0.004)	0.959
Waist-to-height ratio *Z* score	1	−0.820 (−1.704 to 0.063)	0.069	0.269 (−0.915 to 1.452)	0.656	−0.005 (−0.008 to −0.001)	0.020	0.001 (−0.003 to 0.004)	0.674
	3	0.048 (−0.671 to 0.767)	0.895	0.501 (−0.485 to 1.487)	0.319	−0.003 (−0.007 to 0.001)	0.113	0.001 (−0.003 to 0.004)	0.779

Model 1: not adjusted. Model 2: adjusted for axial length, fellow vessel caliber, and BMI. Model 3: adjusted for axial length, CRAE, CRVE, and mean arterial blood pressure. CRAE indicates central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; and D_f, fractal dimension.

microvascular bed could lead to arteriolar narrowing due to a reduction in NO production.[49] Because NO is also an important factor stimulating the expression of vascular endothelial growth factors for angiogenesis during vascular budding,[50] an NO deficit may also lead to microvascular rarefaction.

The primary strength of our study is its population-based design. Our retinal data are obtained objectively using semiautomated computer software with minimal user input and following a standardized protocol. Each retinal photograph was analyzed by trained graders who were masked to the participants' identities. Regarding the limitations of our study, although we demonstrated correlations between retinal vascular changes and hypertensive BP and obesity, exact causal relationships could not be established and thus need to be evaluated through further longitudinal studies. Longitudinal studies are similarly required to investigate the predictive value of retinal vascular parameters on future cardiovascular events. In addition, our study measured BP readings from one, instead of multiple, clinical setting for the diagnosis of hypertension; the prevalence of elevated BP and hypertension in our study therefore may not be directly comparable with reported statistics. Lastly, we cannot exclude the white-coat phenomenon that resulted in higher BP readings for our study.

In summary, our study ascertained the existence of the independent and synergistic effects of hypertensive BP and obesity, as defined by pediatric clinical guidelines, on associations of retinal microvascular health in young children. We demonstrated the presence of early and measurable effects of cardiovascular risk factors on microvascular health, even in early life, before the development of clinical cardiovascular diseases. With the prevalence of childhood obesity and hypertension increasing globally, our study supports the importance of implementing broad public health measures in schools and communities for cardiovascular risk prevention.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of baseline characteristics of the recruited population in this study versus the non-recruited population in the Hong Kong Children Eye Study by independent t-test or chi-squared test.

	Recruited population			Non-recruited population			
Parameter	n	Mean	SD	n	Mean	SD	P-value
Subject age, years	1,006	7.6	1.0	3,251	7.6	1.0	0.38
Sex							
Male	495			1,681			0.17
Female	511			1,570			
Height, cm	1,006	124.7	7.9	3,251	125.1	8.3	0.07
Weight, kg	1,006	25.0	5.7	3,251	25.4	6.1	0.27
Head circumference, cm	1,006	51.9	2.4	3,251	51.9	2.2	0.51
Waist circumference, cm	1,006	57.8	6.6	3,251	58.0	7.2	0.45
Body mass index, kg/m^2	1,006	16.0	2.4	3,251	16.1	2.6	0.78
Heart rate, bpm	1,006	79.6	10.7	3,251	80.0	11.5	0.38
Systolic blood pressure, mmHg	1,006	101.4	10.8	3,251	101.4	10.6	0.90
Diastolic blood pressure, mmHg	1,006	65.1	8.4	3,251	65.4	9.8	0.40
Mean arterial blood pressure, mmHg	1,006	77.2	8.4	3,251	76.9	8.6	0.27
Axial Length, mm	1,006	23.2	1.0	3,251	23.2	0.9	0.52
Spherical Equivalence, diopter	1,006	0.11	1.6	3,251	0.13	1.6	0.71

SD, standard deviation

Table S2. Analysis of covariance of retinal vascular parameters in relation to clinical diastolic blood pressure (DBP) categories.

Parameters	Model	Adjusted mean (95% CI)			P-trend*	P-value†	P-value‡	P-value§
		Normotensive DBP (n= 715)	Elevated DBP (n=110)	Hypertensive DBP (n=181)				
CRAE, μm	1	167.1 (166.3 - 168.0)	162.6 (160.4 - 164.8)	164.2 (162.4 - 165.9)	**<0.001**	**<0.001**	**0.009**	0.824
	2	167.0 (166.3 - 167.7)	163.1 (161.4 - 164.9)	164.5 (163.1 - 165.9)	**<0.001**	**<0.001**	**0.005**	0.731
CRVE, μm	1	232.7 (231.5 - 233.9)	231.5 (228.5 - 234.5)	231.8 (229.4 - 234.1)	0.671	>0.9	>0.9	>0.9
	2	232.0 (231.1 - 233.0)	234.1 (231.7 - 236.5)	232.8 (230.9 - 234.6)	0.258	0.330	>0.9	>0.9
Arteriolar D_f	1	1.241 (1.237 - 1.245)	1.234 (1.225 - 1.244)	1.231 (1.223 - 1.238)	**0.037**	0.642	**0.046**	>0.9
	3	1.240 (1.236 - 1.244)	1.235 (1.226 - 1.245)	1.233 (1.225 - 1.240)	0.182	>0.9	0.246	>0.9
Venule D_f	1	1.222 (1.218 - 1.225)	1.218 (1.209 - 1.227)	1.221 (1.214 - 1.228)	0.750	>0.9	>0.9	>0.9
	3	1.222 (1.218 - 1.226)	1.216 (1.207 - 1.225)	1.221 (1.214 - 1.228)	0.514	0.748	>0.9	>0.9

CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; D_f, fractal dimension; BMI, body mass index

*P-trend across normotensive, elevated DBP and hypertensive DBP groups.

†P-value between normotensive and elevated DBP groups after Bonferroni correction.

‡P-value between normotensive and hypertensive DBP groups after Bonferroni correction.

§P-value between elevated DBP and hypertensive DBP groups after Bonferroni correction.

Model 1: Not adjusted. Model 2: Adjusted for axial length, fellow vessel caliber, BMI. Model 3: Adjusted for axial length, CRAE, CRVE, BMI.