ORIGINAL RESEARCH

# Impact of Ideal Cardiovascular Health in Childhood on the Retinal Microvasculature in Midadulthood: Cardiovascular Risk in Young Finns Study

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***Background*—**This study examined the association between ideal cardiovascular health (CVH) and the retinal microvasculature in midadulthood.

***Methods and Results*—**The Cardiovascular Risk in Young Finns Study included children from 5 Finnish University cities, who were chosen randomly from the national population register. Participants ranged from 12 to 18 years in childhood (1986) and from 37 to 43 years in midadulthood (2011). Ideal CVH was defined according to the American Heart Association criteria. Retinal microvascular measures included diameters, lengths, length:diameter ratio, and tortuosity. From childhood to adulthood, fasting plasma glucose and blood pressure were significantly higher in those with impaired fasting glucose or diabetes mellitus. Childhood ideal CVH was negatively associated with adult arteriolar tortuosity (β=−0.008; 95% confidence interval [CI], −0.01 to −0.003; *P*=0.001). Improved ideal CVH from childhood to adulthood was positively associated with adult arteriolar diameter (β=0.122; 95% CI, 0.01–0.24; *P*=0.033) and negatively associated with adult length:diameter ratio (β=−0.666; 95% CI, −1.25 to −0.08; *P*=0.026). When stratified by glucose metabolism, among those with diabetes mellitus and impaired fasting glucose, there was a negative association between childhood ideal CVH and adult venular diameter (diabetes mellitus: β=−2.75; 95% CI, −5.46 to −0.04; *P*=0.047; impaired fasting glucose: β=−2.13; 95% CI, −4.18 to −0.08; *P*=0.042).

***Conclusions*—**This study is the first to comprehensively examine the impact of CVH from childhood to midadulthood on quantitative measures of the retinal microvasculature. Ideal CVH in childhood and improvement in CVH from childhood to adulthood appears to have a protective effect on the retinal microvasculature in those with, without, and at risk of diabetes mellitus. **(*J Am Heart Assoc*. 2018;7:e009487. DOI: 10.1161/JAHA.118.009487)**

**Key Words:** cardiovascular health • childhood • digital retinal imaging • life course • retinal vascular imaging

Cardiovascular disease (CVD) is the most common cause of death in the general population and in people with type 2 diabetes mellitus.[1] Clinical manifestations arising from CVD usually occur late in the course of diabetes mellitus, whereas subclinical abnormalities in the micro- and macrovasculature occur early.[2] Newly emerging data highlight that the microcirculation plays an important role in both the etiology and pathology of CVD.[3] In particular, the assessment of retinal microvasculature characteristics, captured using retinal imaging techniques, are associated with early stages of subclinical CVD[4] and are predictive of clinical CVD events in both the general population and in people with type 2

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## Clinical Perspective

### What Is New?

- This study is the first to comprehensively examine the impact of cardiovascular health (CVH) from childhood to midadulthood on quantitative measures of the retinal microvasculature.
- We show that a detrimental change to CVH between childhood and midadulthood is associated with narrowing of the retinal arterioles and venular dilation in individuals with diabetes mellitus and impaired fasting glucose.
- CVH in childhood is negatively associated with adult arteriolar tortuosity, and people who improve their CVH between childhood and midadulthood have similar microvascular architecture to those who have ideal CVH status in both childhood and adulthood.

### What Are the Clinical Implications?

- We provide new evidence in support of the assessment of the retinal microvasculature for cardiovascular disease prediction.
- We provide essential insight into the predictive value of CVH assessment in early life and the impact of life-course changes in CVH profile on subsequent outcomes to the microvasculature in midadulthood.
- These findings suggest that the pursuit of ideal CVH throughout the life course is important to prevent unfavorable retinal microvasculature changes but also that children with poor CVH status are not predetermined to maintain the risk if CVH is improved later in life.

diabetes mellitus.[5–7] As such, the retinal microvasculature can be regarded as a unique noninvasive lifetime summative evaluation of the microvascular consequences of exposure to cardiovascular insults and a valuable prognostic tool in predicting future CVD risk.[5–7]

Nevertheless, our understanding of the mechanisms leading to changes in retinal microvascular architecture is limited owing to a lack of longitudinal studies from childhood to adulthood. In the treatment of type 2 diabetes mellitus, intensive glucose management has been shown to reduce the risk of microvascular complications, such as diabetic retinopathy and nephropathy.[8] However, such benefits do not seem to translate to macrovascular and cardiovascular end points.[9] Information that can help predict and stratify people at high and low risk of complications is needed. An individual's cardiovascular risk profile can be determined using a variety of metrics, such as those adopted by the American Heart Association (AHA),[10] comprising body mass index, diet status, physical activity status, smoking status, blood pressure (BP), and fasting plasma glucose. Extensive evidence has demonstrated that low-risk (ideal) cardiovascular profiles are associated with large reductions in cardiovascular morbidity and mortality.[11] In addition, low-risk cardiovascular profiles in childhood and improvement in cardiovascular health (CVH) status in adulthood result in improvement of subclinical CVD risk factors later in life,[12,13] which translates to lower CVD morbidity and mortality.[14] Cross-sectional studies illustrate that those exposed to CVD risk factors early in life concomitantly present suboptimal structural changes in the retinal microvasculature.[15] However, little is known about the long-term impact of CVD risk profile in early life on the structure and function of the retinal microvasculature in later life or about whether this is influenced by changes to CVD risk profile throughout adulthood. As such, our ability to draw causal inferences and to examine the clinical predictive value of retinal imaging remains significantly hampered.

The Cardiovascular Risk in Young Finns Study provides a unique opportunity to investigate the influence of CVD risk profiles during childhood and across the life course into midadulthood on retinal microvasculature architecture and precursors of CVD. In this study, we applied a life-course approach that considers the contribution of CVH in both childhood and adulthood to examine the association between ideal CVH and the retinal microvasculature in midadulthood.

## Methods

The Cardiovascular Risk in Young Finns Study is an ongoing multicenter longitudinal epidemiological study of CVD risk factors in a Finnish cohort from childhood to adulthood.[16] A cross-sectional survey was first performed in 1980 on 3596 children and adolescents aged 3 to 18 years residing across 5 Finnish University cities and their rural surroundings, with individuals being randomly selected from the national population register.[16] Since 1980, several follow-up observations have been conducted, the latest of which was performed in 2011, in which 2063 participants (aged 34–49 years) from the original cohort attended. For the present study, 1986 was chosen as baseline because it was the first year in which glucose values were measured. In total, 418 participants aged 12 to 18 years underwent analysis owing to complete data on CVH metrics from 1986 through 2011 and retinal parameters in 2011. Participants were stratified by glucose metabolism status as *normal* (without diabetes mellitus); *impaired fasting glucose*; or *diabetes mellitus*, as determined by fasting plasma glucose levels.

For CVH, we adopted the metrics outlined by the AHA,[10] comprising body mass index, diet status, physical activity status, smoking status, BP, and fasting plasma glucose. Childhood ideal CVH metrics were applied for all participants at baseline (1986) and subsequent time points (2001, 2007,

and 2011) and were age and sex specific.[10] Data were captured through the completion of questionnaires and biometric analysis.

Fasting glucose concentrations were analyzed enzymatically and classified in children and adults as *ideal* if <5.6 mmol/L (<100 mg/dL)[10]; impaired fasting glucose levels were defined as a fasting plasma glucose between 6.1 and 6.9 mmol/L; type 2 diabetes mellitus was defined as a fasting glucose level >6.9 mmol/L and/or HbA1c ≥48 mmol/mol (6.5%), reported use of oral glucose lowering medication or insulin (but not reported having type 1 diabetes mellitus), or being diagnosed with type 2 diabetes mellitus by a physician. Serum cholesterol was analyzed as described previously,[10] with ideal total cholesterol status defined as <4.4 mmol/L (<170 mg/dL) in children and <5.2 mmol/L (<200 mg/dL) in adulthood. BP was measured using a random-zero sphygmomanometer, with ideal BP status defined as systolic BP and diastolic BP <90th percentile in childhood and systolic BP <120 mm Hg and diastolic BP <80 mm Hg in adulthood. Body mass index (weight in kilograms divided by height in square meters)[10,11] was classified as *ideal* in childhood if <85th percentile and in adulthood as <25. Ideal diet for children and adults was defined as having 2 to 3 ideal diet components (fruits and vegetables, fish, soft drinks) in 1986, as described previously[10,17]; in the 2011, the follow-up ideal diet for children and adults was defined as having 4 to 5 of the ideal diet components of the AHA ideal dietary goals (fruits and vegetables, fish, sodium, whole grains, and sugar-sweetened beverages), as described previously.[17] Ideal smoking status was classified in childhood as never having smoked a cigarette and in adulthood as being a never or former smoker. Ideal physical activity was classified in childhood as ≥7 hours of moderate or vigorous activity per week[17] and in adulthood as ≥1 hour per week of vigorous physical activity, ≥2 to 3 hours per week of moderate physical activity, or ≥2 to 3 hours per week of a combination of moderate and vigorous physical activity.[17]

From these individual health factors, a corresponding ideal CVH score was generated. The score was created by assigning a value of 1 for each metric if the criterion for *ideal* was met. If a health factor did not meet this criterion, a value of 0 was assigned, providing a range of ideal CVH scores from 0 to 7, with a higher score indicating a better CVH profile. Low CVH was defined as ≤3 metrics and high CVH as ≥4 metrics present.[17] From this, we formed 4 groups from the current cohort: high CVH in both childhood and adulthood (high/high CVH); low CVH in childhood but high CVH in adulthood (low/high CVH); high CVH in childhood but low CVH in adulthood (high/low CVH); low CVH in both childhood and adulthood (low/low CVH).

In 2011, 45° digital retinal imaging was performed using a Canon nonmydriatic retinal camera (Canon CR6-45NM) fitted with a Canon 10D digital SLR camera (resolution: 3072×2048 pixels). Images were centered on the macula of each eye. Within the present study, 1 pixel corresponds to 5 μm, and the estimated diameter of arterioles was ≈100 μm. A range of vascular geometric parameters were captured using a semiautomated grading system including arteriolar and venular diameters, as described previously by our group[7]; length:diameter ratio (L:D ratio) of arteriolar segments (as a means of normalizing vessel diameter)[7]; and arteriolar tortuosity, as estimated as the actual length of the vessel divided by the straight-line distance between bifurcations −1.[7] Photographer accreditation was performed before the beginning of the study, with images being read at a single reader center (Imperial College London). Imaging quality control was conducted periodically throughout the study with 1 observer blinded to subject data including the performance of retinal grading and feedback. The reproducibility of this technique was excellent (intraclass correlation coefficients for within-observer measurements were >0.9), and the average absolute difference and standard deviation between measurements of arteriolar diameter was 0.0±0.4 pixels, consistent with previous reports.

The study was conducted in compliance with the Declaration of Helsinki and was approved by local ethics committees, with all participants providing full written informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Statistical Analysis

The data analysis was performed with Stata 12.0 IC (StataCorp) and presented as mean±SD with statistical significance inferred at a 2-tailed $P<0.05$; 95% confidence intervals (CIs) and β coefficients are presented where relevant. Descriptive information for each variable was derived and the distribution assessed to determine normality. One-way ANOVAs were performed to assess conditional differences between groups stratified for glucose metabolism status at each respective time point (Table 1). A life-course epidemiologic approach was used that simultaneously considered the contribution of ideal CVH in both childhood and adulthood.[18] To study the association of childhood ideal CVH score and change in the score (score in 2011 minus score in 1986) with retinal microvasculature measures in adulthood (2011), linear regression models adjusted for baseline scores, changes in the scores, age at baselines, and sex were performed (Table 2 and Figure) with further analysis stratified for glucose metabolism status (Table 3).

## Results

In total, 417 participants underwent retinal imaging and provided complete ideal CVH data. The characteristics of the

**Table 1.** Ideal CVH Scores Across the Life Course and Retinal Microvasculature Measures by Categories of Glucose Metabolism

| | Normal | IFG | DM | *P* Value |
|---|---|---|---|---|
| Participants, n | 386 | 20 | 11 | . . . |
| Characteristics (1986) | | | | |
| Age (12–18 y) | 15±3 | 16±2 | 16±2 | 0.209 |
| Ideal CVH score | 3.5±1.0 | 3.9±0.7 | 3.3±0.9 | 0.282 |
| BMI, kg/m$^2$ | 20.0±2.7 | 20.4±2.4 | 21.8±2.6 | 0.293 |
| Ideal diet, % | 25.7 | 35.0 | 18.2 | 0.544 |
| Ideal physical activity, % | 5.4 | 0.0 | 0.0 | 0.411 |
| Ideal smoking status, % | 24.1 | 20.0 | 27.3 | 0.886 |
| Systolic BP, mm Hg | 115±12 | 115±11 | 121±16 | 0.025 |
| Diastolic BP, mm Hg | 64±9 | 64±11 | 67±11 | 0.443 |
| Fasting glucose, mmol/L | 4.6±0.5 | 4.8±0.5 | 4.9±0.7 | <0.001 |
| Cholesterol, mmol/L | 4.9±1.0 | 4.8±1.0 | 4.5±1.0 | 0.691 |
| Characteristics (2001) | | | | |
| Age (27–33 y) | 30±3 | 31±2 | 31±2 | 0.209 |
| Ideal CVH score | 4.3±1.4 | 2.8±1.4 | 3.8±1.4 | 0.062 |
| BMI, kg/m$^2$ | 24.5±4.1 | 25.8±4.3 | 26.6±4.5 | 0.112 |
| Ideal diet, % | 25.8 | 29.4 | 33.3 | 0.834 |
| Ideal physical activity, % | 57.1 | 31.3 | 63.6 | 0.110 |
| Ideal smoking status, % | 71.8 | 58.8 | 45.5 | 0.091 |
| Systolic BP, mm Hg | 115±13 | 121±11 | 127±18 | 0.026 |
| Diastolic BP, mm Hg | 70±10 | 72±10 | 78±13 | 0.012 |
| Fasting glucose, mmol/L | 5.0±0.5 | 5.4±0.6 | 5.4±0.5 | 0.002 |
| Cholesterol, mmol/L | 5.1±1.0 | 5.1±0.9 | 5.2±1.3 | 0.623 |
| Characteristics (2007) | | | | |
| Age (33–39 y) | 36±3 | 37±2 | 37±2 | 0.209 |
| Ideal CVH score | 3.8±1.4 | 2.5±1.3 | 2.1±1.5 | <0.001 |
| BMI, kg/m$^2$ | 25.3±4.4 | 28.3±4.9 | 29.8±4.5 | <0.001 |
| Ideal diet, % | 6.2 | 6.7 | 0.0 | 0.792 |
| Ideal physical activity, % | 52.0 | 40.0 | 66.7 | 0.441 |
| Ideal smoking status, % | 78.5 | 86.7 | 66.7 | 0.511 |
| Systolic BP, mm Hg | 119±13 | 127±14 | 131±15 | 0.068 |
| Diastolic BP, mm Hg | 74±11 | 83±14 | 83±13 | <0.001 |
| Fasting glucose, mmol/L | 5.2±0.5 | 5.9±0.4 | 6.4±2.3 | <0.001 |
| Cholesterol, mmol/L | 5.0±1.0 | 5.1±0.9 | 5.2±1.0 | 0.905 |
| Characteristics (2011) | | | | |
| Age (37–43 y) | 40±3 | 41±2 | 41±2 | 0.209 |
| Ideal CVH score | 3.8±1.4 | 2.2±0.9 | 2.5±1.4 | <0.001 |
| BMI, kg/m$^2$ | 25.8±4.5 | 29.4±5.5 | 29.3±5.3 | 0.036 |
| Ideal diet, % | 3.7 | 10.0 | 0.0 | 0.243 |
| Ideal physical activity, % | 57.3 | 45.0 | 54.6 | 0.554 |
| Ideal smoking status, % | 83.7 | 80.0 | 54.6 | 0.039 |
| Systolic BP, mm Hg | 116±13 | 126±17 | 125±14 | 0.011 |

Continued

**Table 1.** Continued

| | Normal | IFG | DM | *P* Value |
|---|---|---|---|---|
| Diastolic BP, mm Hg | 74±10 | 82±11 | 80±13 | 0.017 |
| Fasting glucose, mmol/L | 5.2±0.5 | 6.3±0.4 | 7.1±0.4 | <0.001 |
| HbA1c, mmol/mol | 35.7±2.6 | 38.4±3.3 | 52.6±18.3 | <0.000 |
| Cholesterol, mmol/L | 5.2±0.9 | 5.7±0.9 | 5.2±1.3 | 0.466 |
| Retinal microvasculature (2011) | | | | |
| Arteriolar L:D ratio | 22.0±8.6 | 22.8±8.6 | 25.5±12.3 | 0.679 |
| Arteriolar diameter (pixels) | 17.9±1.6 | 18.3±2.3 | 17.5±2.3 | 0.005 |
| Arteriolar tortuosity | 0.04±0.001 | 0.05±0.008 | 0.05±0.011 | 0.274 |
| Venular L:D ratio | 14.9±4.0 | 15.1±4.1 | 15.1±4.9 | 0.417 |
| Venular diameter (pixels) | 20.3±2.6 | 20.3±3.0 | 21.0±2.6 | <0.001 |
| Venular tortuosity | 0.013±0.0004 | 0.013±0.0029 | 0.016±0.012 | 0.624 |

Measures observed in 2011. Data presented as mean±SD except as noted. Ideal physical activity (normal) and ideal smoking status (nonsmoker) are presented as percentage and Pearson chi-square. BMI indicates body mass index; BP, blood pressure; CVH, cardiovascular health; DM, diabetes mellitus; IFG, impaired fasting glucose; L:D, length:diameter.

participants are shown in Table 1. When categorizing by glucose metabolism status, there was a significant difference in systolic BP and fasting plasma glucose in childhood (Table 1). Differences in systolic BP and fasting plasma glucose between groups remained statistically significant from childhood throughout adulthood, coupled with ideal CVH status, from 2007 onward (Table 1).

Table 2 shows the childhood ideal CVH and change in CVH between childhood and adulthood in predicting retinal microvascular complications in adulthood. Adult arteriolar diameter was positively associated with improved ideal CVH from childhood to adulthood (β=0.122; 95% CI, 0.010–0.235; *P*=0.033), whereas no association was evident between adult arteriolar diameter and childhood ideal CVH after adjustment for age and sex. There was a negative association between improved ideal CVH from childhood to adulthood and adult arteriolar L:D ratio (β=−0.666; 95% CI, −1.254 to −0.078; *P*=0.026), with no association evident for childhood ideal CVH, after adjustment for confounding factors. Improved ideal CVH from childhood to adulthood showed no association with adult arteriolar tortuosity, but childhood ideal CVH was negatively associated with adult arteriolar tortuosity (β=−0.008; 95% CI, −0.012 to −0.003; *P*=0.001). No associations were evident between improved ideal CVH from childhood to adulthood or childhood ideal CVH with venular measures.

Table 3 shows the childhood ideal CVH and change in CVH between childhood and adulthood in predicting retinal microvascular complications in adulthood by categories of glucose metabolism. Among those with diabetes mellitus, there was a positive association between childhood ideal CVH and arteriolar length (β=158.6; 95% CI, 51.5–265.7; *P*=0.011) and L:D ratio (β=13.03; 95% CI, 4.96–21.09; *P*=0.008), respectively, with no association evident for improved ideal CVH from childhood to adulthood after adjusting for confounding factors (age and sex). In addition, in those with diabetes mellitus and IFG, there was a negative association between change in ideal CVH from childhood to adulthood in adult venular diameter (IFG: β=−2.13; 95% CI, −4.18 to −0.08; *P*=0.042; diabetes mellitus: β=−2.76; 95% CI, −5.47 to −0.04; *P*=0.047). Table S1 shows the individual ideal CVH factors in childhood and change in individual ideal CVH factors between childhood and adulthood for retinal microvascular architecture in adulthood (using standardized β coefficients).

FiguresA througD show age- and sex-adjusted mean indexes and 95% CI of retinal microvasculature health according to ideal CVH status in childhood and adulthood by arteriolar diameter, length, L:D ratio, and tortuosity, respectively. For each of the aforementioned arteriolar measures (length; diameter; L:D ratio, tortuosity), there was an indication of poorer retinal microvascular health in those with persistently low CVH status in childhood and adulthood and better retinal microvascular health in those with persistently high CVH status in childhood and adulthood (FigureD). The models were additionally rerun replacing fasting plasma glucose with HbA1c to assess the potential mediating impact of a second diagnostic criteria of glucose metabolism status on retinal microvasculature health. There were no significant changes in the association between arteriolar and venular measures with HbA1c.

## Discussion

This study is the first to comprehensively examine the impact of CVH from childhood to midadulthood on quantitative measures of the retinal microvasculature. Using a longitudinal

**Table 2.** Childhood Ideal CVH and Change in CVH Between Childhood and Adulthood in Predicting Retinal Microvascular Complications in Adulthood in the Cardiovascular Risk in Young Finns Study

| | Regression Coefficient | 95% CI | *P* Value |
|---|---|---|---|
| Arteriolar measures | | | |
| Diameter | | | |
| Childhood CVH | 0.031 | −0.157 to 0.220 | 0.747 |
| Change CVH | 0.122 | 0.010–0.235 | 0.033 |
| Length | | | |
| Childhood CVH | −9.31 | −25.41 to 6.78 | 0.256 |
| Change CVH | −8.99 | −18.60 to 0.60 | 0.066 |
| L:D ratio | | | |
| Childhood CVH | −0.577 | −1.577 to 0.409 | 0.251 |
| Change CVH | −0.666 | −1.254 to −0.078 | 0.026 |
| Tortuosity | | | |
| Childhood CVH | −0.008 | −0.012 to −0.003 | 0.001 |
| Change CVH | −0.001 | −0.001 to 0.002 | 0.551 |
| Diameter | | | |
| Childhood CVH | −0.050 | −0.36 to 0.26 | 0.751 |
| Change CVH | −0.004 | −0.19 to 0.18 | 0.970 |
| Length | | | |
| Childhood CVH | −0.44 | −8.54 to 7.67 | 0.916 |
| Change CVH | −1.74 | −6.57 to 3.09 | 0.480 |
| L:D ratio | | | |
| Childhood CVH | −0.002 | −0.48 to 0.47 | 0.994 |
| Change CVH | −0.127 | −0.41 to 0.08 | 0.377 |
| Tortuosity | | | |
| Childhood CVH | −0.0002 | −0.0013 to 0.0008 | 0.661 |
| Change CVH | 0.0002 | −0.0005 to 0.0008 | 0.596 |

Data adjusted for sex and age (1986). Regression coefficients for a 1-U increase in childhood ideal CVH score and ideal CVH change. CI indicates confidence interval; CVH, cardiovascular health; L:D, length:diameter.

life-course approach, we showed that childhood CVH and deterioration in CVH (from childhood to midadulthood) were associated with adverse changes in retinal microvascular architecture in midadulthood. Moreover, we showed that improvement in ideal CVH from childhood to adulthood was associated with a protective effect on the retinal microvasculature.

In the present study, we showed that a detrimental change to CVH status between childhood and mid-adulthood was associated with narrowing of the retinal arterioles. Retinal arteriolar narrowing is associated with chronically elevated BP[19] and is one of the earliest retinal markers of hypertension.[20] This finding is supported consistently in epidemiological studies and meta-analyses that link narrower arteriolar diameter and hypertension.[19,21] Indeed, our group and others have previously demonstrated that chronically elevated BP from childhood has a profound effect on the retinal microvasculature in midadulthood.[22,23] The association of worsening CVH status from childhood to midadulthood with increased L:D ratio supports the findings shown for arteriolar diameters; L:D ratio is used to normalize vessel diameter such that it is relatively independent of refraction-induced magnification effects. In addition, retinal arteriolar narrowing has been reported to be associated with an increased risk of diabetes mellitus in middle-aged people without diabetes mellitus.[24] Our data regarding adult retinal microvasculature characteristics are comparable to recently published normative data.[25] In our study, however, groups were stratified based on fasting plasma glucose to assess microvascular alterations in line with conventional risk factors.[26] Notably, differences in fasting glucose were evident between groups in childhood (1986).

Body mass index as a component of ideal CVH status was higher in those with diabetes mellitus and IFG from childhood throughout adulthood. Those with diabetes mellitus and IFG showed a negative association between changes in ideal CVH from childhood to adulthood in adult venular diameter. Venular dilation is commonly identified in obesity and in individuals presenting with abnormal glucose metabolism including diabetes mellitus[27] and is associated with increased risk of stroke mortality in type 2 diabetes mellitus.[28] Whereas the exact mechanisms providing linkage between obesity and diabetes mellitus and venular dilation remain to be fully established, both obesity and diabetes mellitus represent a state of chronic inflammation, oxidative stress, and vascular dysfunction[29] that influences immunological, metabolic, and cardiovascular function and that are associated with venular dilation of the retina. Consequently, it is plausible that disturbances to retinal venular endothelial function could contribute to the association between change in ideal CVH from childhood to adulthood and adult venular diameter in those with diabetes mellitus and IFG.[30]

Our second key finding, that childhood ideal CVH is negatively associated with adult arteriolar tortuosity, may be clinically significant. Patients presenting with ischemic stroke are known to have a sparser and more tortuous retinal microvascular network,[31] and the Child Heart and Health Study in England[32] has shown an association between arteriolar tortuosity and CVD risk factors (increased triglyceride, total cholesterol, and low-density lipoprotein [LDL] cholesterol, systolic and diastolic BP) among children.[32] The finding that arteriolar tortuosity in midadulthood is associated with ideal CVH in childhood suggests that childhood CVH status may be important in determining how tortuous the retinal vessels are in adulthood. Indeed, the notion that CVD

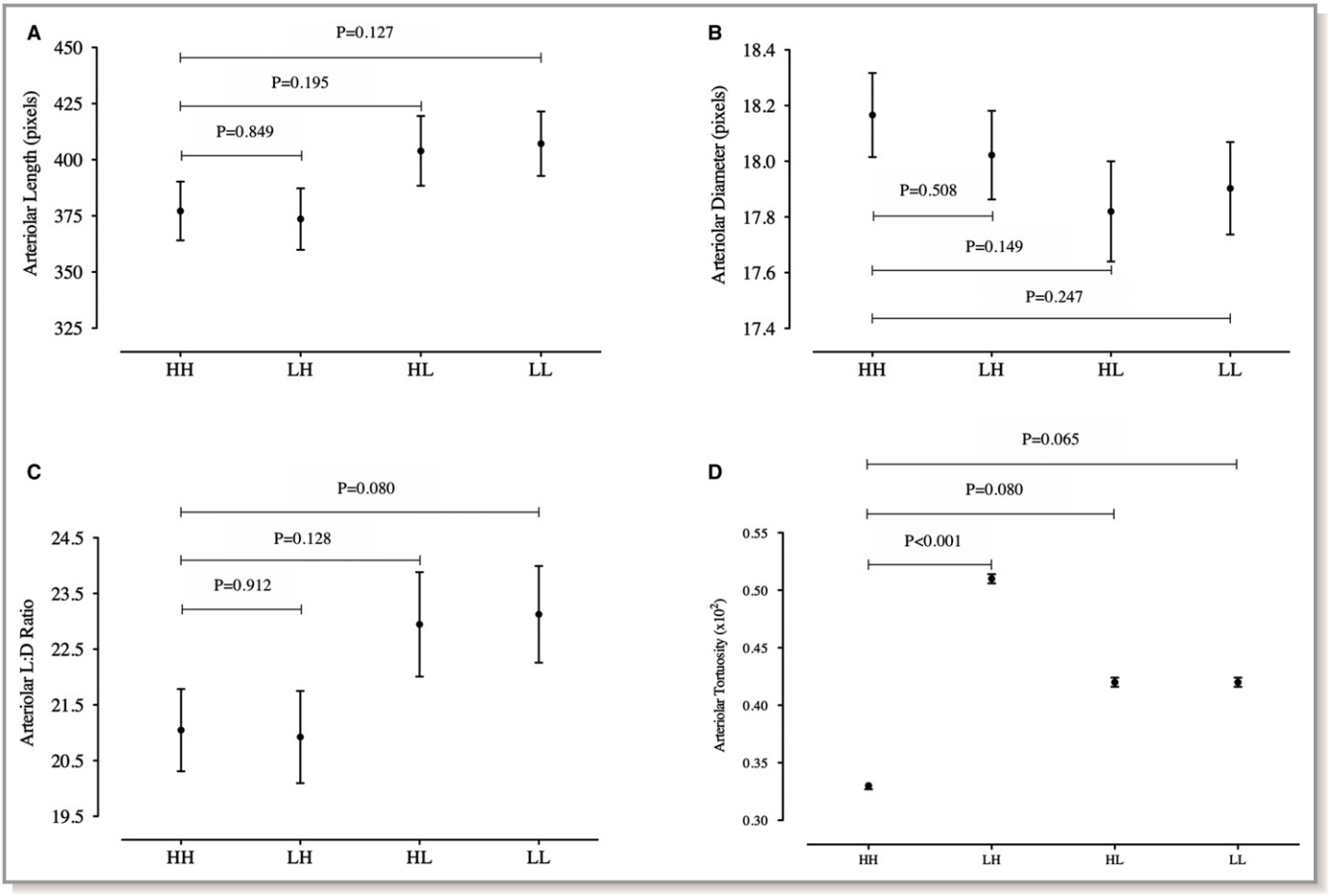


**Figure.** Age- and sex-adjusted mean (SE) indexes of retinal microvasculature health according to ideal cardiovascular health status in childhood and adulthood in the Cardiovascular Risk in Young Finns Study. A, Arterial length. B, Arterial diameter. C, length:diameter (L:D) ratio. D, Arterial tortuosity symmetry. HH indicates high ideal cardiovascular health (CVH) score (≥4 metrics) in both childhood and adulthood (n=117); HL, high ideal CVH score in childhood but low ideal CVH score in adulthood (n=85); LH, low ideal CVH score (≤3 metrics) in childhood but high ideal CVH score in adulthood (n=106); LL, low ideal CVH score in both childhood and adulthood (n=96).

risk has primordial origins and that arterial architecture abnormalities are present before adulthood[33–35] is supported by substantial evidence; it is also known that arterial tortuosity persists following removal of the initiating stimulus.[36] The present study provides further evidence for this and, as such, carries important implications for CVD prevention. Whereas quantitative retinal vascular measures, such as retinal vascular diameter, have been associated with CVD in the general population in several large epidemiological studies,[27,37] these associations have not been extensively studied in people with diabetes mellitus.

The retinal microvasculature assessments made in the current study quantify the geometric branching network. Such retinal vasculature measures reflect the optimal state of blood distribution in the microvasculature.[6,38] The microvasculature, which has a specific role in regulating BP and offering nutrient delivery, is sensitive to hyperglycemia-induced damage. There is a linear relationship between glycosylated hemoglobin levels and the development of microvascular complications[39] such that the criteria (eg, fasting glucose levels) used to define the presence of diabetes mellitus are largely derived from the occurrence of microvascular complications. Hyperglycemia is associated with glycation end products, inflammation, and oxidative stress, which in retina, has been shown to induce abnormalities in the structure and function of the microvasculature. Diabetes mellitus is known to be associated with increased shear stress and microvascular endothelial dysfunction through hyperglycemic-related pathways.[40] In addition to such pathways, other mechanisms such as dyslipidemia and inflammation enhance the development of microvascular disease.[41] Because microvasculature alterations may result in a reduced ability of insulin to mediate glucose uptake in skeletal muscles, microvascular disease has been hypothesized to contribute to the development of diabetes mellitus.[24]

To date, the strength of associations between retinal vascular changes and disease prediction has been relatively modest. Although classical CVD risk factors (elevated serum cholesterol level and BP) are used clinically to assess a

**Table 3.** Childhood Ideal CVH and Change in CVH Between Childhood and Adulthood in Predicting Retinal Microvascular Complications in Adulthood in the Cardiovascular Risk in Young Finns Study by Categories of Glucose Metabolism.

| | Normal | | | IFG | | | DM | | |
|---|---|---|---|---|---|---|---|---|---|
| | Regression Coefficient | 95% CI | *P* Value | Regression Coefficient | 95% CI | *P* Value | Regression Coefficient | 95% CI | *P* Value |
| Arteriolar measures | | | | | | | | | |
| Diameter | | | | | | | | | |
| Childhood CVH | 0.05 | −0.14 to 0.23 | 0.629 | −1.44 | −4.34 to 1.46 | 0.306 | −1.08 | −3.58 to 1.42 | 0.332 |
| Change CVH | 0.14 | 0.02–0.25 | 0.020 | 0.57 | −0.90 to 2.07 | 0.411 | −0.31 | −2.03 to 1.41 | 0.677 |
| Length | | | | | | | | | |
| Childhood CVH | −10.7 | −27.3 to 5.9 | 0.206 | 50.5 | −124.9 to 226.0 | 0.549 | 158.6 | 51.5–265.7 | 0.011 |
| Change CVH | −9.6 | −19.9 to 0.6 | 0.066 | 31.7 | −58.1 to 121.6 | 0.463 | −26.6 | −100.4 to 47.2 | 0.412 |
| L:D ratio | | | | | | | | | |
| Childhood CVH | −0.68 | −1.68 to 0.32 | 0.182 | 4.51 | −7.02 to 16.05 | 0.418 | 13.03 | 4.96–21.10 | 0.008 |
| Change CVH | −0.71 | −1.33 to −0.09 | 0.025 | 1.08 | −4.82 to 6.99 | 0.702 | −1.08 | −6.64 to 4.49 | 0.652 |
| Tortuosity | | | | | | | | | |
| Childhood CVH | −0.01 | −0.01 to −0.00 | 0.001 | 0.01 | −0.06 to 0.07 | 0.859 | −0.01 | −0.08 to 0.05 | 0.623 |
| Change CVH | −0.00 | −0.00 to 0.00 | 0.867 | 0.00 | −0.03 to 0.04 | 0.907 | 0.02 | −0.03 to 0.06 | 0.395 |
| Venular measures | | | | | | | | | |
| Diameter | | | | | | | | | |
| Childhood CVH | −0.03 | −0.34 to −0.28 | 0.836 | −3.21 | −7.20 to 0.89 | 0.108 | 1.25 | −2.29 to 5.19 | 0.465 |
| Change CVH | 0.33 | −0.16 to 0.23 | 0.735 | −2.13 | −4.18 to −0.08 | 0.042 | −2.76 | −5.47 to −0.04 | 0.047 |
| Length | | | | | | | | | |
| Childhood CVH | −0.37 | −8.7 to 8.0 | 0.931 | −30.0 | −94.0 to 36.0 | 0.357 | 31.6 | −83.4 to 76.5 | 0.527 |
| Change CVH | −1.8 | −1.8 to 2.6 | 0.496 | −12.6 | −45.9 to 20.6 | 0.430 | −2.8 | −82.0 to 76.5 | 0.935 |
| L:D ratio | | | | | | | | | |
| Childhood CVH | −0.03 | −0.51 to 0.46 | 0.918 | 0.99 | −4.44 to 6.41 | 0.703 | 1.53 | −4.63 to 7.69 | 0.566 |
| Change CVH | −0.15 | −0.45 to 0.14 | 0.310 | 0.82 | −1.95 to 3.60 | 0.538 | 1.70 | −2.54 to 5.50 | 0.364 |
| Tortuosity | | | | | | | | | |
| Childhood CVH | −0.00 | −0.00 to 0.00 | 0.867 | 0.00 | −0.01 to 0.01 | 0.674 | −0.00 | −0.02 to 0.01 | 0.583 |
| Change CVH | 0.00 | −0.00 to 0.00 | 0.449 | 0.00 | −0.00 to 0.01 | 0.375 | 0.00 | −0.01 to 0.01 | 0.922 |

Data adjusted for sex and age (1986). Regression coefficients for a 1-U increase in childhood ideal CVH score and ideal CVH change. CI indicates confidence interval; CVH, cardiovascular health; DM, diabetes mellitus; IFG, impaired fasting glucose; L:D, length:diameter.



person's risk of CVD, these risk factors do not fully explain the higher risk of CVD events in those with diabetes mellitus. Moreover, our study shows that people who improve their CVH status by some means between childhood and midadulthood have microvascular architecture (arteriolar length, diameter, and L:D ratio; Figure) similar to those who have ideal CVH status in both childhood and adulthood. It is known that disordered structure of the retinal microvasculature is associated with hypertension,[22] diabetes mellitus,[30] and retinopathy.[28] Both narrowing of retinal arteriolar vessels and widening of venules have been demonstrated to predict subsequent ischemic heart disease and stroke.[7,8] Arteriolar narrowing in particular predicts development of hypertension,[27] and studies suggest that venular dilatation, possibly due to localized ischemia, may predict the presence or risk of impaired glucose tolerance and diabetes mellitus.[6] As such, these findings suggest that the pursuit of ideal CVH throughout the life course is important to prevent unfavorable retinal microvasculature changes but also that those children with poor CVH status are not predetermined to maintain the risk if CVH is improved later in life.

The strengths of this study include its prospective design and large sample size, the ascertainment of quantitative retinal microvasculature status, complete data for ideal CVH status from childhood to midadulthood, and the population-representative nature of the cohort at the time of initial

recruitment in 1980. Over time, the study population lost participants to follow-up, which may affect estimates; however, it is important to consider that the current study assessed associations between risk factors and retinal microvasculature outcomes, and it is unlikely that they will have altered because of loss at follow-up unless associations differed in those lost to follow-up. The study had a limited number of participants with IFG and diabetes mellitus; further follow-up in a cohort with a larger number of participants with IFG and diabetes mellitus is warranted.

In conclusion, we provided new evidence in support of the assessment of the retinal microvasculature for CVD prediction and essential insight into the predictive value of CVH assessment in early life and the impact of life-course changes in CVH profile on subsequent outcomes to the microvasculature in midadulthood.

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## Author Contributions

Campbell developed the research question, researched data and wrote the article. Laitinen contributed to the results and discussion and reviewed/edited the article. Hughes reviewed/edited the article. Pahkala reviewed/edited the article. Juonala reviewed/edited the article. Kähönen reviewed/edited the article. Wong contributed to the discussion and reviewed/edited the article. Lehtimäki reviewed/edited the article. Hutri-Kähönen reviewed/edited the article. Raitakari contributed to the results and discussion and reviewed/edited the article. Tapp developed the research question, researched data and wrote the article.

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## Disclosures

None.

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**SUPPLEMENTAL MATERIAL**

**Table S1.** Childhood Ideal Cardiovascular Health factors and Change in Cardiovascular Health between Childhood and Adulthood in predicting Retinal Microvascular Complications in Adulthood in the YSF.

| | | Regression coefficient | P Value |
|---|---|---|---|
| **Arteriolar Diameter** | | | |
| Fasting glucose (mmol/l) | *Childhood CVH* | 0.01 | 0.786 |
| | *Change CVH* | -0.03 | 0.560 |
| Cholesterol | *Childhood CVH* | -0.08 | 0.171 |
| | *Change CVH* | 0.04 | 0.564 |
| **Blood pressure (mm/Hg)** | ***Childhood CVH*** | **0.22** | **<0.001** |
| | ***Change CVH*** | **0.29** | **<0.001** |
| Ideal Diet | *Childhood CVH* | -0.13 | 0.291 |
| | *Change CVH* | -0.12 | 0.333 |
| Ideal Smoking Status | *Childhood CVH* | -0.06 | 0.380 |
| | *Change CVH* | -0.10 | 0.172 |
| Ideal Physical Activity | *Childhood CVH* | 0.00 | 0.941 |
| | *Change CVH* | -0.02 | 0.697 |
| **Arteriolar L-D Ratio** | | | |
| Fasting glucose (mmol/l) | *Childhood CVH* | -0.05 | 0.354 |
| | *Change CVH* | 0.03 | 0.624 |
| Cholesterol | *Childhood CVH* | -0.06 | 0.321 |
| | *Change CVH* | -0.07 | 0.248 |
| **Blood pressure (mm/Hg)** | ***Childhood CVH*** | **-0.21** | **=0.001** |
| | ***Change CVH*** | **-0.21** | **=0.001** |
| Ideal Diet | *Childhood CVH* | 0.08 | 0.523 |
| | *Change CVH* | 0.05 | 0.686 |
| Ideal Smoking Status | *Childhood CVH* | 0.12 | 0.106 |
| | *Change CVH* | 0.09 | 0.261 |
| Ideal Physical Activity | *Childhood CVH* | -0.03 | 0.612 |
| | *Change CVH* | -0.03 | 0.618 |
| **Arteriolar Tortuosity Symmetry** | | | |
| Fasting glucose (mmol/l) | *Childhood CVH* | **0.01** | 0.843 |
| | *Change CVH* | **-0.08** | 0.132 |
| Cholesterol | *Childhood CVH* | -0.09 | 0.137 |
| | *Change CVH* | 0.07 | 0.274 |
| **Blood pressure (mm/Hg)** | ***Childhood CVH*** | **-0.22** | **<0.001** |
| | ***Change CVH*** | **0.12** | **0.046** |
| Ideal Diet | *Childhood CVH* | -0.12 | 0.347 |
| | *Change CVH* | -0.06 | 0.650 |
| **Ideal Smoking Status** | *Childhood CVH* | -0.15 | 0.037 |
| | ***Change CVH*** | **-0.18** | **0.019** |
| **Ideal Physical Activity** | ***Childhood CVH*** | **-0.02** | **0.760** |
| | ***Change CVH*** | **0.14** | **0.013** |
| **Venular Length** | | | |
| Fasting glucose (mmol/l) | *Childhood CVH* | 0.05 | 0.298 |
| | ***Change CVH*** | **0.11** | **0.039** |
| Cholesterol | *Childhood CVH* | -0.04 | 0.544 |
| | *Change CVH* | -0.04 | 0.501 |
| Blood pressure (mm/Hg) | *Childhood CVH* | -0.08 | 0.188 |
| | *Change CVH* | -0.04 | 0.503 |
| Ideal Diet | *Childhood CVH* | 0.04 | 0.737 |
| | *Change CVH* | -0.03 | 0.834 |
| Ideal Smoking Status | *Childhood CVH* | -0.05 | 0.512 |
| | *Change CVH* | -0.02 | 0.823 |
| Ideal Physical Activity | *Childhood CVH* | -0.02 | 0.727 |
| | *Change CVH* | 0.03 | 0.603 |

Data adjusted for sex and age (1986). β = Beta standardized coefficient. Regression coefficients for a 1 unit increase in childhood ideal CVH score and ideal CVH change. L:D ratio = length / diameter ratio