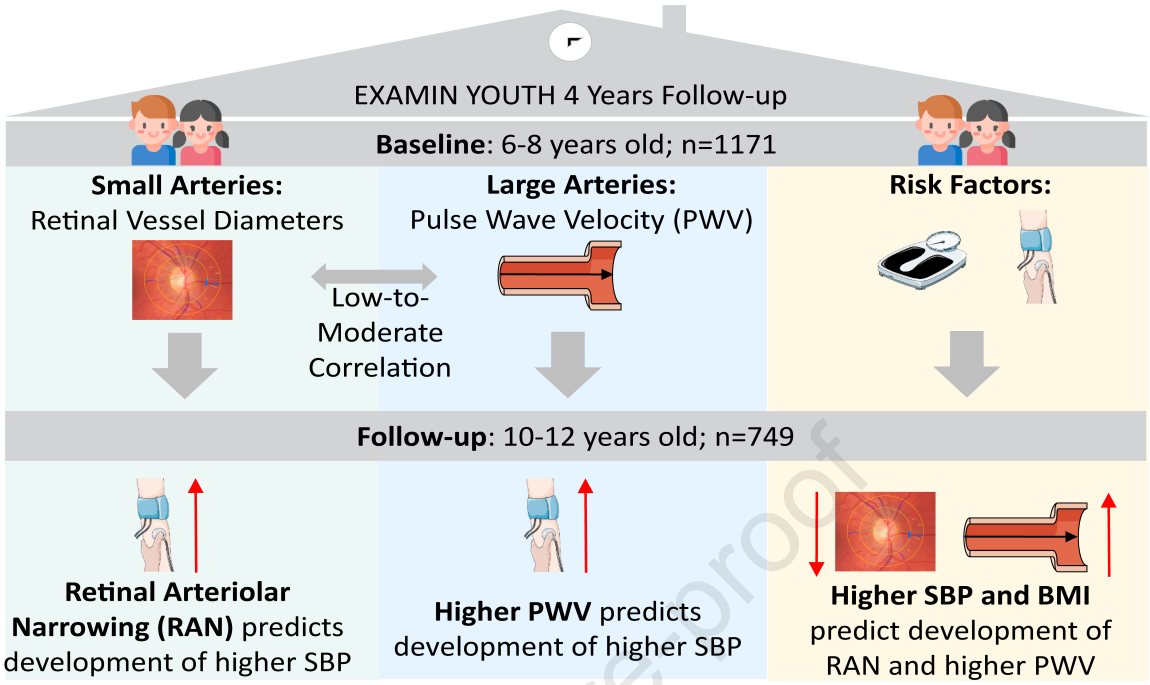

Bivariate relation of vascular health and blood pressure progression during childhood

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Abstract

Background and aims: Hypertension is a major risk factor for the development of cardiovascular disease (CVD) in adulthood. High blood pressure (BP) is associated with subclinical vascular impairments as early as childhood. We aimed to assess the association of retinal microvascular diameters and large artery pulse wave velocity (PWV) with progression of childhood BP.

Methods: In our prospective Basel cohort study, 1171 children aged 6 to 8 years were screened for BP, body mass index, retinal vessel diameters and PWV using standardized protocols. After 4 years, all parameters were assessed in 749 children using the same protocols.

Results: Children with narrower central retinal arteriolar diameters (CRAE) and higher PWV at baseline developed higher systolic BP after 4 years (β [95% CI] 0.6 [0.072 to 1.164] mmHg per 10µm decrease, p=0.026 and β [95% CI] 0.6 [0.331 to 0.838] mmHg per 0.1 m/s increase, p<0.001, respectively). Children with increased systolic BP at baseline developed narrower CRAE and higher PWV at follow-up (β [95% CI] -3.3 [-4.43 to -2.09] µm per 10 mmHg increase, p<0.001 and β [95% CI] 0.13 [0.10 to 0.16] m/s per 10 mmHg increase, p<0.001, respectively).

Conclusions: Retinal arteriolar diameter and PWV independently predict progression of childhood BP, while initial BP is linked with development of micro- and macrovascular impairments, describing a bivariate temporal relationship between vascular health and BP. Childhood may present a window of opportunity for initiation of primary prevention strategies for the treatment of high BP to help prevent manifestation of CVD later in life.

Keywords: retinal vessel diameters, pulse wave velocity, blood pressure, childhood cardiovascular risk, primary prevention

1. Introduction

Hypertension and obesity are main risk factors for the development of cardiovascular disease (CVD) and cardiovascular (CV) mortality across the lifespan.[1] Classical and lifestyle-related risk factors are linked with pre-atherosclerosis and endothelial dysfunction in children, which may lead to CV events later in life.[2, 3] An increased incidence of elevated blood pressure (BP) among children and adolescents has been shown in epidemiological surveys.[4] Childhood hypertension has been shown to track into adulthood.[5] Furthermore, childhood CV risk factors have been related to adult CV events.[6] Systolic BP in late adolescence, for example, has been shown to be an independent predictor of coronary heart disease and stroke in middle adulthood.[7, 8]

Non-invasive assessment of vascular structure and function allows to quantify hypertension- and obesity-related target organ damage in the circulation. Retinal vessel diameters, both arteriolar narrowing and venular widening, have been shown to be valid microvascular biomarkers for CV risk and disease across all age groups.[9] In addition, central pulse wave velocity (PWV) is a non-invasive assessment to quantify macrovascular health and CVD in adulthood.[10, 11] In children, we have previously shown that higher BP and BMI are associated with subclinical vascular changes at the level of the micro- and macrocirculation.[12,13] The previously published baseline results of our study demonstrated that children with high BP and obesity had narrower central retinal arteriolar equivalents (CRAE) and a higher PWV compared to normal weight peers.[14]

In this large scale longitudinal follow-up study, we aimed to assess the association of retinal vessel diameters and PWV at baseline with progression of BP after 4 years for the first time. In turn, to explore the temporal relationship, we also aimed to investigate the association of higher BP and BMI at baseline with development of retinal arteriolar narrowing and increased PWV at follow-up.

2. Patients and methods

2.1 Study design and participants

The baseline data of our study "Exercise and Arterial Modulation in Youth" (EXAMIN YOUTH) were collected in all elementary schools in the City of Basel (Switzerland) in 2016/17 as previously described.[15] Children were between 6 and 8 years old and had written parental consent for medical screening. In the school setting children were assessed for BP, BMI, retinal vessel diameters and pulse wave velocity Follow-up examinations were conducted 4 years later (2020/21) in the same setting and under the same conditions. The study was approved by the Ethics Committee of Northwestern and Central Switzerland (EKNZ, No. 258/12). The reporting of the study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement and complies with the Guidelines for Good Clinical Practice.[16]

2.2 Measurements

2.2.1 Retinal vessel diameters and pulse wave velocity

A fundus camera (Topcon TRC NW) and analysis software (Visualis 3.0, iMEDOS Health GmbH, Jena, Germany) were used for retinal vessel analysis. Two valid images of both eyes, with the optic nerve head at center, were acquired by trained scientific staff at an angle of 45°. Subsequently, retinal arteriolar (CRAE) and venular (CRVE) diameters were evaluated semi-automatically in a range of 0.5 to 1-disc diameter from the edge of the optic nerve head by two experienced examiners (Vesselmap 2, Visualis, iMEDOS Health GmbH) as previously described.[14, 17] Incorporating the Parr-Hubbard formula, CRAE and CRVE were averaged, and the arteriolar-to-venular diameter ratio (AVR) was calculated using CRAE and CRVE.[18] For retinal analysis, initial values from the baseline assessment were used as reference and the same vessels and same vessel segments were marked to ensure optimal standardization.

The oscillometric Mobil-O-Graph monitor (I.E.M. GmbH, Germany) was used to determine central PWV as previously described.[14] Measurement of arterial stiffness by the oscillometer is in good agreement with the conventional tonometric method and has been validated in children (Supplements, Detailed Methods) .[19, 20]

2.2.2 Blood pressure and body mass

Blood pressure assessments were performed in a sitting position after 5 min. of rest. Five measurements were taken by trained scientific stuff with a rest period of one minute in between using the automated oscillometric device Oscilomate 9002 (Oscillomate; CAS Medical Systems, Branford, CT) or Mindray VS-900 (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) as previously described.[14] In brief, the mean of the three measurements with the smallest variation was used for further analysis. Both algorithms to quantify BP have previously been validated in children[21-23] and do not statistically significant differ (Supplements, Detailed Methods).[24, 25]

Body height was measured without shoes and in a standing position using a stadiometer (Seca, Basel, Switzerland). The bioelectric impedance analyzer (InBody 170 Biospace device, InBody Co, Soul, Korea) was used to determine weight in light sportswear and without shoes (Supplements, Detailed Methods).[14, 26]

2.3 Statistical analysis

To describe population characteristics, means and SD were calculated for baseline and follow-up data and compared by a simple t-test of dependent samples. To assess potential selection bias, a simple t-test for independent samples between follow-up and lost to follow-up was performed. Furthermore, to determine changes in population characteristics we have used a

simple t-test to analyze differences from baseline to follow-up. Spearman's correlation was run to quantify the association between CRAE and PWV. To account for missing data of height, weight, SES, CRF and BMI, we imputed 50 datasets using chained equations with predictive mean matching (MICE).[27] To investigate the association between retinal vessel diameters and PWV with BP and BMI, linear mixed regression models were applied, using schools and classes nested within schools as random effects.[28, 29] Distribution of variables were inspected a priori using histograms and assumptions for regression models were checked graphically using residual plots.[30] We have used directed acyclic graphs (DAGs) to identify confounders and reduce risk of bias for each calculation (Supplementary Fig. 1).[31] Based on the DAG, we adjusted the models for age, sex, systolic or diastolic BP, BMI, cardiorespiratory fitness (CRF) and socioeconomic status (SES). The regression analyses are presented with β coefficients and the corresponding 95% confidence intervals (CI). Marginal predicted means were used for graphic representation. Based on data from our previous pilot study, we estimated a > 95% power to detect a regression coefficient of -0.166 for baseline CRAE and systolic BP at follow-up in 250 participants.[32] All tests were 2-sided, and the significance level was set at 0.05. All calculations were performed with Stata 15 (StataCorp, College Station, TX, United States).

3. Results

3.1 Population characteristics

At baseline, 1171 children were assessed at baseline and, of these, 749 children had complete data at follow-up (Figure 1). The follow-up group did not differ with respect to height, weight, arteriolar-to-venular ratio (AVR), CRAE, CRVE, PWV, BP, and BMI from the lost-to-follow-up group (36%). Table 1 shows the population characteristics in absolute values and SD for baseline, follow-up and mean differences over time. At baseline, the prevalence for elevated systolic BP and children with systolic BP in the hypertensive range was 10.5% and 14.8%,

146 respectively.[25] Furthermore, 9.1% of the children at baseline were categorized as having
147 elevated diastolic BP and 15% as having diastolic BP in the hypertensive range. The prevalence
148 of children with overweight and obesity at baseline was 9.4% and 2.8% respectively.[26] Four
149 years later, the prevalence for elevated systolic BP and children with systolic BP in the
150 hypertensive range was 5.8% and 10.1% and of children with elevated diastolic BP and in the
151 hypertensive range was 4.8% and 7.5% respectively.[25] At follow-up, the prevalence of children
152 with overweight and obesity was 11.4% and 3.1%, respectively.[26] Changes in categories over
153 time are presented in Supplementary Table2. During 4 years, children developed a significantly
154 higher BMI (Δ2.5±2.1kg/m^2), systolic BP (Δ5±9.4mmHg) and PWV (Δ0.3±0.3m/s).
155 Furthermore, children at follow-up developed significantly narrower CRAE (Δ-7.2±8.0µm),
156 CRVE (Δ-1.4±8.8µm) and a lower AVR (Δ-0.02±0.04) compared to baseline (Table 1).
157 Children and their families were notified in case of a conspicuity and referred to their
158 pediatrician but not treated within the study setting.

159

160 **3.2 Vascular health and development of blood pressure**

161 The association between micro- and macrovascular heath at baseline and development of BP
162 over four years are presented in Table 2. Children with narrower CRAE at baseline developed
163 significantly higher systolic BP (β [95% CI] 0.6 [0.072 to 1.164] mmHg per 10µm decrease,
164 p=0.026) and diastolic BP (β [95% CI] 0.9 [0.044 to 1.370] mmHg per 10µm decrease,
165 p=<0.001) at follow-up. The corresponding plot with the marginal predicted means of systolic
166 BP at follow-up, based on CRAE at baseline, is shown in Figure 2A. Children with wider CRVE
167 at baseline developed significantly lower diastolic BP over the four-year follow-up period (β
168 [95% CI] -0.5 [-0.879 to -0.311] mmHg per 10µm increase, p=0.035). In addition, children with
169 higher PWV at baseline developed significantly higher systolic BP (β [95% CI] 0.6 [0.331 to
170 0.838] mmHg per 0.1 m/s increase, p<0.001) and diastolic BP (β [95% CI] 0.3 [0.083 to 0.498]

mmHg per 0.1 m/s increase, p=0.006) at follow-up independent of baseline BP levels. The corresponding plot with the marginal predicted means of systolic BP at follow-up based on PWV at baseline is shown in Figure 2B.

3.3 Blood pressure, body mass and development of vascular health

The association between BP at baseline with vascular changes at follow-up are described in Table 3. We found an independent association of higher systolic BP at baseline with CRAE (β [95% CI] -3.3 [-4.43 to -2.09] µm per 10 mmHg increase, p<0.001) and CRVE narrowing (β [95% CI] -1.7 [-3.04 to -0.32] µm per 10 mmHg increase, p=0.015) after 4 years. The corresponding plot with marginal predicted means of CRAE at follow-up based on systolic BP at baseline is shown in Figure 2C. Higher systolic BP was also associated with a higher PWV (β [95% CI] 0.13 [0.10 to 0.16] m/s per 10 mmHg increase, p<0.001) at follow-up (Figure 2F). For diastolic BP at baseline, we found evidence for a linear negative association with CRAE (β [95% CI] -3.3 [-4.55 to -1.95] µm per 10 mmHg increase, p<0.001) and PWV (β [95% CI] 0.12 [0.09 to 0.15] m/s per 10 mmHg increase, p<0.001) at follow-up.

The association between BMI at baseline with vascular changes at follow-up are also described in Table 3. Higher BMI at baseline was associated with narrower CRAE (β [95% CI] -0.6 [-1.089 to -0.0584] µm per 1 kg/m^2 increase, p=0.029) and a higher PWV (β [95% CI] 0.023 [0.011 to 0.0035] m/s per 1 kg/m^2 increase, p<0.001) at follow-up.

3.4 Changes in risk factors and changes in vascular health

The associations between changes from baseline to follow-up in BP and BMI and corresponding changes in vascular health are presented in Supplementary Table1. Children with a relative increase in systolic BP developed narrower CRAE (β [95% CI] -1.5 [-2.15 to -0.74]

μm per 10 mmHg increase, p<0.001) and higher PWV (β [95% CI] 0.06 [0.03 to 0.09] m/s per 10 mmHg increase, p<0.001). A relative increase in diastolic BP was significantly associated with higher PWV (β [95% CI] 0.05 [0.02 to 0.08] m/s per 10 mmHg increase, p=0.002). Children with a relative increase in BMI over the four years developed significantly narrower CRAE (β [95% CI] -0.9 [-1.500 to -0.362] μm per 1 kg/m^2 increase, p=0.001) and a higher PWV (β [95% CI] 0.026 [0.001 to 0.051] m/s per 1 mmHg increase, p=0.039). Supplementary Table3 and S4 present an overview of the temporal changes in BP and BMI categories, along with the average alterations observed in the corresponding vascular parameter.

3.5 Interrelation of vascular biomarkers

The association between CRAE at baseline and PWV at follow-up, and vice versa, are presented in Figure 2D and E. Children with narrower CRAE at baseline developed significantly higher PWV (β [95% CI] 0.03 [0.008 to 0.04] m/s per 10μm decrease, p=0.005) at follow-up (Figure 2D). On the other hand, children with higher PWV at baseline developed significantly narrower CRAE (β [95% CI] -0.4 [-0.79 to -0.04] μm per 0.1m/s increase, p=0.031) at follow-up (Figure 2E). Furthermore, we found a weak to moderate inverse correlation between CRAE and PWV at both time points (r_s= -0.224, p<0.001 and r_s=-0.206, p<0.001, respectively).

4. Discussion

As main findings, narrower CRAE and a higher PWV at baseline were associated with higher systolic and diastolic BP at follow-up. In turn, higher systolic and diastolic BP at baseline were related to retinal arteriolar narrowing and higher PWV at follow-up. Furthermore, children with a relative increase in systolic BP during follow-up developed narrower CRAE and a higher PWV. In addition, a relative increase in BMI was also associated with retinal arteriolar

narrowing and a higher PWV. The inverse correlation between microvascular CRAE and large artery PWV was low to moderate, and the development of both vascular markers after 4 years was interdependent.

The results of our analysis imply that retinal arteriolar diameters and PWV are associated with BP progression in young children. Applying thorough adjustment models, our results were found to be independent of BMI, systolic/diastolic BP, CRF, age, sex and SES. Retinal microvascular diameters and large artery PWV represent different segments of the vascular tree. On the one hand retinal microvascular imaging allows for a unique, non-invasive assessment of the human microcirculation and resistance vessels.[9] Central PWV, on the other hand, provides a valid estimation of large artery wall integrity and macrovascular health.[33] A cross-talk between small and large arteries has previously been described.[34] The vascular beds, however, markedly differ as the microcirculation, for example, is characterized by steady pressure, whereas the macrocirculation is exposed to pulsatile pressure.[35] In two meta-analyses of cross-sectional studies, we have previously shown that higher childhood BP and BMI were associated with retinal arteriolar narrowing[12] and a higher PWV[13]. These findings were confirmed in the baseline assessment of our current EXAMIN YOUTH follow-up study.[14] More evidence is available in adults including associations with CVD outcome. In older adults, narrower arteriolar and wider venular diameters have been associated with severity of hypertension[36], increased risk of stroke[37, 38], and increased CV mortality.[39] Furthermore, increased large artery stiffness has been shown to be an independent predictor for the risk of stroke as well as CV morbidity and mortality in the general population and in patients with CVD.[10, 40-42] Our findings from this large-scale longitudinal study demonstrate that both retinal arteriolar narrowing as well as large artery stiffness can independently predict development of BP during childhood development. Both diagnostic tools, as a standalone approach or in conjunction, may be used to improve CV risk stratification in young children to identify those

at risk of developing high BP. Whether retinal arteriolar narrowing and higher PWV in childhood are predictive for adverse CV outcome in adulthood is unknown and needs to be addressed by future long-term studies across the age-span.

While vascular health was associated with BP progression, we also found that, in turn, higher systolic and diastolic BP as well as higher BMI at baseline were associated with retinal arteriolar narrowing and higher PWV after 4 years. This is clinically relevant as childhood BP and BMI have not only been shown to track into adulthood[5,43], but have also been related to adverse CV outcome later in life.[7, 8, 44, 45] Thus, BP- and BMI-related subclinical arteriolar narrowing and increased PWV appear to represent early stages of CV risk progression and may be related to further deterioration of vascular health and CVD manifestation in adulthood. The Young Finns Study found that higher childhood BP was associated with impaired retinal arteriolar diameters in mid-adulthood.[46] In the Bogalusa Heart Study, childhood BP was a predictor of arterial stiffness in early adulthood.[47] In our study we investigated the long-term interrelation between BP, BMI and micro- as well as macrovascular health in pre-pubertal children for the first time.

Investigating the relationship of changes in risk factors with changes in vascular health may allow to hypothesize about potential reversibility of childhood subclinical vascular damage. In our study, a relative increase in systolic BP and BMI over the 4-year period was associated with retinal arteriolar narrowing and higher PWV. In other words, children with an improvement of systolic/diastolic BP and BMI presented with more favorable vascular health at follow-up. Our results are in line with a previous finding, showing that a change from elevated BP to normal BP in the transition from childhood to adulthood was related to a lower PWV in young adults.[48] Childhood appears to be a sensitive period in life to initiate treatment of hypertension and obesity by lifestyle interventions such as physical activity and diet to potentially reverse or at least reduce subclinical vascular alterations and prevent manifestation of CVD.

A possible mechanism that may explain the association between baseline arteriolar diameters and the increase in BP over four years is increased peripheral vascular resistance. Systemic microvascular vasoconstriction may, for example, be caused by sympathetic overdrive or endothelial dysfunction. Endothelial dysfunction is characterized by a reduced nitric oxide (NO) bioavailability and impairments of shear-stress-induced dilation, leading to an increased peripheral resistance and an increase in peripheral BP.[49, 50] Moreover, structural remodeling, fragmentation of elastic lamellae and deposition of augmented collagen fibers in particular, lead to a stiffening of large arteries.[51, 52] Increased BP and intraluminal pressure induce an auto-regulated myogenic vasoconstriction (Bayliss effect), which may partly explain retinal arteriolar narrowing in children with high initial BP. The aforementioned structural remodeling of large arteries is aggravated by prolonged cyclic stress induced by sustained elevated BP, leading to a further increase in PWV. Furthermore, inflammation and increased BMI are already associated with wider CRVE in childhood and adolescence.[53] Widening of CRVE may contribute to pooling of blood in the microcirculation, resulting in reduced venous return to the heart. Consequently, this may alter ventricular filling and preload, leading to a decrease in diastolic blood pressure. Further research is needed to fully understand the precise mechanism underlying the association between CRVE and diastolic BP, as the mechanism involved remain speculative.

Our study has some limitations. We did not perform a second BP measurement on a separate day or perform a 24h-BP-measurement for the clinical diagnosis of elevated BP or hypertension. Thus, our data indicate BP values in the elevated or hypertensive range rather than defined clinical BP categories. The assessment of pulse wave velocity was performed with an oscillometric device rather than a tonometric carotid-femoral measurement for reason of practicability when screening children in school setting. Furthermore, our study was performed in a predominantly Caucasian population and, therefore, our results cannot be transferred to

other ethnicity. Few children may have entered puberty at follow-up, which was not assessed as part of the screening. Furthermore, we were not able to collect blood samples to identify circulating cardiovascular risk factors, nor environmental factors such as air pollution or passive smoking, which could also have influenced our results. Our follow-up investigations were overshadowed by the Corona pandemic. The related restrictions with a temporary lock-down of schools and the built environment affected physical activity behavior and general well-being and may thus have influenced our results. However, the prevalence of SARS-CoV-2 infections in Swiss school children was very low, even at times of high incidence in the general public, with low spread of unrecognized virus.[54] It is therefore unlikely that SARS-CoV-2 infection had a direct influence on the data collected. To account for missing data of height, weight, SES, CRF and BMI, we imputed 50 datasets using chained equations with predictive mean matching. As a sensitivity analysis, we also conducted a complete-case analysis (results not shown). The results of the complete-case analyses did not markedly differ from the primary analyses using multiple imputation. The strengths of our study are the longitudinal design, the large number of participants and application of standardized methods both at baseline and follow-up. We have used DAGs to identify confounders and reduce risk of bias for each model.[31] The models were refined and adjusted for cofounders such as CRF and SES.

4.1 Conclusions

In our study, a two-way relationship has been shown whereby baseline vascular health determines development of BP, and initial BP determines development of vascular health during childhood. These findings are best described as a bidirectional or bivariate temporal relationship demonstrating an interdependency between vascular health and BP. Microvascular arteriolar narrowing and large artery stiffness show a low to moderate inverse correlation also characterized by an interdependency (Figure 3). Both diagnostic tools, separately or in conjunction, may be used to improve CV risk stratification and to monitor young children at

risk of developing high BP. Childhood appears to be a window of opportunity for CV risk screening and timely initiation of primary prevention strategies such as physical activity and diet interventions. As childhood CV risk tracks into adulthood, aiming at CV risk reduction in childhood may prove to be an effective means to prevent manifestation of CV disease later in life.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Christoph Hauser coordinated data collection, collected data, carried out the initial image analyses as well as statistical analyses, drafted the initial manuscript and critically reviewed and revised the manuscript.

Dr. Giulia Lona and Dr. Sabrina Köchli collected data, carried out the initial image analyses and revised the manuscript.

Dr. Lukas Streese critically reviewed and revised the manuscript.

Dr. Denis Infanger supported the statistical analyses and critically reviewed and revised the manuscript.

Prof. Oliver Faude helped designed the data collection instruments and critically reviewed and revised the manuscript for important intellectual content.

Prof. Dr. med. Henner Hanssen conceptualized and designed the study, designed the data collection instruments, supervised data collection and critically reviewed and revised the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

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Figure Legend

Figure 1 Flow-chart.

Figure 2. Marginal predicted means.
(A) Marginal predicted means of systolic blood pressure at follow-up based on arteriolar vessel diameters at baseline. (B) Marginal predicted means of systolic blood pressure at follow-up based on pulse wave velocity at baseline. (C) Marginal predicted means of arteriolar vessel diameters at follow-up based on systolic blood pressure at baseline. (D) Marginal predicted means of pulse wave velocity at follow-up based on CRAE at baseline. (E) Marginal predicted means of CRAE at follow-up based on pulse wave velocity at baseline. (F) Marginal predicted means of pulse wave velocity at follow-up based on systolic blood pressure at baseline.

Figure 3 Graphical abstract.

Supplemental Material

Detailed Methods
Supplementary Fig. 1 Directed acyclic graph for the association between baseline CRAE and systolic BP at follow-up
Supplementary Table1 Changes in Risk Factors and Changes in Vascular Health
Supplementary Table2 Changes in BP and BMI Categories over the Investigation Period
Supplementary Table3 Changes in BP Categories and Mean Change in Vascular Health
Supplementary Table4 Changes in BMI Categories and Mean Changes in Vascular Health