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Within-visit Systolic Blood Pressure Variability from Childhood to Adulthood and Markers of Cardiovascular End-organ Damage in Mid-life

Short title: Life-time within-visit SBP variability

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Abstract:

Background: Within-visit systolic blood pressure variability is associated with age and systolic blood pressure, but its long-term clinical significance is unknown. We examined the association between child, adult and life-time within-visit systolic blood pressure variability with markers of end-organ damage using data from a 31-year longitudinal study.

Methods: Within-visit systolic blood pressure variability was calculated as the standard deviation of three sitting systolic blood pressure readings among up to 3010 participants aged 6-18 years (childhood) who were re-measured up to 7 times to mid-adulthood. Markers of cardiovascular end-organ damage in adulthood were carotid intima-media thickness, brachial flow mediated dilatation, carotid distensibility, pulse wave velocity, left ventricular mass index, carotid plaque and coronary artery calcification.

Results: The mean (standard deviation) cumulative within-visit systolic blood pressure variability was 2.7 (1.5) mmHg in childhood, 3.9 (1.9) mmHg in adulthood and 3.7 (1.5) mmHg across the observed life-time. Childhood within-visit systolic blood pressure variability was not correlated with its subsequent values measured from 3- to 31-years later. With adjustment for age, sex, cumulative systolic blood pressure, body mass index and serum lipids, neither child, adult or life-time cumulative within-visit systolic blood pressure variability associated with markers of cardiovascular end-organ damage. However, higher child, adult, and life-time cumulative systolic blood pressure significantly associated with higher carotid intima-media thickness, higher pulse wave velocity, lower brachial flow mediated dilatation, lower carotid distensibility in adulthood.

Conclusion: Within-visit systolic blood pressure variability from childhood to adulthood does not provide additional predictive utility over systolic blood pressure over the same period of the life-course.

Keywords: blood pressure**;** cohort; life-course epidemiology; risk factors; end-organ damage; pediatric.

Condensed Abstract:

In a 31-year longitudinal study, the clinical significance of within-visit systolic blood pressure variability was determined from childhood to mid-adulthood among up to 3010 participants. Associations between child, adult and life-time within-visit systolic blood pressure variability with markers of end-organ damage were examined. Within-visit systolic blood pressure variability from childhood to adulthood did not provide additional predictive utility over systolic blood pressure over the same period of the life-course.

Introduction

Blood pressure (BP) measured at a single time-point in childhood and adolescence persists (or tracks) into adulthood[1,2] and associates with markers of adulthood cardiovascular end-organ damage[3]. In addition, long-term BP burden, expressed as cumulative BP from young adulthood to middle age, tends to have increased predictive utility for incident cardiovascular events in middle age over a single measurement obtained across the adult life-course[4]. BP variability might provide additional clinical utility over usual clinic BP[5] by exerting further adverse effects on the development, progression and severity of cardiovascular clinical events and end-organ damage[6-8]. Short- (24 hour)[9] and mid-[10] to long-term (days to years)[11,12] BP variability has been shown to be independent predictors of cardiovascular events among generally healthy adults and high-risk populations.

In contrast, limited and inconsistent evidence exists on the prognostic utility of within-visit BP variability (WVV), which is the transient BP fluctuation during a single office visit. Although WVV is associated with age, BP[13,14], and worse cardiovascular risk profiles, including higher lipids, glucose and resistant hypertension among participants with hypertension[15], WVV was not associated with all-cause and cardiovascular mortality among adults in the Third National Health and Nutrition Examination Survey (NHANES III)[16]. Moreover, no study has determined the potential clinical utility of WVV in an apparently healthy population from childhood to mid-adulthood. Therefore, this study examined the association between child, adult and life-time WVV with markers of cardiovascular end-organ damage using population-based data from a 31-year prospective cohort study.

Methods

Participants

Participants were from the Cardiovascular Risk in Young Finns Study (YFS)[17], a multicentre prospective cohort designed to assess the risk factors of cardiovascular disease from childhood to adulthood among a representative population of Finnish people[18]. In 1980, the first cross sectional study was conducted that included 3596 participants aged 3, 6, 9, 12, 15, and 18 years. Thereafter, seven follow-up surveys were conducted in 1983, 1986, 1989, 1992, 2001, 2007, and 2011. At each time-point, participants who attended the survey had three resting measures of peripheral BP collected, while markers of cardiovascular end-organ damage were collected at the adult follow-up surveys conducted in 2001, 2007, and 2011. The present analyses were restricted to participants aged 6 to 18 years old at baseline in 1980 who had systolic BP measured in childhood and adulthood and who had a marker of cardiovascular end-organ damage collected in adulthood. Measures from participants aged 3 years at baseline in 1980 were not included because BP was measured by an ultrasound device. The sample size available for our analyses differed depending on the outcome examined but was up to 2644 participants. Written informed consent was provided by all participants or their guardians and the study had local ethics committee approval.

Clinical characteristics and cardiovascular risk factors

At all surveys, height and weight were measured and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Weight status was determined by BMI. Participants aged ≤18 years were classified as underweight if BMI was <5th age- and sex-specific percentile, normal if was ≥5th and <85th percentile, overweight if was ≥85th and <95th percentile, obesity if was ≥95th percentile.[19] Weight status in participants aged >18 years were classified as

underweight if BMI was <18.5 kg/m^2, normal if was ≥18.5 kg/m^2 and <25 kg/m^2, overweight if was ≥25 kg/m^2 and <30 kg/m^2, obesity if was ≥30 kg/m^2[20].Venous blood samples were taken after 12 hours of fasting with standard methods applied to measure serum total cholesterol (TC) and triglyceride (TG) concentrations[21]. High density lipoprotein cholesterol (HDL-C) was measured after dextran sulfate and magnesium chloride precipitation[22]. Low density lipoprotein cholesterol (LDL-C) was calculated indirectly using the Friedewald formula[23].

BP measurement and definitions of WVV

Systolic and diastolic BP were measured with a standard mercury gravity sphygmomanometer in 1980 and 1983, and with a random-zero sphygmomanometer (Hawksley & Sons, Lancin, UK) from the 1986 to 2011 surveys. Three BP measurements at 2-3 min intervals were taken on the right arm between 8 and 10 am of participants after 5 minutes rest in the sitting position. The proper cuff size was selected according to the circumference and length of the upper arm. There were two different cuffs (9.5*28 cm and 13*40 cm) for children, with the most appropriate cuff covering at least 2/3 of the upper arm surface. In adults, there were three cuffs: 12 cm wide (for arm diameter 26-32 cm), 14 or 15 cm wide (for arm diameter 33-41 cm) and 18 cm wide (for arm diameter >41 cm). Systolic and diastolic BP were measured as the first and fifth Korotkoff sounds respectively[24]. Readings to the nearest even number of millimetres of mercury were conducted for each measurement, then the average value of these three readings was regarded as mean clinic systolic and diastolic BP. Classification of BP status in participants aged <18 years was determined by the 2016 European Society of Hypertension (ESH) guidelines in children and adolescents[25]. For participants aged ≥18 years , classification of BP status was determined by the 2018 European Society of Cardiology (ESC)/ESH guidelines in adults[26]. BP status in participants aged <18

years were classified as normal if systolic and diastolic BP (fifth phase) were <90th percentile for age, sex, and height, elevated if systolic or diastolic BP were ≥90th and <95th percentile and hypertension if systolic or diastolic BP were ≥95th percentile. BP status in participants aged ≥18 years were classified as normal if systolic BP <130 mmHg and diastolic BP <85 mmHg, elevated if BP ≥130 -139/ 85 - 89 mmHg and hypertension if BP ≥140/90 mmHg or self-reporting the use of antihypertensive medications. In these analyses of prevalence of BP status, BP measurement in each visit was derived from the mean of the last two BP readings.

This study focused on WVV of systolic BP because systolic BP is the most important component of BP and the main determinant of cardiovascular events irrespective of age[27,28]. WVV was calculated for each participant using the three consecutive BP readings collected at each survey visit. WVV was calculated using six indices that have been used previously in the literature: standard deviation (SD), coefficient of variation (CV), average real variability (ARV), the within-visit systolic BP discrepancy (MSBP), the difference between the first and second readings (D12), and the difference between the second and third readings (D23). SD was calculated as the standard deviation of the three successive systolic BP readings in a single survey. CV was calculated as the SD divided by the mean of the three systolic BP measures. ARV=$\frac{1}{N-1}\sum_{k=1}^{N-1}|BP_{k+1}-BP_k|$, where N denotes the number of valid BP measurements, and k denotes the sequence of measurements[29]. MSBP represented the maximum absolute difference between any two readings of three measurements in a single visit[30]. D12 was calculated as second minus first systolic BP reading. D23 was calculated as the third minus the second systolic BP reading. As there is no universal agreement on how WVV is best calculated, we present the main results for the SD of

systolic BP in this manuscript but note that our results did not differ when other WVV indices were used.

Exposure variables: defining cumulative WVV and systolic BP

Cumulative values for WVV and systolic BP were calculated as the summed average measurements for each pair of consecutive examinations multiplied by the time between the two consecutive visits in years[31,32], then divided by the total time interval. For example, a participant who had three WVV measurements during a certain time period, cumulative WVV = [(WVV1+WVV2) * (time1-2) /2 +(WVV2+WVV3) *(time2-3) /2]/ (time1-3). Where WVV1, WVV2, and WVV3 indicates WVV measured at survey 1, 2, and 3, respectively and time1-2, time2-3, and time1-3 indicate the time interval between survey years. We generated child (≤18 years old), adult (aged 21 to 49) and life-time cumulative values (requiring participants to have both child and adult measurements).

Outcome variables: markers of cardiovascular end-organ damage

Markers of cardiovascular end-organ damage were carotid intima media thickness (cIMT), flow mediated dilatation (FMD), carotid distensibility (cD), pulse wave velocity (PWV), left ventricular mass index (LVMI), carotid plaque, and coronary artery calcification. Where measurements were available for an individual at multiple adult time-points, the most recent measurement was used.

The left common carotid artery was scanned on up to 2265 participants in 2001 (mean age 31.7 years; age range 24-39) and 2197 participants in 2007 (mean age 37.7 years; age range 30-45) using B‐mode ultrasound (Sequoia 512; Acuson) equipped with 13.0 MHz linear array transducer with concomitant electrocardiogram monitoring according to standardized protocols. Carotid ultrasound studies were performed on the left carotid artery, including the common carotid artery and carotid bifurcation. At least four measurements were recorded manually using ultrasonic callipers at end-diastole

238 approximately 10 mm proximal to the carotid bifurcation, with the mean value from
239 these four measurements used as cIMT[33]. Carotid plaque was defined as the presence
240 of a distinct area of the carotid wall including either the common carotid artery or the
241 carotid bifurcation that protruded more than 50% into the lumen than the adjacent
242 intima-media layer.[34] cD was calculated as ([systolic diameter – diastolic
243 diameter]/diastolic diameter)/(systolic BP – diastolic BP).[35] The common carotid
244 artery diameter was measured in end-diastole and end-systole at least twice with the
245 mean of the measurements used in the cD equation. End-systole was determined from
246 the end of the T wave and end-diastole from the peak of R wave, each derived from an
247 electrocardiogram. Brachial artery scans were performed for 2109 participants in 2001
248 (mean age 31.7 years; age range 24-39) and 2182 participants in 2007 (mean age 37.7
249 years; age range 30-45) using B‐mode ultrasound at rest and during reactive
250 hyperaemia. Increased flow was induced by the inflation of a BP cuff on the forearm to
251 250 mmHg for 4.5 minutes, followed by a release. Brachial artery diameter
252 measurements at baseline and during reactive hyperaemia (at 40, 60 and 80 seconds
253 after cuff release) were measured at end-diastole at a fixed distance from an anatomic
254 marker.[36] Brachial FMD was determined as: $100 \times (\text{peak diameter}_{40/60/80} - \text{resting}$
255 diameter)/resting diameter (%). All measures were performed offline by a single
256 measurer blinded to participant details but not blinded to the phase of the recording (i.e.
257 at rest and 40, 60, and 80 seconds after cuff release). Reliability of the method for this
258 study has been reported as follows: the 2-hour between-study CV was 9% for FMD
259 measurements and; the 3-month between-visit CV was 3.2% for brachial artery diameter
260 measurements and 26.0% for FMD measurements.[37]

Estimated PWV was collected on up to 1872 participants in 2007 by means of a whole-body impedance cardiography apparatus (CircMon B202, JR Medical Ltd., Tallinn, Estonia), as previously detailed.[38]

Echocardiography examinations were conducted in the 2011 follow-up survey on 1910 participants (mean age 41.8years; age range 34-49) using Acuson Sequoia 512 (Acuson, Mountain View, CA, USA) ultrasonography with a 3.5 MHz scanning frequency phased-array transducer. Trained sonographers recorded images from parasternal long and short axis in 2D and M mode and apical four chamber.[39] Left ventricular mass (LVM) was calculated as: 0.8× [1.04((Left ventricular end-diastolic diameter + posterior wall thickness + interventricular septum thickness)^3– left ventricular end - diastolic diameter)^3] + 0.6 g. LVMI was calculated as LVM divided by height to the power of 2.7[40].

Coronary arteries calcification was performed in a subset of participants at three centres (Turku, Kuopio, Tampere) among the three oldest birth cohorts using a GE Discovery 64-slice CT/positron emission tomography device (GE Healthcare), a Siemens Somatom Sensation 16-slice CT device (Siemens Healthcare), and a Philips Brilliance 64-slice CT device (Philips Medical Systems). According to the Agatston method, absence of calcification was defined as an Agatston score of 0 and presence of coronary artery calcification was defined as an Agatston score of 1 or greater [41].

Statistical methods

Participants characteristics at baseline and follow-up visits

Participant characteristics at each time-point are presented as percentages for categorical variables and as mean (SD) for normal distributed continuous variables, and as median and interquartile range (IQR) for skewed data. The WVV at each time-point estimated using each of the six variability indices are presented as mean (SD) for normally

distributed indices, and as median and interquartile range (IQR) for indices with a skewed distribution.

Tracking of WVV from childhood to adulthood

The persistence, or tracking, of WVV levels from baseline to each subsequent follow-up were performed using Spearman's rank-order correlation coefficients. WVV in each year was transformed into an age- and sex-specific Z-score [Z-score= (original values-sample mean values)/sample standard deviation].

The effects of age and sex on WVV

To examine associations of repeated longitudinal WVV with age and sex across time, we used individual growth curve (IGC) modelling [42], which is a type of multilevel mixed effects model able to deal with repeated measurements and different numbers of individual observations at unequal time intervals. Full details are provided in the online supplement. Briefly, we added linear and higher power items of age into the models sequentially to identify the best shape of WVV changes across the observed life-time, here referred as WVV trajectories. To avoid collinearity of age with its higher-order terms, we centred age to the mean age of 22.43 years. The models were selected by Akaike's information criterion (AIC) or Bayesian information criterion (BIC) and likelihood ratio test. Then we added interaction terms of sex and all power terms of age into the best fitted models to test if sex modified the average WVV level of the participants' WVV trajectories over time. The detailed steps are provided in the supplement materials.

The associations between cumulative WVV and systolic BP with markers of cardiovascular end-organ damage

The associations between child, adult and life-time cumulative WVV with markers of cardiovascular end-organ damage measured in adulthood were evaluated by

multivariable linear regression for continuous outcomes and log binomial regression[43] for dichotomous outcomes. We selected potential cofounders according to previous experience and existing literature, and all models included cumulative (child, adult, or life-time depending on the model) systolic BP and WVV. We fitted three models: Model 1 adjusted for age and sex; Model 2 included Model 1 covariates plus cumulative BMI. Model 3 included Model 2 covariates plus cumulative LDL-C, HDL-C and TG. All variables were standardized into Z-scores. Cumulative Z-scores were calculated for some covariates (systolic BP, BMI, LDL-C, HDL-C, TG) as: (individual cumulative value-sample mean cumulative value)/sample standard deviation cumulative value. For example, childhood cumulative BMI Z -score = (individual childhood cumulative BMI – sample mean of childhood cumulative BMI) / standard deviation of sample childhood cumulative BMI. We computed variance inflation factor to assess collinearity among variables in fully adjusted regression models (Model 3). We used scatter plots between predicted values and regression standardized residuals to exclude heteroscedasticity of the distribution. To evaluate if age, sex or clinic systolic BP modified the association between WVV and our markers of cardiovascular end-organ damage, we included WVV*age, WVV*sex and WVV*cumulative systolic BP interaction terms separately into Model 3. We found no evidence for interaction, thus the final models do not stratify by age, sex, or systolic BP.

Sensitivity analyses

Given the possible effects of antihypertensive medication on WVV[44], we repeated the analyses using the outcomes of markers for cardiovascular end-organ damage after removing participants treated with antihypertensive medication. Also, considering there is no universal agreement on the quantification of WVV and different indices may have different results, we repeated all analyses replacing our main exposure with WVV

336 measured as ARV, MSBP, D12, and D23. Because cIMT, cD, FMD and carotid plaque
337 were measured at multiple adult time points, with the most recent being used, there was
338 the possibility of different lengths to follow-up in our sample. Therefore, we fit
339 additional models for these outcomes that adjusted for length to follow-up in the
340 regression model based on model 3. Finally, given that alcohol intake, physical activity,
341 smoking, glucose may affect WVV, we repeated the analyses based on model 3, and
342 additionally adjusted for cumulative alcohol intake, cumulative physical activity,
343 cumulative glucose and cumulative smoking pack years.
344 Exact P-values are reported for the main analyses with statistical significance considere
345 d as a two-tailed P-value <0.05. “Lme4” package of R studio (version 3.5.2) was used
346 for performing IGC, Stata 15.0 (StataCorp, College Station, USA) was used for other
347 analyses.
348

Results

Participants characteristics at baseline and follow-up visits

Characteristics of study participants and the levels of WVV indices at baseline and each follow-up time point according to survey year are presented in Table 1. The WVV values at each visit time point according to the BP status are shown in Supplementary Figure 1. WVV was highest amongst those in the "hypertension" group and lowest in the "normal" BP group across all visits. The mean (SD) length of follow-up was 22.98 (11.09) years and the mean (SD) number of WVV measures was 4.39 (1.76). With respect to the development of diabetes during follow up. Participants were categorized as having prediabetes or type 2 diabetes if fasting glucose levels were ≥5.6 mmol. The prevalence of prediabetes or type 2 diabetes was 11.4% (261/2283) in 2001, 22.2% (489/2204) in 2007 and 24.8% (508/2046) in 2011.

Tracking of WVV from childhood to adulthood

Spearman's correlations of WVV from 1980 to 2011 are presented in Table 2. All tracking coefficients were low (rho <0.2), irrespective of baseline age, sex, and the length of follow-up (3- to 31-years). Overall, correlations ranged from -0.10 to 0.12 for males and -0.12 to 0.16 for females. Similar results were obtained for other indices of WVV (CV, ARV, MSBP, D12 and D23, data not shown).

The effects of age and sex on WVV

Figure 1 shows estimated average age-related WVV across the observed life course by sex. The best non-linear model included a quartic term for age and with the random intercept only (age: β 0.06 mmHg, 95%CI 0.05, 0.07; age^2: -2.59×10^{-3}, -3.34×10^{-3}, -1.84×10^{-3}; age^3: -2.42×10^{-5}, -6.51×10^{-5}, 1.67×10^{-5}; age^4: 2.39×10^{-6}, 3.62×10^{-7}, 4.41×10^{-6}). On average, the WVV tended to slightly increase before age 30 years, then plateau thereafter to age 49 years. We observed no difference between males and females (age×

sex: β 0.01, 95%CI -6.04×10^{-3}, 0.03; age^2×sex: β -1.39×10^{-4}, 95%CI 1.10×10^{-3}, 8.23×10^{-4}; age^3×sex: β -4.59×10^{-5}, 95%CI -1.24×10^{-4}, 3.17×10^{-5}; age^4×sex: β 2.13×10^{-6}, 95%CI -1.27×10^{-6}, 5.53×10^{-6}).

Associations between child, adult and life-time cumulative WVV and systolic BP with markers of cardiovascular end-organ damage

Associations between child, adult, and life-time cumulative WVV and corresponding cumulative systolic BP with markers of cardiovascular end-organ damage are shown in Table 3 (continuous outcomes) and Table 4 (dichotomous outcomes). Cumulative WVV during any life period (child, adult, life-time) did not show statistically significant associations with any markers of cardiovascular end-organ damage. Compared with cumulative systolic BP, associations for cumulative WVV (regression coefficients in Table 3, relative risks in Table 4) at all three life-stages (child, adult, life-time) were weak and inconsistent in their direction of effect. In contrast to the findings for WVV, consistent associations between cumulative systolic BP and outcomes were observed. Cumulative systolic BP in childhood was positively associated with cIMT (β=9.93 um, 95%CI 5.42, 14.44) and PWV (β=0.21 m/s, 95%CI 0.13, 0.29), and negatively associated with cD (β=-0.05 %/10 mmHg, 95%CI -0.09, -0.02). Cumulative systolic BP in adulthood was positively associated with cIMT (β=10.30 um, 95%CI 6.43, 14.17), PWV (β=0.46 m/s, 95%CI 0.39, 0.52) and LVMI (β=0.58 g/m$^{2.7}$, 95%CI 0.27, 0.89), and was negatively associated with FMD (β=-0.27 %, 95%CI -0.46, -0.07) and cD (β=-0.14 %/10 mmHg, 95%CI -0.17, -0.11). Life-time cumulative systolic BP was positively associated with cIMT (β=7.90 um, 95%CI 3.57, 12.23) and PWV (β=0.43 m/s, 95%CI 0.36, 0.50), and was negatively associated with FMD (β=-0.34 %, 95%CI -0.56, -0.12) and cD (β=-0.009 %/10 mmHg, 95%CI -0.13, -0.06).Similar results to those shown in Tables 3 and 4 were obtained using other indices of WVV and after excluding

399 participants using antihypertensive medication (data not shown). Furthermore, similar
400 results to associations between WVV with cIMT, FMD, cD and carotid plaque were
401 obtained after additionally adjusting for length to follow-up based on model 3 (data not
402 shown). Meanwhile, similar results were observed after adjusting for cumulative
403 alcohol intake, cumulative physical activity, cumulative glucose and cumulative
404 smoking pack years additionally, based on model3.

Discussion

Unlike other major cardiovascular risk factors, such as mean BP and lipids [45], we found limited evidence for the tracking or persistence of WVV with time; age and sex were not the major determinants of WVV throughout the observed life-course; and exposure to cumulative WVV in childhood, adulthood, and across the observed life-course did not associate with several markers of cardiovascular end-organ damage. These findings provide novel information that the predictive utility of WVV for future cardiovascular risk (at least as it relates to our sample and outcomes) is highly limited.

To our knowledge, this is the first study to examine the tracking of WVV from childhood to mid-life and encompasses an extensive follow-up time (i.e. up to 31-year). The findings regarding the weak tracking of WVV were consistent with previous literature from two other tracking studies with shorter follow-up times (ranging from 1 to 4 years) and much smaller sample sizes (n=355 and n=123)[46,47]. Among 355 children aged 8 to 18 years who were followed over four consecutive years, Rosner et al[46] found that WVV in year 1 was not significantly associated with measurements in years 2, 3, or 4, with the maximum Spearman's correlation of 0.062. Similarly, no significant association was found between WVV measured at year 1 and 2 among 123 adults aged 30 to 69 years at baseline[47].Compared with mean systolic BP, the tracking coefficients of WVV we observed were substantially weaker. The Childhood Determinants of Adult Health Study showed 20-year tracking of mean systolic BP in 798 Australian participants with baseline ages of 9, 12, and 15 years with Spearman correlation coefficients of 0.21-0.43[1]. 27-year tracking of mean systolic BP from childhood to adulthood in the YFS were consistent with those from Australia, with Spearman correlation coefficients of 0.23-0.39[45]. The weak and inconsistent associations we observed for WVV tracking mean that the measure is less stable and

that WVV measures in early life are a poor indicator of future levels of WVV. Cumulative BP is a well-recognized independent risk factor for the development of cardiovascular-related outcomes. Using data from 2479 participants in the CARDIA Study, Kishi et al showed that 25-year cumulative systolic BP from age 18-30 years to age 43-55 years was associated with reduced cardiac function[48]. Our data for cumulative adulthood systolic BP is consistent with these data from CARDIA but extends knowledge to other markers of cardiovascular end-organ damage over a critical period of the life-course (childhood and adolescence).

The study is also the first to be performed in a large apparently healthy cohort, whilst other reports have only examined WVV in people with high(er) risk for cardiovascular disease, and most of these were cross-sectional design. One previous study found that WVV (calculated as ARV) did not provide additional predictive utility over mean systolic BP in terms of correlation with future cIMT. Although the findings were similar, that study was only in adults aged >18 years and had a median 2.6 year follow up [49] as opposed to our study design. In contrast, Grassi et al. [15] showed that those with WVV in the highest quartile, defined using either SD or CV of systolic BP, was cross-sectionally associated with worse cardiovascular risk profiles (higher cholesterol, blood glucose, resistant hypertension) among 6425 hypertensive patients aged 30-75 years. However, this study was limited by the inclusion of only hypertensive individuals and the authors did not include adjustment for mean systolic BP or other factors that might confound the reported associations between WVV and outcomes.

Our study is the first to investigate the effects of age and sex on WVV from childhood to adulthood. The best non-linear model included a quartic term for age with the random intercept only, suggesting that there were inter-individual differences, on average, in WVV levels. WVV increased slightly to age 30 years and was stable

thereafter, but there were no sex differences, which suggests that the inter individual differences may be more due to noise than to systematic differences in WVV patterns of change. This information implies that WVV measurements were more affected by other random factors other than age and sex. In contrast, other common cardiovascular risk factors, such as systolic BP, are expected to have significant relationships with age and sex (e.g. systolic BP increases with age and is higher among men). The lack of association between WVV with age and sex provides further confirmation that WVV may lack clinical relevance, as we saw for the markers of end-organ damage examined in this study.

In the context of repeated cuff measures performed in a single clinic visit, our observational data suggest limited clinical utility of knowing WVV in a young, apparently healthy population. Our measure of WVV can be affected by a variety of factors, such as cuff size and position, posture and the state of relaxation of the subject[16], as well as environmental[50], neural and humoral factors[51]; all variables that could explain why our WVV measures did not track and were not associated with markers of cardiovascular end-organ damage. Therefore, we are unable to discount that other measures of short-term variability, such as beat-to-beat BP variability[52], would have better utility in predicting target organ damage. Furthermore, the range of WVV in our study, the median (interquartile range, IQR) life-course WVV is 3.5 (2.6 to 4.4) mmHg, is comparable to what has been seen in older adult populations. For example, Muntner et al.[16] showed that WVV, expressed as SD of systolic BP, was 3.1 mm Hg (2.1 to 5.0 mm Hg) [median (IQR)] in the Third National Health and Nutrition Examination Survey study. The authors found no association between all-cause and cardiovascular mortality with WVV after adjustment for mean systolic BP, age, sex, race, and other cardiovascular risk factors. However, other child risk factors, such as

LDL-C and systolic BP levels[53], have been strongly associated with these outcomes in other papers using the YFS sample. Taken together, a lower WVV range or distribution of its levels is unlikely to be explaining our findings (Supplementary Table 1).

Our study has limitations. First, bias due to differential loss to follow-up is possible. However, compared with other similar studies, participant retention in the YFS is high, non-participants at earlier surveys have re-entered at later time-points, and baseline risk factor levels between participants and non-participants in adult surveys have largely been comparable[54]. Second, there is no consensus on the preferred index to quantify WVV. Nontheless, we examined the potential associations of all known WVV parameters and results were consistent. Third, because markers of cardiovascular end-organ damage were not available from youth, we were unable to assess if differences in these markers already existed between participants much earlier in the life-course for our exposure measures of WVV and systolic BP. Fourth, although our outcomes have been shown to associate with cardiovascular events, we were unable to examine cardiovascular events in our sample owing to the current low event rates. Fifth, the impedance cardiography method used to estimate PWV (CircMon) is not the gold standard measure of carotid-to-femoral PWV. This might have resulted in higher variance (less precision) in PWV, albeit noting that the CircMon device has been shown to have acceptable agreement with the gold standard in an invasive comparator study[55]. Sixth, because our markers of cardiovascular end-organ damage were only measured in adulthood and not measured at all time-points, as was the case for BP and WVV, we were unable to determine the possible temporal associations of WVV from childhood to adulthood on markers of cardiovascular end-organ damage. Seventh, as clinics were performed a minimum of 3-years apart, classification of BP status in our

sample was based on BP readings collected at a single visit or time-point. Thus, a clinical diagnosis of neither elevated BP nor hypertension could be confirmed according to repeat BP measurements on two or more close but separate occasions (e.g., within days or weeks). Eighth, our study population had a relatively high prevalence of elevated BP and hypertension in childhood, which could infer limited generalizability. A potential explanation for higher prevalence is that the definition of elevated BP and hypertension in our study was based on BP values measured at a single survey visit instead of three or more visits as per guidelines. In any case, the prevalence of elevated BP and hypertension in childhood that we observed is similar to that reported in other population-based white cohorts, such as the Muscatine study (39%) conducted in the US [56], the Childhood Determinants of Adult Health Study (33%) conducted in Australia [56] and in a sample of healthy Portuguese children (35%).[57] These studies also defined elevated BP and hypertension using BP values from a single visit.

The findings of most novelty and importance in this study relate to that WVV did not have any prognostic significance to the cardiovascular over and beyond mean systolic pressure level from childhood to mid-life in the general population. The main strength of this study was the long length to follow-up in a well-established cohort of apparently healthy participants that allowed us to account for key confounders and to test the cumulative effects of WVV from childhood to mid adulthood on multiple markers of cardiovascular end-organ damage.

In conclusion, although differences occur among and between individuals, the WVV at one point in time is a poor predictor of future WVV and cumulative child, adult, and life-time WVV does not associate with future markers of cardiovascular end-organ damage among the general population. Collectively, our findings suggest that

knowledge of WVV in the early life-course does not provide additional predictive utility over traditional risk factors.

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717 Table 1. Participant characteristics at six surveys of the Cardiovascular Risk in Young Finns Study

Characteristics	Year											
	1980		1983		1986		2001		2007		2011	
	N	Values	N	Values	N	Values	N	Values	N	Values	N	Values
Female, n (%)	3019	1550 (51)	2991	1531(51)	2799	1477(53)	2621	1446 (55)	2243	1236 (55)	2115	1,157 (55)
Age (years)	3019	11.9 (4.1)	2991	13.0 (4.9)	2799	16.0 (5.0)	2621	31.5 (5.0)	2243	37.7 (5.0)	2115	41.8 (5.0)
Height (cm)	3012	149.0 (20.3)	2886	152.3 (20.4)	2501	161.1 (15.5)	2278	172.1 (9.1)	2176	172.1 (9.3)	2051	172.3 (9.3)
Body mass index (kg/m^2)	3009	18.3 (3.2)	2886	18.8 (3.4)	2500	20.0 (3.5)	2276	25.1 (4.4)	2170	26.0 (4.8)	2049	26.5 (5.1)
Weight Status*												
Underweight (%)	122	4.1	135	4.7	102	4.1	46	2.0	28	1.3	19	1.0
Normal (%)	2556	85.0	2397	83.1	2094	83.8	1240	54.5	984	45.4	863	42.1
Overweight (%)	244	8.1	268	9.3	233	9.3	710	31.2	783	36.1	743	36.3
Obesity (%)	87	2.9	86	3.0	71	2.8	280	12.3	375	17.3	424	20.7
Low density lipoprotein cholesterol (mmol/l)	3002	3.43 (0.84)	2849	3.14 (0.89)	2460	3.04 (0.90)	2251	3.28 (0.84)	2158	3.10 (0.79)	1999	3.27 (0.83)
High density lipoprotein cholesterol (mmol/l)	3002	1.57 (0.31)	2850	1.68 (0.34)	2489	1.52 (0.29)	2281	1.29 (0.32)	2193	1.34 (0.33)	2044	1.33 (0.33)
Triglyceride (mmol/l)	3002	0.59 (0.45-0.80)	2868	0.79 (0.63-1.04)	2486	0.84 (0.67-1.08)	2283	1.10 (0.80-1.60)	2204	1.15 (0.85-1.66)	2046	1.05 (0.75-1.56)
Clinic SBP (mmHg)	3010	114 (11)	2886	115(12)	2493	114(13)	2254	117 (13)	2182	121 (14)	2032	119 (14)
Clinic diastolic blood pressure (mmHg)	2991	69 (10)	2835	66 (10)	2462	65 (10)	2246	71 (11)	2175	76 (11)	2032	75 (10)
Normal blood pressure† (%)	2217	74.2	2113	74.9	2020	82.1	1813	80.7	1503	69.1	1498	73.7
Elevated blood pressure † (%)	392	13.1	397	14.1	273	11.1	272	12.1	340	15.6	298	14.7
Hypertension (%) †	377	12.6	310	11.0	167	6.8	161	7.4	332	15.3	236	11.6
Antihypertensive medication (%)	NA	NA	NA	NA	NA	NA	65	2	152	7	201	10
Standard deviation of SBP (mmHg)	3010	2.00 (1.15-3.06)	2886	2.31 (1.15-3.06)	2493	3.46 (2.31-5.29)	2254	3.46 (2.31-5.29)	2182	3.46 (2.00-5.29)	2032	3.06 (2.00-5.03)
Coefficient of variation of SBP (unitless)	3010	0.02 (0.01-0.03)	2886	0.02 (0.01-0.03)	2493	0.03 (0.02-0.05)	2254	0.03 (0. 02-0.05)	2182	0.03 (0.02-0.05)	2032	0.03 (0.02-0.04)
Average real variability (mmHg)	3010	2.70 (1.00-4.00)	2886	2.00 (1.00-4.00)	2493	4.00 (3.00-6.00)	2254	4.00 (3.00-6.00)	2182	4.00 (3.00-7.00)	2032	4.00 (2.00-6.00)
Difference between reading one and two ‡	3010	-0.77 (4.03)	2886	-0.87 (3.96)	2493	-2.17 (6.53)	2254	-1.72 (6.62)	2182	-0.96 (7.09)	2032	-1.14 (6.06)
(mmHg)												

Difference between reading two and three‡(mmHg)	3010	-0.42 (3.57)	2886	-0.45 (3.42)	2493	-0.91 (5.51)	2254	-0.94 (5.97)	2182	-0.86 (6.30)	2032	-0.67 (5.78)
Maximum absolute difference§ (mmHg)	3010	4.43 (2.00-6.00)	2886	4.00 (2.00-6.00)	2493	6.00 (4.00-10.00)	2254	6.00 (4.00-10.00)	2182	6.00 (4.00-10.00)	2032	6.00 (4.00-10.00)
Carotid intima-media thickness (um)	NA	NA	NA	NA	NA	NA	2265	580.9 (92.3)	2197	626.5 (96.6)	NA	NA
Brachial artery flow mediated dilation (%)	NA	NA	NA	NA	NA	NA	2109	7.8 (4.4)	2185	8.9 (4.5)	NA	NA
Carotid artery distensibility (%/10mmHg)	NA	NA	NA	NA	NA	NA	2255	2.17 (0.74)	2187	1.90 (0.69)	NA	NA
Pulse wave velocity (m/s)	NA	NA	NA	NA	NA	NA	NA	NA	1813	10.5 (2.0)	NA	NA
Left ventricular mass index ($g/m^{2.7}$)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1908	30.8 (6.6)
Presence of carotid plaque (%)	NA	NA	NA	NA	NA	NA	38	2	77	4	NA	NA
Presence of coronary artery calcification(%)	NA	NA	NA	NA	NA	NA	NA	NA	113	11	NA	NA

718 Values are continuous data with normal distribution expressed as mean (standard deviation); continuous data with non-normal distribution
719 shown as median (25th percentile-75th percentile); categorical data expressed as proportion. For the presence of carotid plaque (%) and
720 presence of coronary artery calcification (%), “values” indicate proportions.

721 Abbreviation: NA, not available.

722 *Weight status was determined by BMI. Participants aged ≤18 years were classified as underweight if BMI was <5th age- and sex-specific
723 percentile, normal if was ≥5th and <85th percentile, overweight if was ≥85th and <95th percentile, obesity if was ≥95th percentile. Weight
724 status in participants aged >18 years were classified as underweight if BMI was <18.5kg/m^2, normal if was ≥18.5 kg/m^2 and <25 kg/m^2,
725 overweight if was ≥25 kg/m^2 and <30 kg/m^2, obesity if was ≥30 kg/m^2.

† Classification of BP status in participants aged <18 years was determined by the 2016 European Society of Hypertension (ESH) guidelines in children and adolescents. For participants aged ≥18 years, classification of BP status was determined by the 2018 European Society of Cardiology (ESC)/ESH guidelines in adults.

‡ Difference between reading one and two is equal to reading two minus reading one. Difference between reading two and three is equal to reading three minus reading two.

§ Maximum absolute difference between any two readings of three measurements on a single occasion.

Table 2. Spearman's rank-order correlation coefficients (rho) for 3- to 31- year tracking of within-visit SBP variability across sex and baseline age strata.

Age in 1980 (years old)	Tracking years (survey year)														
	3 (1983)			6 (1986)			21 (2001)			27 (2007)			31(2011)		
	N	r	P value	N	r	P value	N	r	P value	N	r	P value	N	r	P value
Males															
6	250	0.05	0.40	234	-0.04	0.51	151	0.08	0.30	142	-0.02	0.78	137	0.09	0.32
9	290	0.07	0.23	240	-0.01	0.92	188	-0.06	0.39	173	-0.03	0.68	169	0.11	0.17
12	251	0.10	0.11	182	-0.09	0.25	174	0.03	0.73	172	0.09	0.24	158	0.09	0.25
15	201	0.06	0.37	155	0.12	0.15	182	-0.03	0.68	179	0.04	0.59	160	-0.10	0.22
18	154	0.00	0.96	130	0.07	0.44	163	0.06	0.42	154	0.10	0.23	159	-0.02	0.80
All Male	1146	0.07	0.01	941	-0.00	0.88	858	0.01	0.39	820	0.04	0.21	783	0.03	0.26
Females															
6	264	0.02	0.72	241	-0.06	0.38	208	0.11	0.11	204	-0.00	0.98	174	0.00	0.97
9	277	0.16	0.01	245	0.03	0.64	208	0.02	0.75	190	-0.00	0.99	182	0.07	0.34
12	286	0.08	0.17	230	0.02	0.81	233	-0.01	0.88	228	-0.00	1.00	208	0.06	0.40
15	236	-0.06	0.37	177	-0.10	0.19	213	-0.12	0.08	214	0.03	0.69	199	-0.01	0.93
18	180	0.09	0.22	171	-0.01	0.92	198	0.02	0.77	190	-0.10	0.16	193	0.02	0.83
All Female	1243	0.05	0.04	1064	-0.03	0.48	1060	-0.00	0.81	1026	-0.01	0.80	956	0.03	0.36
All	2389	0.06	0.001	2005	-0.01	0.54	1918	0.00	0.46	1846	0.01	0.52	1739	0.03	0.16

Note. Only participants with at least two measurements were included in these analyses.

Table 3. Associations between child, adult and life-time cumulative SBP and within visit SBP variability with continuous markers of cardiovascular end-organ damage in adulthood

Preclinical markers	Cumulative exposure*	Time period measured †	Model 1			Model 2			Model 3		
			N	β (95% CI)	P Value	N	β (95% CI)	P Value	N	β (95% CI)	P Value
Carotid intima-media thickness (um)	WVV	child	2626	-2.26 (-5.71 to 1.20)	0.201	2626	-2.24 (-5.67 to 1.20)	0.202	2623	-1.98 (-5.41 to 1.46)	0.26
		adult	2644	0.44 (-3.09 to 3.97)	0.81	2639	0.25 (-3.23 to 3.72)	0.889	2614	-0.31 (-3.79 to 3.17)	0.862
		total	2617	0.33 (-3.14 to 3.81)	0.68	2613	-0.59 (-4.02 to 2.84)	0.928	2526	-0.42 (-3.86 to 3.03)	0.813
	SBP	child	2626	14.41 (10.15 to 18.67)	**$3.99*10^{-11}$**	2626	10.50 (6.00 to 14.99)	**$2.67*10^{-7}$**	2623	9.93 (5.42 to 14.44)	**$1.64*10^{-5}$**
		adult	2644	16.45 (12.78 to 20.13)	**$3.17*10^{-18}$**	2639	10.43 (6.62 to 14.24)	**$8.72*10^{-8}$**	2614	10.30 (6.43 to 14.17)	**$1.96*10^{-7}$**
		total	2617	16.37 (12.52to 20.22)	**$1.21*10^{-16}$**	2613	8.11(3.88 to 12.34)	**$1.76*10^{-4}$**	2581	7.90 (3.57to 12.23)	**$3.50*10^{-4}$**
Brachial artery flow mediated dilation (%)	WVV	child	2597	0.07 (-0.10 to 0.24)	0.44	2597	0.06 (-0.10 to 0.24)	0.438	2594	0.07 (-0.10 to 0.24)	0.417
		adult	2613	-0.01 (-0.19 to 0.16)	0.87	2608	-0.01 (-0.19 to 0.16)	0.881	2583	-0.002 (-0.18 to 0.17)	0.98
		total	2588	0.07 (-0.11 to 0.24)	0.46	2584	0.04 (-0.13 to 0.21)	0.639	2552	0.04 (-0.13 to 0.21)	0.666
	SBP	child	2597	-0.07 (-0.28 to 0.14)	0.54	2597	-0.16 (-0.38 to 0.06)	0.162	2594	-0.16 (-0.38 to 0.06)	0.161
		adult	2613	-0.06 (-0.24 to 0.13)	0.54	2608	-0.23 (-0.43 to -0.04)	**0.017**	2583	-0.27 (-0.46 to -0.07)	**0.008**
		total	2588	-0.07 (-0.26 to 0.12)	0.48	2584	-0.32 (-0.54 to -0.11)	0.003	2552	-0.34 (-0.56 to -0.12)	**0.002**
Carotid artery distensibility (%/10mmHg)	WVV	child	2623	-0.01 (-0.03 to 0.02)	0.72	2623	-0.005 (-0.03 to 0.02)	0.71	2620	-0.01 (-0.03 to 0.02)	0.68
		adult	2641	-0.02 (-0.04 to 0.01)	0.23	2636	-0.02 (-0.04 to 0.01)	0.22	2611	-0.01 (-0.04 to 0.01)	0.25
		total	2614	0.002 (-0.02 to 0.03)	0.87	2610	0.004 (-0.02 to 0.03)	0.72	2578	0.003 (-0.02 to 0.03)	0.837
	SBP	child	2623	-0.07 (-0.10 to -0.03)	**$3.67*10^{-5}$**	2623	-0.05 (-0.09 to -0.02)	**0.002**	2620	-0.05 (-0.09 to -0.02)	**0.003**
		adult	2641	-0.17 (-0.20 to -0.15)	**$1.53*10^{-36}$**	2636	-0.15 (-0.18 to -0.12)	**$1.71*10^{-24}$**	2611	-0.14 (-0.17 to -0.11)	**$2.31*10^{-21}$**
		total	2614	-0.12 (-0.15 to -0.09)	**$9.13*10^{-17}$**	2610	-0.09(-0.12 to -0.06)	**$6.80*10^{-9}$**	2578	-0.09 (-0.13 to -0.06)	**$9.65*10^{-9}$**
Pulse wave velocity (m/s)	WVV	child	1851	-0.01 (-0.07 to 0.05)	0.67	1851	-0.01 (-0.07 to 0.05)	0.68	1849	-0.01 (-0.07 to 0.05)	0.68
		adult	1867	0.04 (-0.02 to 0.10)	0.202	1864	0.04 (-0.02 to 0.10)	0.24	1854	0.03 (-0.03 to 0.09)	0.28
		total	1851	-0.02 (-0.07 to 0.04)	0.62	1849	-0.02 (-0.08 to 0.04)	0.51	1833	-0.02 (-0.08 to 0.04)	0.59
	SBP	child	1851	0.20 (0.12 to 0.27)	**$2.76*10^{-7}$**	1851	0.21 (0.13 to 0.29)	**$1.26*10^{-7}$**	1849	0.21 (0.13 to 0.29)	**$2.17*10^{-7}$**
		adult	1867	0.49 (0.43 to 0.55)	**$1.30*10^{-49}$**	1864	0.48 (0.38 to 0.52)	**$7.19*10^{-43}$**	1854	0.46 (0.39 to 0.52)	**$1.62*10^{-38}$**
		total	1851	0.46 (0.39 to 0.53)	**$2.381*10^{-38}$**	1849	0.45 (0.38 to 0.52)	**$1.12*10^{-33}$**	1833	0.43 (0.36 to 0.50)	**$2.93*10^{-30}$**
Left ventricular mass index ($g/m^{2.7}$)	WVV	child	1889	-0.31 (-0.59 to -0.02)	0.04	1889	-0.29 (-0.57 to -0.02)	0.04	1887	-0.27 (-0.55 to 0.002)	0.05
		adult	1907	-0.10 (-0.41 to 0.21)	0.52	1907	-0.07 (-0.35 to 0.21)	0.62	1897	-0.08 (-0.36 to 0.20)	0.571
		total	1888	-0.15 (-0.45 to 0.14)	0.31	1888	-0.22 (-0.49 to 0.05)	0.107	1870	-0.21 (-0.49 to 0.06)	0.121
	SBP	child	1889	0.67 (0.31 to 1.02)	**$2.32*10^{-4}$**	1889	-0.06 (-0.42 to 0.30)	0.74	1887	-0.08 (-0.45 to 0.28)	0.66
		adult	1907	1.53 (1.21 to 1.85)	**$2.79*10^{-20}$**	1907	0.54 (0.23 to 0.84)	**$4.76*10^{-4}$**	1897	0.58 (0.27 to 0.89)	**$2.17*10^{-4}$**
		total	1888	1.41 (1.04to 1.77)	**$4.71*10^{-14}$**	1888	0.07 (-0.28 to 0.43)	**0.681**	1870	0.13 (-0.23 to 0.50)	**0.470**

Abbreviations: CI, confidence interval; SBP, SBP; WVV, within visit SBP variability calculated as standard deviation of SBP.

β and corresponding P values from linear regression models. β Represents regression coefficient per SD increments in exposures. All models are conducted separately for cumulative variables measured during different time period. All models include both WVV and SBP. Model 1 adjusted for baseline age and sex. Model 2 adjusted for model 1 covariates and additionally for cumulative body mass index. Model 3 adjusted for model 2 covariates and additionally for cumulative triglyceride, cumulative high-density lipoprotein cholesterol and cumulative low-density lipoprotein cholesterol.

*Cumulative values are calculated as the summed average measurements for each pair of consecutive examinations multiplied by the time between these two consecutive visits in years, then divided by the total time interval. For example, a participant with three SBP measurements during a certain time period, cumulative SBP= {[(SBP1+SBP2) * (time 1-2) /2] +[(SBP2+SBP3) *(time 2-3) /2]}/ (time1-3), where SBP1, SBP2, and SBP3 indicates SBP measured at physical examination 1, 2, and 3, respectively and time 1-2, time 2-3, time 1-3 indicate the time interval between examinations in years. All values are standardized into Z scores.

† Child: ≤18 years; adult: >18 years (range 21-49 years); total: only participants with both child and adult measurements included (range 6-49 years).

768 Table 4. Associations between child, adult and life-time cumulative SBP and SBP variability
769 with categorical markers of cardiovascular end-organ damage in adulthood

Preclinical markers	Cumulative exposure *	Time period measured†	Model 1			Model 2			Model 3		
			N	RR (95% CI)	P Value	N	RR (95% CI)	P Value	N	RR (95% CI)	P Value
Carotid plaque	WVV	child	2626	0.94 (0.77 to 1.13)	0.50	2626	0.94 (0.77 to 1.13)	0.51	2623	0.95 (0.79 to 1.15)	0.62
		adult	2644	1.05 (0.85 to 1.30)	0.66	2639	1.06 (0.85 to 1.31)	0.63	2614	1.02 (0.82 to 1.27)	0.84
		total	2617	1.05 (0.87 to 1.28)	0.80	2617	1.06 (0.87 to 1.29)	0.561	2581	1.05 (0.87 to 1.28)	0.597
	SBP	child	2626	1.06 (0.84 to 1.33)	0.65	2626	1.08 (0.84 to 1.38)	0.55	2623	1.02 (0.79 to 1.31)	0.88
		adult	2644	1.13 (0.85 to 1.30)	0.29	2639	1.18 (0.94 to 1.49)	0.16	2614	1.12 (0.88 to 1.42)	0.35
		total	2617	1.19 (0.95 to 1.51)	0.12	2,617	1.25 (0.97 to 1.60)	0.08	2581	1.16 (0.91 to 1.48)	0.242
Coronary artery calcification	WVV	child	589	0.92 (0.78 to 1.08)	0.31	589	0.92 (0.78 to 1.08)	0.29	588	0.93 (0.80 to 1.09)	0.38
		adult	574	0.94 (0.77 to 1.14)	0.50	574	0.93 (0.77 to 1.14)	0.50	573	0.92 (0.75 to 1.13)	0.41
		total	574	0.86 (0.71 to 1.03)	0.107	574	0.86 (0.71 to 1.03)	0.099	571	0.82 (0.67 to 1.002)	0.052
	SBP	child	589	1.15 (0.95 to 1.39)	0.16	589	1.12 (0.91 to 1.37)	0.29	588	1.08 (0.91 to 1.28)	0.37
		adult	574	1.17 (0.99 to 1.39)	0.07	574	1.16 (0.96 to 1.39)	0.12	573	1.15 (0.96 to 1.39)	0.14
		total	574	1.19 (0.999 to 1.418)	0.052	574	1.17 (0.98 to 1.41)	0.086	571	1.19 (0.99 to 1.44)	0.07

770 Abbreviations: CI, confidence interval; SBP, SBP; RR, risk ratio; WVV, within visit SBP
771 variability calculated as standard deviation of SBP.

772 RR and corresponding P values from log-binomial regression models. All models are
773 conducted separately for cumulative variables measured during different time period. All
774 models include both WVV and SBP. Model 1 adjusted for baseline age and sex. Model 2

adjusted for model 1 covariates and additionally for cumulative body mass index. Model 3 adjusted for model 2 covariates and additionally for cumulative triglyceride, cumulative high-density lipoprotein cholesterol and cumulative low-density lipoprotein cholesterol.

*Cumulative values are calculated as the summed average measurements for each pair of consecutive examinations multiplied by the time between these two consecutive visits in years, then divided by the total time interval. For example, a participant with three SBP measurements during a certain time period, cumulative SBP = {[(SBP1+SBP2) * (time 1-2) /2] +[(SBP2+SBP3) *(time 2-3) /2]}/ (time 1-3), where SBP1, SBP2, and SBP3 indicates SBP measured at physical examination 1, 2, and 3, respectively and time 1-2, time 2-3, time1-3 indicate the time interval between examinations in years. All values are standardized into Z scores.

† Child: ≤18 years; adult: >18 years (range 21-49 years old); total: only participants with both child and adult measurements included (range 6-49 years).

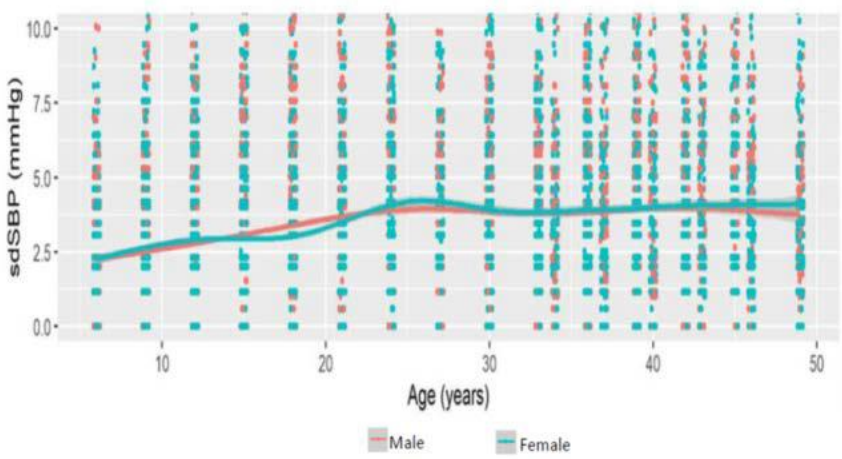


Figure 1. Individual growth curves of within-visit systolic blood pressure variability among participants aged 6 to 49 years by sex. The red and blue line represent estimated average age-related within visit systolic blood pressure variability (calculated as standard deviation of three consecutive systolic blood pressure readings) across the life course for males and females.

Online Supplement

Steps for IGC modelling

IGC is a multilevel regression model that quantifies change in a variable over time both at the participant- (level 2) and observation-level (level 1). IGC incorporates fixed effects, the mean slopes and mean intercepts of all individuals in the sample, and random effects, the individual variability around the mean growth parameters (i.e. intercept and slope). Individuals are matched to the mean curve by shifting their starting points (representing differences in mean level) and rate of change (representing differences in growth tempo). Parameters were estimated using the maximum likelihood method, with models selected according to Akaike's information criterion (AIC) and likelihood ratio test (LRT). Linear and higher power items of age were added into the model sequentially. If the higher power items were not statistically significant, or if the AIC value of the model was not improved, then these higher-order terms were excluded. Concurrently, if Stata reported singularity or non-convergence when the higher power item was included in the model, the higher-order term was dropped. To avoid collinearity of age with its higher-order terms, we centred age to the mean (22.43 years). After constructing the best fitted model, we added sex to the model to test how sex modifies the WVV trajectories, which can be interpreted as inter-individual differences of WVV development throughout the life course, herein referred to as intra-individual change. IGC analyses include sequentially testing a number of models as follows:

Step 1 Unconditional means (UM) model. The UM model is the simplest multilevel model that contains no predictor. This model assesses (1) the grand mean of WVV and (2) the amount of variance in the outcome that is attributed to differences between individuals by intraclass correlation coefficient (ICC).

Step 2 Potential unconditional growth (UG) models (i.e. participant-level random intercept). UG models fit WVV as a function of age, with each participant regarded as a random

intercept. In our study, we added linear and higher power items of age into the model construction sequentially to explore linear and curvilinear UG models for WVV across the observed life-course. Then we used the likelihood ratio test or AIC/BIC criteria to compare increasingly complex models throughout the IGC analyses, (*1) likelihood ratio tests (LRT):* When models are nested within each other (one is a special case of the other), LRT can be used. This method calculates -2 times the difference between the two models residual log likelihoods (-2RLL) and compares it to the χ^2 distribution with degrees of freedom equal to the difference in the number of parameters for the two models). Models are preferred where the -2RLL is smaller. 2) *AIC or BIC* was used to compare non-nested models; models with the smallest AIC or BIC was prioritized.

Step 3 Model the random effect structure (i.e. participant-level random intercept and slope). After the best UG model was determined, the model was expanded by adding random slope terms for linear and higher power terms of age. This allowed us to test sequentially if each additional random parameter (i.e. random intercept, random linear slope, random quadratic slope…) improved the fit of the UG models using LR tests and AIC.

Step 4 The conditional growth (CG) models (i.e. between-participant model). After the random intercept and slope of the UG model was determined, we added sex to the UG model to determine if individual growth varies across males and females.

(1) Whether or not sex affects the intercept of the UG model? We added sex to the intercept parts of UG model then tested the improvement of the model by using LR tests and AIC.
(2) Whether or not sex affects the slope of the UG model? We added interaction terms of age or a higher power term of age with sex to the UG model. Then we tested

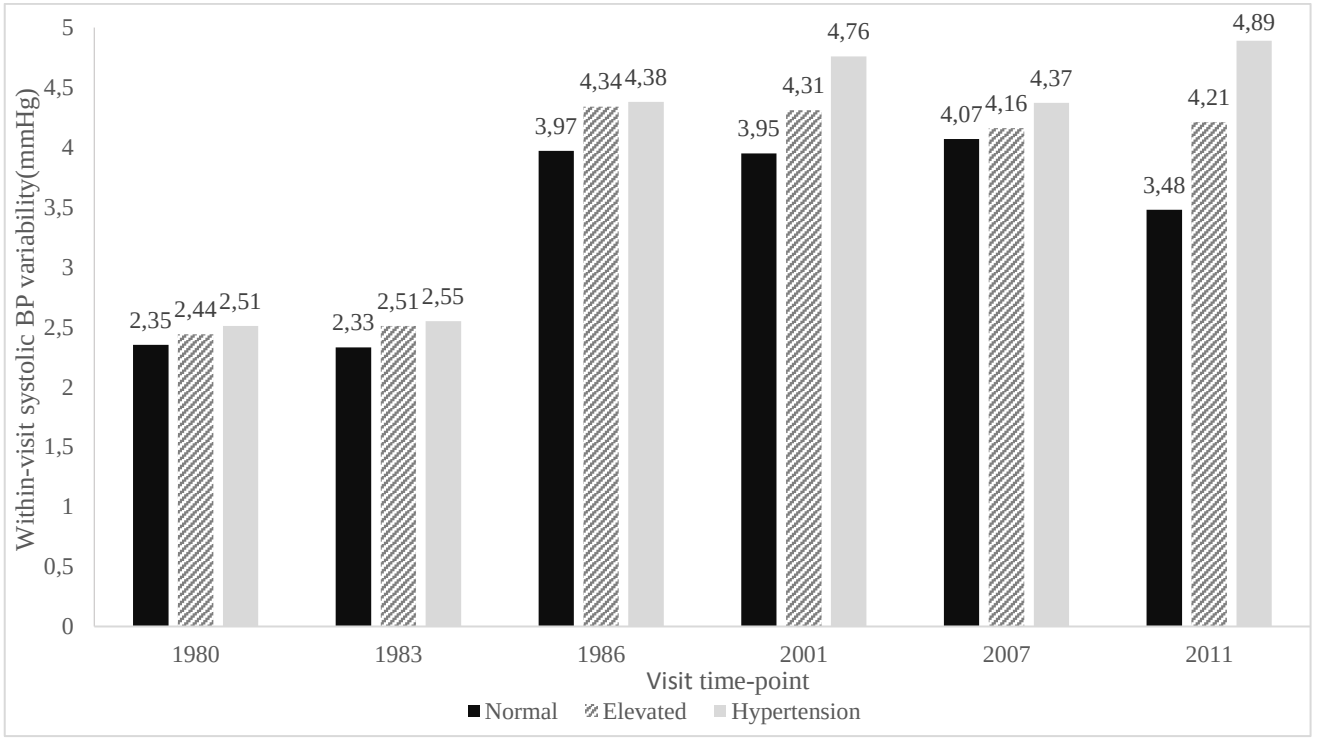
sequentially if each additional interaction term (i.e. age with sex, quadratic term of age with sex…) improved the fit of the UG models using LR tests and AIC.

(3) Whether or not sex affects both the slope and intercept of the UG model? The UG model was expanded by introducing both sex and interaction terms of sex with age or the higher power term of age, then compared the current model with the UG model using LR tests and AIC.

Supplementary Table 1. Median (25th percentile-75th percentile) within-visit systolic blood pressure variability in each visit among participants in the Young Finns Study aged 6 to 49 years

Age groups (years)	Female		Male		All	
	N	sdSBP (mmHg)	N	sdSBP (mmHg)	N	sdSBP (mmHg)
6	536	2.00 (1.15-3.06)	531	2.00 (1.15-3.06)	1,067	2.00 (1.15-3.06)
9	834	2.31 (1.15-3.46)	811	2.31 (1.15-3.46)	1,645	2.31 (1.15-3.46)
12	885	2.31 (1.15-4.00)	888	2.31 (1.15-3.46)	1,773	2.31 (1.15-3.46)
15	923	2.31 (1.15-4.16)	865	3.06 (1.15-4.16)	1,788	2.31 (1.15-4.16)
18	821	2.31 (1.15-4.16)	717	3.06 (2.00-4.62)	1,538	3.06 (1.15-4.16)
21	432	3.06 (1.15-4.16)	375	3.06 (2.00-4.62)	807	3.06 (2.00-4.62)
24	424	4.00 (2.31-5.93)	340	3.46 (2.00-5.29)	764	3.46 (2.31-5.29)
27	271	3.05 (2.00-5.03)	200	3.46 (2.00-5.29)	471	3.46 (2.00-5.29)
30	407	3.46 (2.00-5.29)	371	3.46 (2.00-5.29)	778	3.46 (2.00-5.29)
33	438	3.06 (2.00-4.62)	318	3.06 (2.00-5.03)	756	3.06 (2.00-5.03)
34	150	3.06 (2.00-4.62)	137	3.06 (2.00-4.62)	287	3.06 (2.00-4.62)
36	404	3.46 (2.00-5.29)	356	3.46 (2.00-5.29)	760	3.46 (2.00-5.29)
37	175	3.06 (2.00-5.29)	139	3.06 (2.00-4.62)	314	3.06 (2.00-5.13)
39	426	3.46 (2.08-5.29)	335	4.00 (2.31-5.29)	761	4.00 (2.31-5.29)
40	182	3.06 (2.00-4.93)	170	3.06 (2.00-4.36)	352	3.06 (2.00-4.62)
42	215	4.00 (2.31-6.11)	179	3.46 (2.31-6.11)	394	3.76 (2.31-6.11)
43	208	3.06 (2.15-5.11)	158	3.06 (2.00-4.73)	366	3.06 (2.00-5.03)
45	190	3.46 (2.00-6.11)	155	3.46 (2.00-5.29)	345	3.46 (2.00-5.77)
46	200	3.06 (2.31-5.03)	160	3.06 (2.00-4.78)	360	3.06 (2.04-4.97)
49	193	3.46 (2.31-5.29)	160	3.21 (2.20-5.03)	353	3.46 (2.31-5.13)

Abbreviation: sdSBP, standard deviation of three consecutive systolic blood pressure readings in each visit.



Supplementary Figure 1: Within-visit systolic blood pressure (BP) variability, represented as the standard deviation of three repeated systolic BP readings at each visit, stratified by BP status (i.e., normal, elevated and hypertension) at each visit time-point.