Obesity, Blood Pressure, and Retinal Vessels: A Meta-analysis
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CONTEXT: Retinal vessel imaging is a noninvasive diagnostic tool used to evaluate cardiovascular risk. Childhood obesity and elevated blood pressure (BP) are associated with retinal microvascular alterations.

OBJECTIVE: To systematically review and meta-analyze associations between obesity, BP, and physical activity with retinal vessel diameters in children.

DATA SOURCES: We conducted a literature search through the databases of PubMed, Embase, Ovid, Web of Science, and the Cochrane Register of Controlled Trials.

STUDY SELECTION: School- and population-based cross-sectional data.

DATA EXTRACTION: General information, study design, participants, exposure, and outcomes.

RESULTS: A total of 1751 studies were found, and 30 full-text articles were analyzed for eligibility. Twenty-two articles (18 865 children and adolescents) were used for further assessment and reflection. Eleven articles were finally included in the meta-analysis. We found that a higher BMI is associated with narrower retinal arteriolar (pooled estimate effect size $-0.37$ [95% confidence interval (CI): $-0.50$ to $-0.24$]) and wider venular diameters ($0.35$ [95% CI: $0.07$ to $0.63$]). Systolic and diastolic BP are associated with retinal arteriolar narrowing (systolic BP: $-0.63$ [95% CI: $-0.92$ to $-0.34$]; diastolic BP: $-0.60$ [95% CI $-0.95$ to $-0.25$]). Increased physical activity and fitness are associated with favorable retinal vessel diameters.

LIMITATIONS: Long-term studies are needed to substantiate the prognostic relevance of retinal vessel diameters for cardiovascular risk in children.

CONCLUSIONS: Our results indicate that childhood obesity, BP, and physical inactivity are associated with retinal microvascular abnormalities. Retinal vessel diameters seem to be sensitive microvascular biomarkers for cardiovascular risk stratification in children.
Cardiovascular disease (CVD) has its origin in early life because of classic and lifestyle-associated risk factors that initiate endothelial dysfunction and preatherosclerosis during childhood. In children, hypertension and obesity are gradually becoming a health hazard with an increasing global prevalence of unhealthy and sedentary lifestyles among children. Childhood physical inactivity (PIA) plays a key pathophysiological role in the development of obesity-related CVD and seems to be an important link between obesity, hypertension, inflammation, insulin resistance, and incidence of atherosclerosis in adulthood.

Epidemiologic surveys of the past 20 years have revealed an increase in the population-based prevalence of prehypertension and hypertension in children and adolescents, which is related to the concomitant increase of overweight and obesity in childhood. The longitudinal Cardiovascular Risk in Young Finns study showed that elevated blood pressure (BP) in childhood tracks through adulthood. A high prevalence of obesity can be observed early in life and persists into adulthood. Obesity is associated with deleterious health effects for children and adults alike. Worldwide, almost every fourth child is overweight or obese. Every obese child is at risk for becoming an obese adult and to suffer from adult CVD. It has recently been shown that, in a population of 2.3 million adolescents, obesity is associated with a substantially increased cardiovascular mortality in middle age. It therefore seems necessary to focus cardiovascular prevention on excessive weight gain and high BP in children and adolescents to counteract the present and future socioeconomic burden and health hazard of childhood obesity and hypertension.

The mechanisms of early subclinical vascular impairments during childhood are still poorly understood. Over the last decades, several studies have used retinal vessel imaging as a noninvasive diagnostic tool for the evaluation of microvascular health. Retinal vessels are part of the cerebrovascular bed and have been described as a window to the heart. Central retinal arteriolar equivalents (CRAEs) and central retinal venular equivalents (CRVEs) can be used for cardiovascular risk stratification during life span. It has recently been shown that retinal vessel diameters can predict long-term adult cardiovascular outcomes, suggesting that retinal vessel diameters are a reproducible biomarker with additive value for atherosclerotic CVD event risk prediction. In adults, large cohort studies have revealed that smaller CRAEs and larger CRVEs are associated with increased risk of stroke, hypertension, and a higher cardiovascular mortality and morbidity. In a meta-analysis in adults, obesity has been associated with narrower retinal arteries and wider venules. In 2 large population-based cross-sectional studies, lower levels of physical activity (PA) and higher television consumption were associated with wider retinal venules in adults.

Subclinical changes in the retinal microcirculation exist long before manifestation of CVD can be diagnosed. Given the predictive value of alterations in retinal vessel diameters for CVD outcomes in adults, early identification of subclinical changes in the retinal microcirculation in children is a promising and clinically important approach to improve primary prevention of CVD and to optimize risk stratification. In this systematic review and meta-analysis, we aim to give an overview on the association of childhood BMI, BP, and PA with retinal vessel diameters and the related risk for the development of CVD in adulthood.

METHODS

This systematic review, meta-analysis, and meta-regression was conducted according to the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data Source and Study Selection

In December 2016 as well as June 2017, an electronic literature search was performed throughout the databases of PubMed, Embase, Ovid, Web of Science, and the Cochrane Register of Controlled Trials. As an additional measure of precaution, we screened the reference lists of all full-text articles we assessed for eligibility to find relevant articles not listed in the databases. Inclusion criteria were availability of full text and use of English or German language. Articles were included if retinal vessel diameters were assessed in a standardized manner and compared with either BMI, BP, or PA and/or PIA in children and adolescents (aged 3–18 years). School- or population-based cross-sectional data were included only. Studies were excluded if the investigated population was >18 years old, not human, or had a history of diabetes mellitus or other reasons for vascular dysfunction. We also excluded systematic reviews and meta-analyses. Each database was searched by using the main key words of interest on the basis of a systematic search string. The population search terms were as follows: child, adolescent. This was combined with the following characteristic search terms: overweight, obesity, obese, blood pressure, hypertension, prehypertension, physical activity, exercise, sport, fitness, training, motor skills, physical inactivity, screen time, television viewing. The descriptor search terms included...
the following: retinal vessel diameter/caliber, retinal arteriolar/venular narrowing, retinal arteriolar ratio, retinal microcirculation.

For every search source, different adaptations were made on the basis of the following search string: (arteriolar narrowing OR retinal arteriolar caliber OR retinal venular caliber OR retinal vasculature OR retinal vascular caliber OR retina arteriovenous ratio OR retinal microcirculation OR retinal vessel* OR retinal vessel diameter*) AND (child OR childhood OR children OR schoolchildren OR youth OR adolescent* OR infant OR young people OR young adj people OR young OR teenage*) AND (obesity OR BMI OR body mass index OR waist-to-hip ratio OR waist circumference OR physical activity OR exercise OR sport OR physical education OR television viewing OR physical inactivity OR sedentary OR tv viewing OR fitness OR physical fitness OR cardiorespiratory fitness OR cardiovascular fitness OR motor activity OR training OR walk* OR high blood pressure OR blood pressure OR high-normal blood pressure OR prehypertension OR prehypertensive OR pre hypertension OR pre-hypertension OR pre-hypertensive OR hypertension OR hypertensive).

An external reviewer independently screened the citations from the search results and decided which full texts should be included. Discrepancies between the reviewers were discussed until a consensus was reached.

Data Extraction Form

The extraction form included general information such as authors name, journal, year of publication, study design, participants (sample size, age, percentage of sex), exposure, and outcomes (and its SDs). Data and information of the included studies were independently extracted from both reviewers. Differences in extracted data were discussed on the basis of the original full-text article. For further analysis, the information of using eye drops for pupil dilatation was additionally added. To assess risk of bias, the Joanna Briggs Institute appraisal tool was used.32 Two authors independently screened the articles in terms of methodological quality assessment. In case of discrepancies, consensus was reached in discussion with a third reviewer. Risk of bias was assessed by using descriptive items including selection and detection bias, exposure and outcome measures, statistical analysis, and confounding factors. By using the summary of risk of bias assessment, each study was categorized as low, medium, or high risk of bias.

Retinal Vessel Analysis

A standard retinal fundus image allows noninvasive measurement of retinal microvasculature. Retinal vessel analysis is a reproducible, computer-based, semiautomated procedure to assess retinal arteriolar and venular diameters. In principle, static retinal vessel analysis involves a fundus camera and an image processing software. Images are usually taken at an angle of 45° with the optic disc at the center. Retinal vessel diameters are detected in a ring zone covering an area of 0.5 to 1.0 disc diameters from the optic disc margin. By using the Parr-Hubbard formula,33 the diameters are averaged to CRAEs and CRVEs by using these values to calculate the arteriolar-to-venular diameter ratio (AVR). CRAEs and CRVEs are recorded in micrometers under the assumption that 1 measuring unit corresponds to 1 μm in the Gullstrand’s normal eye. Retinal vessel analysis is highly reproducible in all age groups with an intraclass correlation of ~0.90 to 0.95 and coefficient of variation of ~2% in young children.34

Statistical Analysis

We extracted unstandardized regression coefficients and corresponding SEs from regression models in which the retinal vessel variables served as outcomes (CRAE, CRVE, AVR). Regression coefficients were extracted for the focal predictors BMI and BP. Standardized regression coefficients and SEs were back-transformed to the original scale. If SEs were not reported directly, they were inferred from P values or confidence intervals (CIs).35 Regression coefficients were combined by use of random-effects meta-analysis for each retinal vessel variable.36 We examined heterogeneity between studies with standard χ² tests and calculated I² statistics, which are used to measure the proportion of variation in regression coefficients due to between-study heterogeneity.37 We plotted prediction intervals (PIs) in addition to CIs for the combined effects in case of substantial heterogeneity.38 PI is an estimate of an interval in which future observations will fall with a certain probability on the basis of what has already been observed. Because the original regression models were not always adjusted for the same covariates, we compared the estimates from regression models that were adjusted for the same covariates as a sensitivity analysis. We compared estimates of subgroups of studies using meta-regression.39 Meta-regression with mean age, percentage of boys, and mean BMI (only in BP analyses) as predictor per study was used to assess the potential association between age and magnitude of the effect of BMI and BP on the retinal vessel variables. P values <.05 were considered statistically significant. All statistical analyses were done in Stata version 14.40

RESULTS

Study Selection

After a last electronic search in June 2017, a total of 1751 studies were found. In addition, 2 studies were included after the manual search of interest. Duplicates were rejected,
and 1350 articles were screened on the basis of title and abstract. After reviewing the abstracts, 30 full-text articles were analyzed for eligibility. Five articles represented the same cohort and results as previously included papers. Three studies did not fulfill 1 or more of the inclusion criteria. Finally, 22 articles were included for further assessment and reflection. In all studies, the same method to analyze retinal vessel diameters was applied. However, there were 5 studies in which eye drops for pupil dilatation were not used.

We therefore used the published data only. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram reveals the detailed study selection (Fig 1). In total, 18 865 participants were included in this systematic review.

The meta-analysis was conducted including all 11 studies. All other studies of the systematic review did not report β coefficients or other relevant parameters for the meta-analysis. Because all studies contained reports of different adjusted models, we analyzed only unadjusted models or basic models with <6 covariates (including age, sex, axial length, iris color, ethnicity, and image grader) in the meta-analysis. As a sensitivity analysis, we compared the results of the meta-analysis of the basic models with the meta-analysis of the full models. An overview of the included studies and participants is shown in Table 1.

BMI and Retinal Vessel Diameters

The authors for 13 articles investigated the relationship between BMI and retinal microvascular diameters in children and adolescents. Overall, 15 710 participants were screened and assessed for BMI and retinal vessel diameters. Sample sizes ranged from 136 to 4145 children. A higher BMI was associated with retinal arteriolar narrowing and venular widening. Only 2 studies revealed no significant correlation between BMI and retinal vessels. From the available data, it seemed that BMI affected arteriolar narrowing and venular widening to a similar extent in children. Eight studies contained reports of the associations between BMI and retinal vessel diameters with a β coefficient and were included in the meta-analysis. The pooled estimate effect size (ES) of the association between BMI and retinal arteriolar diameters was −0.37 (95% CI: −0.50 to −0.24; P = .04 [Fig 2A]).

BP and Retinal Vessel Diameters

Peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) were frequently assessed in the included studies. The authors of 12 studies (13 412 participants) have published the relationship between BP and retinal vessel diameters. All of these studies revealed a significant correlation between SBP and CRAE. A higher SBP was consistently associated with narrower retinal arterioles. The results were similar for DBP. Only 2 studies revealed no association between DBP and

* Refs 49,52,53,55,57,58,60,62,63,66,68

FIGURE 1

Flow diagram of the systematic review and meta-analysis including identification and selection of studies.

Records identified through database search (n = 1751)

Additional records identified through other sources (n = 2)

Records after duplicates removed (n = 1349)

Records excluded in which retinal vessel diameters and BMI or BP or PA were not examined (n = 1319)

Records screened (n = 1349)

Full-text articles assessed for eligibility (n = 30)

Studies included in qualitative synthesis (n = 22)

Studies did not contain reports of β coefficients or other relevant parameters for meta-analysis (n = 11)

Studies included in quantitative synthesis (meta-analysis) (n = 11)
### TABLE 1 Overview of the Included Studies

<table>
<thead>
<tr>
<th>Authors (y)</th>
<th>Sample Size (% Male)</th>
<th>Mean Age, y</th>
<th>Country, Ethnicity</th>
<th>Predictor</th>
<th>CRAE (Association)</th>
<th>CRVE (Association)</th>
<th>Intraclass Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheung et al (2007)</td>
<td>768 (52.5)</td>
<td>7.9</td>
<td>Singapore, Southeast Asia</td>
<td>BMI</td>
<td>β = no</td>
<td>β = positive</td>
<td>0.85 (CRAE) 0.97 (CRVE)</td>
</tr>
<tr>
<td>Cheung et al (2012)</td>
<td>1225 (49.4)</td>
<td>11.9</td>
<td>Singapore, Southeast Asia</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = positive</td>
<td>0.85 (CRAE) 0.97 (CRVE)</td>
</tr>
<tr>
<td>Gishti et al (2015)</td>
<td>4145 (50)</td>
<td>6</td>
<td>Netherlands, white</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Gishti et al (2015)</td>
<td>4007 (50.2)</td>
<td>6</td>
<td>Netherlands, white</td>
<td>SBP</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Gopinath et al (2010)</td>
<td>2272 (50.8)</td>
<td>12.7</td>
<td>Australia, South Pacific</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Gopinath et al (2011)</td>
<td>2179 (50.5)</td>
<td>12.7</td>
<td>Australia, South Pacific</td>
<td>BMI</td>
<td>Cat = inverse</td>
<td>Cat = positive</td>
<td>Not available</td>
</tr>
<tr>
<td>Gopinath et al (2013)</td>
<td>379 (52.8)</td>
<td>4.6</td>
<td>Australia, South Pacific</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Hanssen et al (2012)</td>
<td>578 (56.9)</td>
<td>11.1</td>
<td>Germany, white</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = positive</td>
<td>0.92 (CRAE) 0.97 (CRVE)</td>
</tr>
<tr>
<td>Hanssen et al (2014)</td>
<td>391 (48.8)</td>
<td>7.3</td>
<td>Switzerland, white</td>
<td>CRF</td>
<td>β = no</td>
<td>β = inverse</td>
<td>0.94 (CRAE) 0.95 (CRVE)</td>
</tr>
<tr>
<td>Imhof et al (2016)</td>
<td>381 (48.8)</td>
<td>7.3</td>
<td>Switzerland, white</td>
<td>BMI</td>
<td>β = no</td>
<td>β = no</td>
<td>0.94 (CRAE) 0.95 (CRVE)</td>
</tr>
<tr>
<td>Kurniawan et al (2014)</td>
<td>412 (49.2)</td>
<td>7.9resp.</td>
<td>Singapore, Southeast Asia</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Li et al (2011)</td>
<td>385 (50.7)</td>
<td>5</td>
<td>Singapore, Southeast Asia</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Li et al (2011)</td>
<td>136 (45.6)</td>
<td>11.2</td>
<td>Singapore, Southeast Asia</td>
<td>BMI</td>
<td>β = no</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Mitchell et al (2007)</td>
<td>1572 (50.8)</td>
<td>6.3resp.</td>
<td>Singapore, Southeast Asia</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Murgan et al (2013)</td>
<td>121 (56.2)</td>
<td>16.2</td>
<td>Germany, white</td>
<td>BMI</td>
<td>Cat = inverse</td>
<td>Cat = no</td>
<td>Not available</td>
</tr>
<tr>
<td>Siegrist et al (2014)</td>
<td>381 (58.5)</td>
<td>11.1</td>
<td>Germany, white</td>
<td>PA</td>
<td>Cat = no</td>
<td>Cat = no</td>
<td>0.92 (CRAE) 0.97 (CRVE)</td>
</tr>
<tr>
<td>Tapp et al (2013)</td>
<td>333 (58.5)</td>
<td>11.1</td>
<td>England, white</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Taylor et al (2007)</td>
<td>1608 (50.7)</td>
<td>6.7</td>
<td>Australia, South Pacific</td>
<td>BMI</td>
<td>Cat = inverse</td>
<td>Cat = positive</td>
<td>Not available</td>
</tr>
<tr>
<td>Van Aart et al (2017)</td>
<td>171 (53.8)</td>
<td>12.4</td>
<td>Belgium, white</td>
<td>BMI</td>
<td>β = no</td>
<td>β = no</td>
<td>—</td>
</tr>
<tr>
<td>Xiao et al (2015)</td>
<td>287 (46.3)</td>
<td>9.52</td>
<td>China, Asia</td>
<td>BMI</td>
<td>β = no</td>
<td>β = no</td>
<td>&gt;0.90 (CRAE) 0.90 (CRVE)</td>
</tr>
<tr>
<td>Zheng et al (2013)</td>
<td>444 (46.4)</td>
<td>14.4</td>
<td>China, Asia</td>
<td>BMI</td>
<td>β = inverse</td>
<td>β = positive</td>
<td>&gt;0.90 (CRAE) 0.90 (CRVE)</td>
</tr>
</tbody>
</table>

Cat, category (representing quartiles, tertiles, percentiles, or median); zBMI, z score BMI; —, not applicable.

a Included in the meta-analysis.
b Information given for AVR only.
FIGURE 2
A. Forest plot of the $\beta$ coefficient for CRAE and BMI. B. Forest plot of the $\beta$ coefficient for CRVE and BMI. *Study contains reports of 2 independent, different age groups and is therefore listed twice. Note: weights are from random effects analysis.
CRAE. With respect to CRVE, no association between SBP and DBP was found. In contrast, Gishti et al. found an inverse correlation between SBP and CRVE, whereas Li et al. found a positive correlation between the 2. Hanssen et al. were the only researchers to find an inverse correlation between DBP and CRVE.

In the meta-analysis, 6 studies (7687 participants) could be included in which the association between BP and retinal vessel diameters was analyzed. With respect to the association of SBP with CRAE, a pooled estimate of −0.63 was found (95% CI: −0.92 to −0.34; 95% PI: −1.48 to 0.22; I² = 95.1%; P < .001 [Fig 3A]). Between SBP and CRVE, the pooled estimate was −0.07 (95% CI: −0.21 to 0.06; 95% PI: −0.40 to 0.25; I² = 54.3%; P = .041 [Fig 3B]). Between DBP and CRAE, we found a pooled estimate of −0.60 (95% CI: −0.95 to −0.25; 95% PI: −1.62 to 0.42; I² = 91.5%; P < .001 [Fig 4A]). A pooled estimate of −0.06 (95% CI: −0.14 to 0.03; 95% PI: −0.24 to 0.12; I² = 17.1%; P = .3) was found between DBP and CRVE (Fig 4B).

**PA and Retinal Vessel Diameters**

Only 3 articles contained investigations of the effect of PA and PIA on retinal vessel diameters, including a total of 2234 children. Sample size ranged from 351 to 1492 participants. The results of a German study revealed that PIA was associated with a lower AVR in young school children because of wider venular diameters. The authors of an Australian study demonstrated that more time spent in outdoor activity was associated with wider arteriolar diameters and sedentary behavior resulted in narrower arteriolar diameters.

In our Swiss study, children who spent more time in indoor activity had wider arteriolar diameters. No effect of sedentary behavior was evident. Furthermore, in this study, we investigated the association of objectively measured endurance performance with retinal vessel diameters. Children with a higher cardiorespiratory fitness (CRF), as assessed by a shuttle run test, showed narrower venular diameters. It was not possible to conduct a meta-analysis regarding the associations between retinal vessel diameter and PA or PIA because all 3 studies contained reports of the β coefficient of PA or PIA in different units (days/week, minutes/day, hours/day).

**Meta-regression and Heterogeneity**

Substantial heterogeneity (I² >50%) was present for the associations between SBP and DBP and CRAE and between BMI and SBP and CRVE. We therefore performed a meta-regression analysis to investigate possible sources of heterogeneity: mean age, percentage of boys, mean BMI of the children, and sample size (Supplemental Tables 3 through 6) or pupil dilatation (data not shown). We could not find any associations between retinal vessel diameters, mean age, percentage of boys, or mean BMI (CRAE: 0.24 < β < 0.91; CRVE: 0.05 < β < 0.63). Therefore, heterogeneity was unexplained for remaining outcomes.

**Risk of Bias**

Assessment of risk of bias is shown in Table 2. There were no interrater discrepancies between the reviewers in selection and detection bias, exposure and outcome bias, and appropriate statistical analysis. However, agreement on confounding bias differed in 4 of 22 studies. The overall k for risk of bias assessment between the raters was 0.96. In general, in healthy young children confounding factors, such as the presence of undiagnosed systemic disease, were difficult to assess. However, all included studies demonstrated low risk of bias.

**DISCUSSION**

Alterations in retinal vessel diameters can predict the incidence of CVD in adulthood. Cardiovascular risk factors such as obesity and hypertension have been related to impaired retinal microvascular health in adults and children. In this study, we aimed to investigate the association of obesity, BP, and PA with retinal vessel diameters in children and adolescents. In our systematic review, we demonstrate that BMI levels are associated with narrower arteriolar and wider venular diameters in children and adolescents. In the meta-analysis, it becomes evident that childhood obesity is predominantly associated with retinal arteriolar narrowing. A positive association between retinal venular diameters and BMI was found, although the PI shows that this association may not be consistent. These results were confirmed by using sensitivity analyses (data not shown).

Potential pathophysiological mechanisms explaining the association of obesity with retinal vessels need to be discussed. Childhood obesity is related to proinflammatory and pro-oxidative processes. Obesity is characterized by an excessive accumulation of adipose tissue that triggers the release of a number of bioactive substances and adipose tissue inflammation. Nitric oxide (NO) bioavailability has been shown to be decreased in obesity. NO is a key endothelial derived relaxing factor and vasodilator regulating perfusion. Lower NO levels in childhood obesity may be a contributing factor for narrower arteriolar diameters. There is also evidence that markers of inflammation are associated with wider retinal venules. Inflammation may be a main mechanism by which obesity alters retinal veins. In our previous study in children, inflammation, as measured by...
FIGURE 3
A, Forest plot of the \( \beta \) coefficient for CRAE and SBP. B, Forest plot of the \( \beta \) coefficient for CRVE and SBP.  \(^a\) Study contains reports of 2 independent, different groups separated by country and is therefore listed twice. Note: weights are from random effects analysis.

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FIGURE 4
A. Forest plot of the β coefficient for CRAE and DBP. B, Forest plot of the β coefficient for CRVE and DBP. * Study contains reports of 2 independent, different groups separated by country and is therefore listed twice. Note: weights are from random effects analysis.
c-reactive protein, was independently associated with wider venular diameters in children.\textsuperscript{57}

Our systematic review reveals that higher SBP and DBP are consistently associated with narrower retinal arterioles. In our meta-analysis, a negative association between SBP and DBP and CRAE has been established. Furthermore, CRVE was negatively associated with SBP and DBP, although the PI shows no consistent results. It is therefore possible that the results of future studies may not confirm the negative association of CRVE with BP. The sensitivity analysis confirmed these results (data not shown).

In adults, arteriolar narrowing has been related to hypertension and risk of coronary heart disease and stroke.\textsuperscript{20,74,76} A higher childhood BP is associated with the development of hypertension and cardiovascular mortality in adulthood.\textsuperscript{8,77} The pathophysiology linking retinal arteriolar narrowing with hypertension includes structural and functional mechanisms. In healthy young children with a short exposure time to higher BP, functional adaptations are more likely to occur at early stages. A rise in BP induces myogenic arterial vasoconstriction, also known as the Bayliss effect. This constrictive effect, in balance with the NO-induced vasodilation in response to shear stress, regulates local retinal perfusion pressure and vascular tone. Elevated BP and the related mechanical stress induce a vasoconstrictive response resulting in narrower arteriolar diameters. NO bioavailability has been shown to be reduced in hypertension, and low levels of NO may add to the increased vascular tone and vasoconstriction. The imbalance between myogenic vasoconstriction and reduced NO production may be the main underlying mechanism explaining arteriolar narrowing in children with elevated BP. Systemic and chronically elevated BP may also lead to structural remodeling of the vascular wall, which further aggravates arteriolar narrowing.\textsuperscript{78}

Different questionnaire-based PA levels were associated with favorable retinal vessel diameters across the 3 studies that were included.\textsuperscript{34,54,64} Objectively measured CRF was only measure in a single study.\textsuperscript{34} CRF, measured by shuttle run stages, was associated with narrower venular diameters. Similar results have been described in adults. We have previously shown that higher physical fitness levels are associated with a higher retinal AVR and that regular endurance exercise induced an increase in CRAE as well as a reduction in CRVE, leading to a significantly improved AVR in middle-aged lean and obese individuals.\textsuperscript{79}

Screen time as a marker of PIA does not seem to be associated with vascular alterations in middle European regions.\textsuperscript{34,64} However, in an Australian study, a relation between screen time and retinal arteriolar diameters was found.\textsuperscript{54} An explanation may be the differences in average screen time per day. On average, screen time of the Australian

\begin{table}
\centering
\caption{Risk of Bias Assessment}
\begin{tabular}{lcccccccc}
\hline
Authors (y) & Selection Bias, Detailed Study Design & Detection Bias, Appropriate Exposure Measures & Detection Bias, Appropriate Outcome Measures & Appropriate Statistical Analysis & Assessment of Confounding & Overall Risk of Bias \\
\hline
Cheung et al\textsuperscript{50} (2007)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Cheung et al\textsuperscript{49} (2012) & Yes & Yes & Yes & Yes & Yes & Low \\
Gishti et al\textsuperscript{51} (2015) & Yes & Yes & Yes & Yes & Yes & Low \\
Gishti et al\textsuperscript{52} (2015)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Gopinath et al\textsuperscript{53} (2010) & Yes & Yes & Yes & Yes & Yes & Low \\
Gopinath et al\textsuperscript{54} (2011) & Yes & Yes & Yes & Yes & Yes & Low \\
Gopinath et al\textsuperscript{55} (2011) & Yes & Yes & Yes & Yes & Yes & Low \\
Gopinath et al\textsuperscript{56} (2013)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Hanssen et al\textsuperscript{57} (2012) & Yes & Yes & Yes & Yes & Yes & Low \\
Imhof et al\textsuperscript{58} (2016) & Yes & Yes & Yes & Yes & Yes & Low \\
Imhof et al\textsuperscript{59} (2016)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Kurniawan et al\textsuperscript{60} (2014)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Li et al\textsuperscript{61} (2011)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Li et al\textsuperscript{62} (2011) & Yes & Yes & Yes & Yes & Yes & Low \\
Mitchell et al\textsuperscript{63} (2007)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Murgan et al\textsuperscript{64} (2013) & Yes & Yes & Yes & Yes & Yes & Low \\
Siegrist et al\textsuperscript{65} (2014) & Yes & Yes & Yes & Yes & Yes & Low \\
Tapp et al\textsuperscript{66} (2013) & Yes & Yes & Yes & Yes & Yes & Low \\
Taylor et al\textsuperscript{67} (2007)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
Van Aart et al\textsuperscript{68} (2017) & Yes & Yes & Yes & Yes & Yes & Low \\
Xiao et al\textsuperscript{69} (2015) & Yes & Yes & Yes & Yes & Yes & Low \\
Zheng et al\textsuperscript{70} (2013)\textsuperscript{a} & Yes & Yes & Yes & Yes & Yes & Low \\
\hline
\end{tabular}
\footnotesize{\textsuperscript{a} Included in the meta-analysis.}
\end{table}
children was more than twice as high as the mean screen time of the Swiss children. A threshold may be postulated at which screen time and the associated PIA negatively affect microvascular health.

Early life conditions such as obesity, elevated BP, and PIA seem to influence vascular health in children and have been linked to the development of cardiovascular risk in adulthood. BMI, BP, and PA are often mutually dependent in adults and children. PA is known for its potential to improve vascular function in all age groups. The few available studies indicate that PA is independently and beneficially associated with retinal microvascular health.

In adults, retinal vessel diameters as surrogate markers have been shown to be predictive for cardiovascular morbidity and mortality. Retinal vessels resemble the cumulative effects of cardiovascular risk factors on the microvascular end organ and therefore appear to be a good surrogate marker. Treatment initiation and strategies should, however, not be based on specific threshold levels of single markers. It is of importance for future clinical practice concepts to implement retinal vessel imaging within a broader cardiovascular risk assessment as a clinically relevant factor for treatment decision and as an option for treatment monitoring. Retinal vessel imaging seems to be a promising diagnostic tool for primary prevention of CVD manifestation as early as childhood, and it can be applied in population screening on a large scale. However, future researchers will have to ensure that retinal vessel imaging during childhood development has a prognostic value for the adult clinical outcome of pediatric populations.

Despite the careful selection criteria of this review, there are limitations to the present review and meta-analysis that need to be mentioned. This is a cross-sectional–based review only. Prospective long-term studies are needed to prove the prognostic relevance of retinal vessel diameters for cardiovascular risk development in children and adolescents. Few researchers have included AVR in their analysis and, therefore, no overall judgment can be made for the association of BMI, BP, and PA with AVR in childhood. Adjustment for confounders, such as pubertal status, was not possible and needs to be addressed in future studies. Only a small number of studies was available to investigate the effect of PA on retinal vessel diameters. Few of the studies contained reports of β coefficients and could be included in the meta-analysis. Therefore, we could not use funnel plots to test for asymmetry because the test power would have been too low to distinguish chance from asymmetry. A meta-analysis for PA and PIA and physical fitness could not be conducted because of incomparable methods and measurements. Study heterogeneity may have affected the reliability of the results, although meta-regression did not identify responsible characteristics for this heterogeneity.

CONCLUSIONS

Our results demonstrate that retinal vessel diameters are a valid and sensitive microvascular biomarker for cardiovascular risk stratification in childhood. Retinal microvascular impairments can be diagnosed early in life and timely initiation of cardiovascular screening in childhood may help to substantially counteract the increasing burden of manifest CVD in adulthood. Regular retinal vessel screening may have the potential to be implemented in future medical examination programs to optimize therapy guidance in children and adolescents.

**ABBREVIATIONS**

AVR: arteriolar-to-venular diameter ratio

BP: blood pressure

CI: confidence interval

CRAE: central retinal arteriolar equivalent

CRF: cardiorespiratory fitness

CRVE: central retinal venular equivalent

CVD: cardiovascular disease

DBP: diastolic blood pressure

ES: effect size

NO: nitric oxide

PA: physical activity

PI: prediction interval

PIA: physical inactivity

SBP: systolic blood pressure

**REFERENCES**


27. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/ sclerosis in the Atherosclerosis Risk in


Obesity, Blood Pressure, and Retinal Vessels: A Meta-analysis
Sabrina Köchli, Katharina Endes, Denis Infanger, Lukas Zahner and Henner Hanssen
Pediatrics 2018;141;
DOI: 10.1542/peds.2017-4090 originally published online May 9, 2018;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/141/6/e20174090

Data Supplement at:
http://pediatrics.aappublications.org/content/suppl/2018/05/08/peds.2017-4090.DCSupplemental