

# Retinal Microvasculature and Cardiovascular Health in Childhood

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## abstract

**BACKGROUND AND OBJECTIVE:** Alterations in retinal microvasculature are associated with increased risk of cardiovascular disease. We examined the associations of retinal vessel caliber with cardiovascular markers in school-age children.

**METHODS:** Among 4007 school-age children (median age of 6.0 years), we measured cardiovascular markers and retinal vessel calibers from digitized retinal photographs.

**RESULTS:** Narrower retinal arteriolar caliber was associated with higher systolic and diastolic blood pressure ( $-0.20$  SD score [SDS] [95% confidence interval (CI)  $-0.24$  to  $-0.18$ ] and  $-0.14$  SDS [ $-0.17$  to  $-0.11$ ], respectively, per SDS increase in retinal arteriolar caliber), mean arterial pressure, and pulse pressure, but not with carotid-femoral pulse wave velocity, heart rate, cardiac output, or left ventricular mass. A wider retinal venular caliber was associated with lower systolic blood pressure, mean arterial pressure, and pulse pressure and higher carotid-femoral pulse wave velocity (carotid-femoral pulse wave velocity difference =  $0.04$  SDS [95% CI  $0.01$  to  $0.07$ ] per SDS increase in retinal venular caliber). Both narrower retinal arteriolar and venular calibers were associated with higher risk of hypertension at the age of 6 years, with the strongest association for retinal arteriolar caliber (odds ratio  $1.35$  [95% CI  $1.21$  to  $1.45$ ] per SDS decrease in arteriolar caliber). Adjustment for parental and infant sociodemographic factors did not influence the observed associations.

**CONCLUSIONS:** Both retinal arteriolar and venular calibers are associated with blood pressure in school-age children, whereas retinal venular caliber is associated with carotid-femoral pulse wave velocity. Microvascular adaptations in childhood might influence cardiovascular health and disease from childhood onward.



## WHAT'S KNOWN ON THIS SUBJECT:

Microvasculature alterations are associated with increased risk of hypertension in adults. Not much is known about the association of retinal vessel caliber with cardiovascular risk factors among children.

**WHAT THIS STUDY ADDS:** Narrower retinal arteriolar caliber is associated with higher blood pressure, mean arterial pressure, and pulse pressure in school-age children, whereas wider retinal venular caliber is associated with higher carotid-femoral pulse wave velocity. Microvascular adaptations might influence cardiovascular health from childhood onward.

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It has been suggested that the development of hypertension might originate in early life.<sup>1</sup> Early alterations in microvasculature structure might be part of the underlying mechanism leading to the development of hypertension.<sup>2</sup> Studies in rats have shown that alterations in the microvascular structure, and hence increased peripheral resistance, precede the development of hypertension.<sup>3</sup> Over the last few decades, advances in retinal photography have allowed us to noninvasively assess microvasculature in humans. Several cross-sectional and longitudinal studies among adults have shown that retinal arteriolar narrowing is associated with an increased risk of hypertension,<sup>4,5</sup> whereas wider retinal venular caliber is associated with an increased risk of metabolic syndrome and inflammation.<sup>6</sup> However, it remains unclear whether microvascular abnormalities also affect cardiovascular risk factors in childhood. The few studies among children that have examined the associations of retinal vessel caliber with cardiovascular risk factors have suggested that retinal arteriolar narrowing correlates with increased blood pressure levels in children at 6 and 12 years old.<sup>7,8</sup> However, these studies did not have information about other cardiovascular markers.

Therefore, in 4007 school-age children, we examined the cross-sectional associations of retinal vessel caliber with detailed cardiovascular markers.

## METHODS

### Study Design

This study was embedded in the Generation R Study in Rotterdam, Netherlands.<sup>9</sup> The study protocol was approved by the Medical Ethical Committee of the University Medical Center Rotterdam. In total, 6523 children participated in detailed follow-up measurements at the median age of 6.0 years (95% range

5.7 to 8.0). Retinal vessel calibers were available in 4007 children. Missing retinal vessel measurements were mainly due to the later start of these measurements during the follow-up visits (Supplemental Figure 2). Birth weight was lower in children who were not included in the analyses than in children who were included (Supplemental Table 4).

### Retinal Microvasculature Assessment

Retinal photographs were taken by well-trained staff in a dedicated research center. Digital retinal photographs centered on the optic disc were taken in 1 eye, at image resolution 4096 by 3072 pixels, using a Topcon digital retinal camera (model TRC-NW300, Oakland, New Jersey). We used the same methods and protocols as described in previous studies among adults<sup>10,11</sup> to measure retinal vascular caliber from the digitized retinal photographs. Briefly, a semiautomatic computer imaging program was used to measure the caliber of the 6 largest retinal arterioles and venules located 0.5 to 1 disc diameter from the optic disc margin.<sup>12</sup> Using the revised Knudtson-Parr-Hubbard formula, absolute arteriolar and venular diameter were estimated in micrometers and were summarized as central retinal arteriolar and venular equivalents, representing the average arteriolar and venular calibers, respectively, of that eye.<sup>13</sup> Graders, masked to birth parameters and other participant characteristics, operated the computer program and monitored all retinal measurements. We constructed grader-specific SD scores for both central retinal and arteriolar equivalents. Interclass correlation coefficients between graders were 0.79 for retinal arteriolar caliber and 0.89 for retinal venular caliber, which suggests adequate reproducibility.

### Cardiovascular Markers

We measured blood pressure at the right brachial artery with the child

lying quietly in supine position, 4 times at 1-minute intervals, using a validated automatic sphygmomanometer (Datascop Accutor Plus, Paramus, New Jersey).<sup>14</sup> A cuff was selected with a width ~40% of the arm circumference and long enough to cover 90% of the arm circumference. We calculated the mean value for systolic and diastolic blood pressure using the last 3 blood pressure measurements of each participant. We subsequently calculated the mean arterial pressure (mean arterial pressure = [systolic blood pressure + 2 × blood pressure]/3) and pulse pressure (pulse pressure = [systolic blood pressure – diastolic blood pressure]). We defined hypertension as systolic and diastolic blood pressure above the 95th percentile, using age- and height-specific cut points defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure.<sup>15</sup> Carotid-femoral pulse wave velocity was assessed by using the automatic Complior SP device (Artech Medical, Pantin, France) with participants in supine position, as previously described in detail.<sup>16</sup> The distance between the recording sites at the carotid (proximal) and femoral (distal) artery was measured over the surface of the body to the nearest centimeter. Carotid-femoral pulse wave velocity was calculated as the ratio of the distance traveled by the pulse wave and the time delay between the waveforms, as expressed in meters per second. Carotid-radial pulse wave velocity can be measured reliably in large pediatric population-based cohorts, with interclass correlation coefficients within and between technicians higher than 0.96.<sup>17</sup> Two-dimensional echocardiography was used to measure the interventricular end-diastolic septal thickness, left ventricular end-diastolic diameter, left ventricular end-diastolic posterior wall thickness, heart rate, and cardiac output. These

measurements were performed using methods recommended by the American Society of Echocardiography and were used to calculate the left ventricular mass and left ventricular relative wall thickness ( $2 \times [\text{diastolic posterior wall thickness} \div \text{left ventricular end-diastolic diameter}]$ ).<sup>18,19</sup>

### Covariates

Using questionnaires, we collected information about maternal age, parity, educational level, prepregnancy BMI, smoking during pregnancy, and folic acid supplement use. Maternal and paternal blood pressure were assessed at enrollment. Information on ethnicity was obtained from the first questionnaire at enrollment in the study.<sup>9</sup> Gestational age at birth was based on fetal ultrasound examination during the first ultrasound visit. Birth weight was obtained from medical records. Information on breastfeeding and average TV watching time were assessed by questionnaire. At the child's age of 6 years, we measured height and weight and calculated BMI ( $\text{kg}/\text{m}^2$ ).

### Statistical Analyses

First, we examined the correlations between all retinal vessel calibers and cardiovascular markers using Pearson correlation coefficients. Second, we used multiple linear regression models to assess the associations of retinal vessel calibers with vascular outcomes (systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, and carotid-femoral pulse wave velocity) and cardiac outcomes (heart rate, cardiac output, left ventricular mass, and left ventricular relative wall thickness). For these analyses, we constructed SD scores (SDSs) ( $[\text{observed value} - \text{mean}]/\text{SD}$ ) for all variables to enable comparison in effect size of different outcome measures. Because the outcomes were highly correlated, we divided

them into 3 groups and applied Bonferroni–Holm correction, taking into account 3 groups of outcomes. Third, we used logistic regression models to examine the association of retinal vessel caliber with the risk of hypertension in childhood. All analyses were adjusted for image grader and child age, gender, and ethnicity. We additionally adjusted these models for parental and infant sociodemographic factors, birth outcomes, and childhood BMI. We tested for interaction terms between gender and BMI with retinal vessel caliber in relation to cardiovascular risk factors in childhood. Because no significant interaction terms were present, no further stratified analyses were performed. Analyses were performed by using the Statistical Package of Social Sciences version 21.0 (SPSS, Chicago, Illinois).

## RESULTS

### Subject Characteristics

Table 1 shows characteristics of the study population. The mean (SD) arteriolar and venular calibers were 159.0 (14.9) and 219.0 (20.2)  $\mu\text{m}$ , respectively. Supplemental Table 5 gives the correlation coefficients between the retina vessel calibers and cardiovascular markers.

### Retinal Vessel Calibers and Cardiovascular Markers in Childhood

Table 2 shows that in the models adjusted for image grader and child age, gender, and ethnicity, narrower retinal arteriolar caliber was associated with higher systolic and diastolic blood pressure ( $-0.20$  SDS [95% confidence interval (CI)  $-0.24$  to  $-0.18$ ] and  $-0.14$  SDS [ $-0.17$  to  $-0.11$ ], respectively), mean arterial pressure ( $-0.18$  SDS [ $-0.21$  to  $-0.15$ ]), and pulse pressure ( $-0.10$  SDS [ $-0.13$  to  $-0.06$ ]) per SDS increase in retinal arteriolar caliber. No association was present for retinal arteriolar caliber with carotid-femoral pulse wave velocity.

Narrower retinal venular caliber was associated with higher systolic blood pressure ( $-0.05$  SDS [95% CI  $-0.08$  to  $-0.02$ ] per SDS increase in retinal venular caliber), mean arterial pressure, and pulse pressure, but not with diastolic blood pressure in childhood. Wider retinal venular caliber was associated with higher carotid-femoral pulse wave velocity (0.04 SDS [95% CI 0.01 to 0.07] per SDS increase in retinal venular caliber). Additional adjustment for parental and infant sociodemographic factors and birth outcomes did not materially affect the observed associations. These associations remained significant even after taking multiple testing into account.

Table 3 shows that no associations were present for retinal arteriolar and venular calibers with heart rate, cardiac output, left ventricular mass, and left ventricular relative wall thickness. A sensitivity analysis performed among preterm-born children and children born with a low birth weight showed results similar to those of the total group (data not shown).

### Retinal Vessel Caliber and Risk of Hypertension

Fig 1 shows that narrower retinal arteriolar and venular calibers were associated with higher risk of hypertension at the age of 6 years, with the strongest associations for retinal arteriolar caliber (odds ratio 1.35 [95% CI 1.21 to 1.45] and 1.19 [1.00 to 1.32] per SDS decrease in arteriolar and venular caliber, respectively). Additional adjustment for parental and infant sociodemographic factors and birth outcomes did not influence the observed associations.

## DISCUSSION

We observed, in a low-risk community-based population of school-age children, that narrower retinal arteriolar caliber was associated with higher systolic and

**TABLE 1** Characteristics of the Study Population

Characteristic	Values
<b>Maternal characteristics</b>	
Age, y	31.0 (19.7–39.9)
Height, cm	167.0 (7.4)
Prepregnancy weight, kg	67.0 (12.7)
Prepregnancy BMI, kg/m <sup>2</sup>	22.7 (18.1–34.9)
Systolic blood pressure, mm Hg	115 (12)
Diastolic blood pressure, mm Hg	68 (10)
Nulliparous	55.7
Higher education	46.1
No folic acid use	26.0
Smoked during pregnancy	25.9
Paternal systolic blood pressure, mm Hg	130 (13)
Paternal diastolic blood pressure, mm Hg	73 (10)
<b>Birth and infant characteristics</b>	
Male gender	50.2
Gestational age at birth, wks	40.1 (36.0–42.3)
Birth weight, g	3438 (542)
European ethnicity	63.2
Ever breastfed	92.6
TV watching ≥2 h per day	19.2
<b>Child characteristics</b>	
Age, y	6.0 (5.7–8.0)
BMI, kg/m <sup>2</sup>	15.9 (13.6–21.4)
Retinal arteriolar caliber, μm	159.0 (14.9)
Retinal venular caliber, μm	219.0 (20.2)
Systolic blood pressure, mm Hg	103 (8)
Diastolic blood pressure, mm Hg	61 (7)
Mean arterial pressure, mm Hg	75 (7)
Pulse pressure, mm Hg	42 (7)
Carotid-femoral pulse wave velocity, cm/s	5.5 (0.9)
Heart rate, beats/min	82 (12)
Cardiac output, L/min	3.2 (0.7)
Left ventricular mass, g/m <sup>2</sup>	53.6 (11.9)
Left ventricular relative wall thickness	0.30 (0.05)

Values are expressed as the medians (95% range), means (SD), or %.

diastolic blood pressure, mean arterial blood pressure, and pulse pressure, whereas wider retinal venular caliber was associated with lower systolic blood pressure and higher carotid-femoral pulse wave velocity. Children with narrower

retinal arteriolar and venular calibers were more likely to have an increased risk of elevated blood pressure.

### Methodological Considerations

We used a population-based cohort study design with a large number of

subjects. Of all children participating in follow-up measurements at the age of 6 years, 64% participated in the retinal vessel and cardiovascular follow-up studies. Nonresponse could lead to biased effect estimates if the associations of different obesity measures and cardiovascular risk factors with retinal vessel calibers were different between children included and not included in the analyses.<sup>9</sup> Birth weight was lower in children who were not included in the current analyses compared with those who were included ( $P < .01$ ). We used validated techniques to measure retinal vessel caliber. We did not take into account other ocular factors, such as axial length and refractive error, that might affect retinal vessel measurement.<sup>20</sup> However, it has been previously shown among adults that these factors have only a small impact on the measurement of retinal vessel caliber.<sup>21</sup> Because of the cross-sectional nature of the analyses, we were not able to explore directions and causality of the observed associations.

### Interpretation of Main Findings

Cardiovascular risk factors at younger ages are associated with higher risk of disease and premature death in adulthood.<sup>22</sup> Previous studies have hypothesized that microvasculature alterations might be part of early underlying mechanisms in the development of cardiovascular

**TABLE 2** Associations of Retinal Arteriolar and Venular Calibers With Vascular Outcomes in Childhood ( $N = 4007$ )

Retinal Vessel Calibers in SDS	Vascular Outcomes in SDS				
	Systolic Blood Pressure	Diastolic Blood Pressure	Mean Arterial Pressure	Pulse Pressure	Carotid Femoral Pulse Wave Velocity ( $n = 3821$ )
<b>Retinal arteriolar caliber</b>					
Basic model	-0.20 (-0.24 to -0.18)*	-0.14 (-0.17 to -0.11)*	-0.18 (-0.21 to -0.15)*	-0.10 (-0.13 to -0.06)*	0.02 (-0.01 to 0.05)
Full model	-0.19 (-0.21 to -0.16)*	-0.13 (-0.16 to -0.10)*	-0.17 (-0.20 to -0.14)*	-0.10 (-0.12 to -0.07)*	0.02 (-0.02 to 0.05)
<b>Retinal venular caliber</b>					
Basic model	-0.05 (-0.08 to 0.02)*	-0.01 (-0.04 to 0.02)	-0.03 (-0.06 to -0.00)*	-0.03 (-0.07 to -0.00)*	0.04 (0.01 to 0.07)*
Full model	-0.05 (-0.08 to 0.02)*	-0.01 (-0.04 to 0.02)	-0.03 (-0.06 to 0.00)	-0.05 (-0.08 to -0.02)*	0.04 (0.01 to 0.08)*

Values are expressed as linear regression coefficients (95% CI). The estimates represent differences in vascular outcomes per SDS increase in retinal arteriolar or venular caliber. Basic models are adjusted for image grader and child age, gender, and ethnicity. Full models are additionally adjusted for maternal age, parity, education, prepregnancy BMI, and smoking and folic acid supplement during pregnancy; parental blood pressure at intake; and child's breastfeeding, TV watching, gestational age, weight at birth, and BMI.

\* $P < .05$

**TABLE 3** Associations of Retinal Arteriolar and Venular Calibers With Cardiac Outcomes in Childhood

Retinal Vessel Calibers in SDS	Cardiac outcomes in SDS			
	Heart Rate	Cardiac Output	Left Ventricular Mass	Left Ventricular Relative Wall Thickness
<i>n</i>	3537	3520	3817	3809
Retinal arteriolar caliber				
Basic model	-0.03 (-0.06 to 0.00)	-0.03 (-0.06 to 0.00)	0.00 (-0.03 to 0.03)	0.00 (-0.03 to 0.03)
Full model	-0.03 (-0.06 to 0.01)	-0.02 (-0.06 to 0.01)	0.00 (-0.02 to 0.03)	0.01 (-0.03 to 0.04)
Retinal venular caliber				
Basic model	0.03 (0.00 to 0.06)	0.00 (-0.03 to 0.04)	0.01 (-0.02 to 0.04)	0.01 (-0.02 to 0.04)
Full model	0.03 (-0.00 to 0.06)	0.00 (-0.03 to 0.03)	0.01 (-0.02 to 0.03)	-0.01 (-0.02 to 0.04)

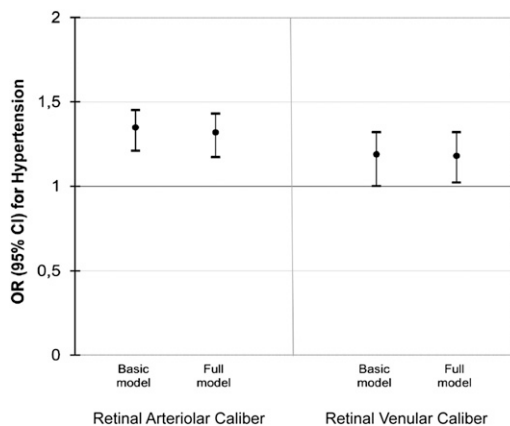
Values are expressed as linear regression coefficients (95% CI). The estimates represent differences in cardiac outcomes per SDS increase in retinal arteriolar or venular caliber. Basic models are adjusted for image grader and child age, gender, and ethnicity. Full models are additionally adjusted for maternal age, parity, education, prepregnancy BMI, and smoking and folic acid supplement during pregnancy; parental blood pressure at intake; and child's breastfeeding, TV watching, gestational age, weight at birth, and BMI.

disease.<sup>2</sup> These studies were mostly conducted among adults and focused on the association of retinal vessel caliber with blood pressure. Among adults, retinal arteriolar narrowing is strongly associated with higher pressure and independently predicted the risk of stroke,<sup>23,24</sup> whereas wider retinal venular caliber was associated with increased risk of metabolic syndrome and measures of inflammation.<sup>6</sup> It remains unclear whether microvascular abnormalities are a result of cardiovascular disease or are part of the factors that relate to the development of these diseases. Thus, examining the associations among children without clinical cardiovascular disease may provide further insight into the pathways underlying these associations.

Increased blood pressure is the leading factor for cardiovascular disease, and pulse pressure has been recognized as a risk factor for stroke.<sup>25</sup> Previously, a study among 5628 adults showed that narrower retinal arteriolar caliber is associated with increased blood pressure, independent of baseline blood pressure and BMI.<sup>26</sup> Studies among children also observed significant inverse associations between retinal arteriolar caliber and blood pressure.<sup>27,28</sup> Two cross-sectional studies among 1953 children age 6 to 8 years and 587 children age 11 years found significant inverse associations between retinal arteriolar caliber and systolic and diastolic blood pressure levels and mean arterial pressure.<sup>8,27</sup> We also observed that narrower

retinal arteriolar caliber was associated with higher systolic and diastolic blood pressure, mean arterial pressure, and pulse pressure, independent of parental and infant sociodemographic factors and childhood BMI. Results from previous studies on the association of retinal venular caliber with blood pressure are inconsistent.<sup>8,27,28</sup> A study among 578 children at the age of 11 years observed that narrower retinal venular caliber was associated with higher diastolic, but not systolic, blood pressure.<sup>27</sup> Another cross-sectional study among children age 4 to 5 years showed that increased systolic blood pressure was associated with wider venular caliber.<sup>28</sup> In our study, we observed that narrower retinal venular caliber was associated with higher systolic blood pressure and pulse pressure, but not with diastolic blood pressure. Retinal arteriolar and venular calibers were positively correlated ( $r = 0.43$ ). Therefore, the observed associations of retinal venular caliber with systolic blood pressure might be due to confounding by retinal arteriolar caliber.<sup>29</sup>

A meta-analysis showed that retinal arteriolar narrowing, likely indicative of increased peripheral vascular resistance, leads to subsequent development of hypertension in adults.<sup>30</sup> Also, cross-sectional studies among children age 6 to 8 and 12.7 years have shown that narrower retinal arterioles were significantly correlated with increased risk of

**FIGURE 1**

Associations of retinal vessels with the risk of hypertension in children ( $N = 4007$ ). Values are expressed as the odds ratio (OR) (95% CI). The estimates represent risk of hypertension per SD score decrease in retinal vessel caliber. The basic model is adjusted for image grader and child age, gender, and ethnicity. Full models are additionally adjusted for maternal age, parity, education, prepregnancy BMI, and smoking and folic acid supplementation during pregnancy; parental blood pressure at intake; and child's breastfeeding, TV watching, gestational age, weight at birth, and BMI.

hypertension.<sup>8,31</sup> In line with these studies, we also found significant associations of narrower retinal arteriolar and venular calibers with increased risks of elevated blood pressure in school-age children.

Carotid-femoral pulse wave velocity is a marker of arterial stiffness and is associated with cardiovascular disease in adults.<sup>32</sup> Among adults, a cross-sectional study among 135 individuals showed that arterial stiffness measured by central pulse pressure was inversely correlated with wall-to-lumen ratio of retinal arterioles.<sup>33</sup> Another study among 197 adults found that retinal arteriolar narrowing was associated with higher carotid-femoral pulse wave velocity.<sup>34</sup> No previous study in children examined the associations of retinal vessel calibers with carotid-femoral pulse wave velocity. In our study, we observed that wider retinal venular caliber was associated with a higher carotid-femoral pulse wave velocity, suggesting that microvasculature alterations might affect carotid-femoral pulse wave velocity already from childhood onward.

Increased left ventricular mass is an early pathogenic process in the development of heart failure.<sup>35</sup> In children, increased left ventricular mass is correlated with higher adiposity and hypertension.<sup>36,37</sup> A longitudinal study among 132 children showed that increased left ventricular mass tends to track with age, between 13 and 27 years.<sup>36</sup> The few studies that examined associations of retinal microvasculature with left ventricular mass were all conducted among adults. A study among 4593 adults showed that narrower retinal arteriolar caliber was associated with left ventricular

mass remodeling, independent from traditional risk factors for cardiovascular diseases.<sup>38</sup> In contrast, in our population of school-age children, we did not find significant associations of retinal vessel caliber with left ventricular mass. These associations may become more apparent at older ages. We also did not find significant associations of retinal vessel caliber with cardiac output and heart rate, which are important cardiac measures and are shown to contribute to cardiovascular disease development. To the best of our knowledge, no previous study examined the association of retinal vessel caliber with these cardiac measures.

Our findings suggest that microvasculature alterations might be involved in the early mechanisms leading to cardiovascular disease in later life. The retinal vessels share similar anatomic and physiological properties with coronary and cerebral microcirculation and have been suggested as biomarkers to estimate systemic vascular health.<sup>6,39</sup> Eutrophic remodeling<sup>40</sup> and anatomic alterations such as intimal thickness and hyalinization may be mechanisms leading to narrowing retinal arteriolar vessels, which as a consequence might lead to an increase in peripheral resistance and higher blood pressure in later life.<sup>2</sup> Although the observed effect estimates for the associations of retinal vessel caliber with different cardiovascular markers were small, these findings are important from an etiological perspective. Previous studies have shown that cardiovascular risk factors tend to track with age from childhood into adulthood.<sup>1,41</sup> A large meta-analysis

showed that blood pressure tracks from childhood into adulthood, and early-life blood pressure is associated with increased cardiovascular risk in later life.<sup>42</sup> Thus, these studies suggest that subclinical differences in risk factors for cardiovascular disease in childhood are related to the development of cardiovascular disease in later life. Further studies are needed to examine the long-term consequences of the observed differences in cardiovascular indices throughout the life course.

## CONCLUSIONS

We observed that narrower retinal arteriolar caliber was associated with higher systolic and diastolic blood pressure, mean arterial blood pressure, and pulse pressure, whereas wider retinal venular caliber was associated with lower systolic blood pressure and higher carotid-femoral pulse wave velocity. These results suggest that retinal arteriolar and venular adaptations are markers of microvascular pathways that ultimately lead to the development of cardiovascular risk factors in later life. Further studies are needed to examine the predictive value of alterations in the retinal microvasculature in the development of clinical cardiovascular diseases throughout the life course.

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## REFERENCES

1. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61–73
2. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation*. 2001;104(6):735–740
3. Komolova M, Friberg P, Adams MA. Altered vascular resistance properties and acute pressure-natriuresis mechanism in neonatal and weaning spontaneously hypertensive rats. *Hypertension*. 2012;59(5):979–984
4. Park JB, Schiffrin EL. Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension. *J Hypertens*. 2001;19(5):921–930
5. Sasongko MB, Wong TY, Wang JJ. Retinal arteriolar changes: intermediate pathways linking early life exposures to cardiovascular disease? *Microcirculation*. 2010;17(1):21–31
6. Klein R, Klein BE, Knudtson MD, Wong TY, Tsai MY. Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. *Arch Ophthalmol*. 2006;124(1):87–94
7. Kurniawan ED, Cheung N, Cheung CY, Tay WT, Saw SM, Wong TY. Elevated blood pressure is associated with rarefaction of the retinal vasculature in children. *Invest Ophthalmol Vis Sci*. 2012;53(1):470–474
8. Mitchell P, Cheung N, de Haseth K, et al. Blood pressure and retinal arteriolar narrowing in children. *Hypertension*. 2007;49(5):1156–1162
9. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol*. 2012;27(9):739–756
10. Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. *Hypertension*. 2004;44(4):442–447
11. Mitchell P, Liew G, Rochtchina E, et al. Evidence of arteriolar narrowing in low-birth-weight children. *Circulation*. 2008;118(5):518–524
12. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269–2280
13. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27(3):143–149
14. Wong SN, Tz Sung RY, Leung LC. Validation of three oscillometric blood pressure devices against auscultatory mercury sphygmomanometer in children. *Blood Press Monit*. 2006;11(5):281–291
15. 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(2 suppl 4th Report):555–576
16. de Jonge LL, Langhout MA, Taal HR, et al. Infant feeding patterns are associated with cardiovascular structures and function in childhood. *J Nutr*. 2013;143(12):1959–1965
17. Donald AE, Charakida M, Falaschetti E, et al. Determinants of vascular phenotype in a large childhood population: the Avon Longitudinal Study of Parents and Children (ALSPAC). *Eur Heart J*. 2010;31(12):1502–1510
18. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2(5):358–367
19. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57(6):450–458
20. Patton N, Maini R, MacGillivray T, Aslam TM, Deary IJ, Dhillon B. Effect of axial length on retinal vascular network geometry. *Am J Ophthalmol*. 2005;140(4):648–653
21. Wong TY, Wang JJ, Rochtchina E, Klein R, Mitchell P. Does refractive error influence the association of blood pressure and retinal vessel diameter? The Blue Mountains Eye Study. *Am J Ophthalmol*. 2004;137(6):1050–1055
22. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med*. 2010;362(6):485–493
23. Cheung CY, Ikram MK, Sabanayagam C, Wong TY. Retinal microvasculature as a model to study the manifestations of hypertension. *Hypertension*. 2012;60(5):1094–1103
24. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. *Neurology*. 2006;66(9):1339–1343
25. Huang CM, Wang KL, Cheng HM, et al. Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. *J Hypertens*. 2011;29(3):454–459
26. Wong TY, Klein R, Sharrett AR, et al; Atherosclerosis Risk in Communities Study. Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med*. 2004;140(4):248–255
27. Hanssen H, Siegrist M, Neidig M, et al. Retinal vessel diameter, obesity and metabolic risk factors in school children (JuvenTUM 3). *Atherosclerosis*. 2012;221(1):242–248
28. Li LJ, Cheung CY, Liu Y, et al. Influence of blood pressure on retinal vascular caliber in young children. *Ophthalmology*. 2011;118(7):1459–1465
29. Liew G, Wong TY, Mitchell P, et al. Are narrower or wider retinal venules associated with incident hypertension? *Hypertension*. 2006;48(2):e10; author reply e1
30. Ding J, Wai KL, McGeechan K, et al; Meta-Eye Study Group. Retinal vascular caliber

- and the development of hypertension: a meta-analysis of individual participant data. *J Hypertens*. 2014;32(2):207–215
31. Gopinath B, Baur LA, Wang JJ, et al. Blood pressure is associated with retinal vessel signs in preadolescent children. *J Hypertens*. 2010;28(7):1406–1412
  32. Tounian P, Aggoun Y, Dubern B, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*. 2001; 358(9291):1400–1404
  33. Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE. Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. *Hypertension*. 2013;61(6):1340–1345
  34. Katsi V, Vlachopoulos C, Souretis G, et al. Association between retinal microcirculation and aortic stiffness in hypertensive patients. *Int J Cardiol*. 2012; 157(3):370–373
  35. Bolognese L, Neskovic AN, Parodi G, et al. Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. *Circulation*. 2002;106(18):2351–2357
  36. Sivanandam S, Sinaiko AR, Jacobs DR Jr, Steffen L, Moran A, Steinberger J. Relation of increase in adiposity to increase in left ventricular mass from childhood to young adulthood. *Am J Cardiol*. 2006;98(3):411–415
  37. Stabouli S, Kotsis V, Rizos Z, et al. Left ventricular mass in normotensive, prehypertensive and hypertensive children and adolescents. *Pediatr Nephrol*. 2009;24(8):1545–1551
  38. Cheung N, Bluemke DA, Klein R, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. *J Am Coll Cardiol*. 2007;50(1):48–55
  39. de Jong FJ, Ikram MK, Witteman JC, Hofman A, de Jong PT, Breteler MM. Retinal vessel diameters and the role of inflammation in cerebrovascular disease. *Ann Neurol*. 2007;61(5):491–495
  40. Mulvany MJ. Are vascular abnormalities a primary cause or secondary consequence of hypertension? *Hypertension*. 1991;18(3 Suppl):152–157
  41. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. 2008; 117(25):3171–3180
  42. McCarron P, Smith GD, Okasha M. Secular changes in blood pressure in childhood, adolescence and young adulthood: systematic review of trends from 1948 to 1998. *J Hum Hypertens*. 2002;16(10):677–689

**SUPER BOWL HEROICS:** *My wife is an actuary and works as an insurance analyst for the State of Vermont, so we occasionally discuss somewhat arcane insurance topics. For example, we have discussed whether liability insurance can exclude pollution, whether credit scores should be tied to auto insurance rates, and who will insure cars that drive themselves. The other day, however, she surprised me when she announced that the Super Bowl most likely had saved the day. I was confused as she is not a great fan of professional football and I cannot remember her voicing much enthusiasm for watching the Super Bowl.*

*As reported in Forbes (Realspin: December 9, 2014), however, the issue has to do with the Terrorism Risk Insurance Act (TRIA). The act was passed shortly after the terrorist bombings in September 2001 and was designed to provide a financial backstop for private insurance companies in case of a catastrophic terrorist attack. The 9/11 bombings resulted in thousands of lost lives and 23 billion dollars in insurable losses. After the attack, insurance companies were reluctant to write new policies in which they could be exposed to huge losses, and construction in some parts of the country practically stopped as contractors could not find insurance. The TRIA caps the losses that can be assumed by the private insurers with the federal government providing coverage for catastrophic losses. The bill has been extended several times, but in December 2014 Congress allowed it to expire.*

*In the first week of January 2015, insurance companies were busy re-writing liability policies to exclude acts of terrorism. This threatened the viability of new construction projects and huge public events such as the Super Bowl. The National Football League and other professional sports leagues banded together to lobby Congress to reauthorize TRIA as soon as possible. Most Americans would probably not notice if a construction project in California was delayed, but most would notice if the Super Bowl was canceled. Fortunately, Congress did re-enact TRIA in January, so we will never know if the Super Bowl really would have been canceled – but it did prompt my wife’s exclamation that a football game had saved the day.*

Noted by WVR, MD



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