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ORIGINAL RESEARCH

Relative Contribution of Blood Pressure in Childhood, Young- and Mid-Adulthood to Large Artery Stiffness in Mid-Adulthood

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BACKGROUND: Blood pressure associates with arterial stiffness, but the contribution of blood pressure at different life stages is unclear. We examined the relative contribution of childhood, young- and mid-adulthood blood pressure to mid-adulthood large artery stiffness.

METHODS AND RESULTS: The sample comprised 1869 participants from the Cardiovascular Risk in Young Finns Study who had blood pressure measured in childhood (6–18 years), young-adulthood (21–30 years), and mid-adulthood (33–45 years). Markers of large artery stiffness were pulse wave velocity and carotid distensibility recorded in mid-adulthood. Bayesian relevant life course exposure models were used. For each 10-mm Hg higher cumulative systolic blood pressure across the life stages, pulse wave velocity was 0.56 m/s higher (95% credible interval: 0.49 to 0.63) and carotid distensibility was 0.13%/10 mm Hg lower (95% credible interval: −0.16 to −0.10). Of these total contributions, the highest contribution was attributed to mid-adulthood systolic blood pressure (relative weights: pulse wave velocity, childhood: 2.6%, young-adulthood: 5.4%, mid-adulthood: 92.0%; carotid distensibility, childhood: 5.6%; young-adulthood: 10.1%; mid-adulthood: 84.3%), with the greatest individual contribution coming from systolic blood pressure at the time point when pulse wave velocity and carotid distensibility were measured. The results were consistent for diastolic blood pressure, mean arterial pressure, and pulse pressure.

CONCLUSIONS: Although mid-adulthood blood pressure contributed most to mid-adulthood large artery stiffness, we observed small contributions from childhood and young-adulthood blood pressure. These findings suggest that the burden posed by arterial stiffness might be reduced by maintaining normal blood pressure levels at each life stage, with mid-adulthood a critical period for controlling blood pressure.

Key Words: blood pressure ■ epidemiology ■ hypertension ■ paediatrics ■ risk factors

Stiffness of the large elastic arteries (aorta, carotid) is a robust surrogate marker for cardiovascular events.[1,2] Carotid-femoral pulse wave velocity (PWV) is considered the gold standard for the non-invasive measurement of large artery stiffness and a recognized screening test for hypertension-mediated organ damage.[3] PWV, determined from the transit time of the pressure pulse between large artery beds, is a marker of regional arterial stiffness, whereas carotid distensibility (cD), assessed at a single location[4] by the extent of carotid artery expansion and recoil across the cardiac cycle, represents local arterial

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CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, this is the first study to identify the relative contribution of blood pressure measured at different life stages to large artery stiffness in mid-adulthood.
- Of the total contribution of blood pressure levels across the life course to mid-adulthood large artery stiffness, the highest contribution was attributed to mid-adulthood blood pressure, concurrent with the observed outcomes.
- The relative contribution of blood pressure for large artery stiffness presents in childhood and becomes most pronounced the closer to when large artery stiffness is measured.

What Are the Clinical Implications?

- To decrease the potential burden posed by large artery stiffness to subsequent cardiovascular health, preventive interventions aimed at reducing blood pressure might be most effective if implemented in mid-adulthood.
- Prevention and intervention efforts aimed at maintaining normal blood pressure levels in children and young adults might help further reduce the burden posed by future large artery stiffness.

Nonstandard Abbreviations and Acronyms

BRLM	the Bayesian relevant life course exposure model
cD	carotid distensibility
CrI	credible interval
DBP	diastolic blood pressure
PP	pulse pressure
PWV	pulse wave velocity
SBP	systolic blood pressure
YFS	the Cardiovascular Risk in Young Finns Study

stiffness.[4] Decreased cD reflects early pathophysiological changes to the artery and is associated with atherosclerotic burden,[5] incident stroke,[6] and all-cause mortality.[7] As important precursors of adverse cardiovascular outcomes, there is a need to fully understand risk factors for the development of large artery stiffening.

Arterial wall stiffness is intrinsically dependent on the blood pressure (BP) level at the time of arterial stiffness measurement.[8] On the other hand, chronic exposure to high BP also contributes to structural arterial wall changes and increased stiffness.[4] Underlying mechanisms behind the association of BP and large artery stiffening is that elevated BP increases arterial wall stress, leading to smooth muscle hypertrophy and upregulation of collagen synthesis, as well as arterial wall fatigue and fracture of the elastic elements within the media.[9] The relative contribution of BP exposure at different life stages on adulthood arterial stiffness has been reported using various analytical methods.[10–13] For example, childhood systolic BP (SBP) was inversely associated with cD in adulthood, but this association was attenuated by about half when adulthood BP was considered.[10] However, these analyses were unable to determine whether exposure to higher BP levels at discrete life stages contributed differently to the life course association with large artery stiffness. Clarifying this could have potential implications for the timing of prevention and intervention strategies. We conducted this study with the aim of identifying the relative contribution of BP measured at different life stages from childhood on adulthood large artery stiffness using Bayesian relevant life course exposure modeling in a large cohort of participants.

METHODS

Study Overview

This study used data from YFS (the Cardiovascular Risk in Young Finns Study), a population-based prospective cohort of Finnish children from 5 cities with university hospitals and their rural surrounds followed-up to adulthood that aimed to identify early life factors associated with adult cardiometabolic outcomes. Here we use data collected on BP measured at up to 7 times across the life course (at childhood aged from 6 years to mid-adulthood aged up to 45 years in 3-year intervals) to determine the associations with markers of large artery stiffness collected in mid-adulthood.

The data set supporting the conclusions of this article were obtained from the YFS after submission and approval of our study plan by the YFS coordinators. The YFS data set comprises health-related participant data and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these legal restrictions, the data from this study cannot be stored in public repositories or otherwise made publicly available. However, data access may be permitted on a case by case basis upon request only. Data sharing outside the group is done in collaboration with YFS group and requires a data-sharing agreement. Investigators can submit an expression of

interest to the chairman of the publication committee (Prof. Mika Kähönen, Tampere University, Finland).

Study Population

The first cross-sectional survey of the YFS was conducted in 1980 among 3596 participants aged 3, 6, 9, 12, 15, and 18 years (participants were born in 1977, 1974, 1971, 1968, 1965, and 1962, respectively). Participants were a nationally representative sample of children and adults randomly selected from the Finnish national population register. Since the first survey in 1980, follow-up studies have been conducted in 1983, 1986, 1989, 1992, 2001, 2007, and 2011. Detailed information on the population and protocol have been reported elsewhere.[14,15] Cohort design of the YFS is summarized in Table S1. In this study, participants from the youngest birth cohort (aged 3 years at baseline in 1980) were not included because their BP was collected by an ultrasound device in 1980 and they did not have measurements of large artery stiffness collected according to our definition of mid-adulthood (aged 33–45 years) in 2007. The sample comprised up to 1869 participants from the remaining 5 birth cohorts who had their BP measured in childhood (aged 6–18 years), young- (aged 21–30 years), and mid-adulthood (aged 33–45 years) and who had PWV or cD measured in mid-adulthood. The study was approved by local ethics committees according to the Declaration of Helsinki. All participants or their parents gave written informed consent.

BP Measurements

SBP and diastolic BP (DBP) 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 2007 surveys by trained examiners. Of the 3596 participants enrolled at baseline, of whom 53 (1.5%), 710 (19.7%), 1103 (30.7%), 3220 (89.5%), 3150 (87.6%), 1342 (37.3%) and 1414 (39.3%) did not have SBP measurements in 1980, 1983, 1986, 1989, 1992, 2001, and 2007, respectively. The pattern of missing SBP values from 1980 to 2007 was a mix of intermittent and mixed drop out (Figure S1). In the current study, the data were missing because they were not collected or recorded by clinicians or there were economic constraints in some surveys (1989 and 1992). But, on those occasions, if participants did not attend those follow-ups, data were missing for all variables, so that the pattern of "missingness" was consistent with a missing at random process. Interobserver reproducibility of BP measurements for >630 paired observations in the YFS for SBP and DBP in which the correlation coefficients were satisfactory (SBP, 0.72; DBP, 0.51).[16] Between 8 am and 10 am, 3 successive BP measurements (with 3-minute intervals) were taken on the right arm of participants after 5-minutes rest in the seated position and using an appropriate cuff size. SBP and DBP were measured as the first and fifth Korotkoff sounds, respectively, to the nearest even number of millimeters of mercury. The average of the 3 readings was regarded as the BP measurement at each point. Pulse pressure (PP) was calculated by subtracting DBP from SBP. Mean arterial pressure (MAP) was calculated by adding 40% of PP to DBP.[17] Because SBP is the most important component of BP and the main determinant of cardiovascular events,[18] our main results focus on SBP. Results for DBP, PP, and MAP are provided in Table S5.

Markers of Large Artery Stiffness

PWV was estimated between the aortic arch and the popliteal artery using whole-body impedance cardiography (CircMon B202, JR Medical Ltd., Tallinn, Estonia).[11] The average of 3 measurements recorded after 15 minutes supine rest were used in the analysis. Full measurement protocols, validation, and reproducibility of the CircMon device have been reported.[13,19,20] cD was measured in duplicate at the left common carotid artery using B-mode ultrasound and 13.0-MHz linear array transducers (Sequoia 512, Acuson, CA, USA) as previously detailed.[10] End-systole was determined from the end of the T-wave and end-diastole from the peak of R wave, each derived from a concomitant ECG. cD was calculated as ([systolic diameter—diastolic diameter]/diastolic diameter) / (SBP – DBP). The mean of 2 BPs measured during the ultrasound procedure with an automated device (Omron M4, Omron Matsusaka Co., Ltd., Japan) was used for calculation of cD.

Covariates

At all surveys, height and weight were measured. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting heart rate was recorded from the participants in a sitting position when BP was measured. Venous blood samples were taken after a 12-hour fast with standard methods applied to measure serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol[21]. Low-density lipoprotein cholesterol was calculated indirectly using the Friedewald formula.[22] In 1986, 2001, and 2007, plasma glucose concentrations were analyzed enzymatically.[14] Participants were categorized as having type 2 diabetes if they had fasting plasma glucose of ≥7.0 mmol/L, or reported use of oral glucose-lowering medication or insulin but not reported having type 1 diabetes, or reported a diagnosis of type 2 diabetes by a physician at any of the age-points during the observed life course. Smoking habits were self-reported using questionnaires in participants aged ≥12 years.[14]

Participants were defined as "current smokers" if they currently (i.e., in 2007) smoked daily, "ex-smokers" if they had previously smoked daily but quit before 2007, and "never smokers" if they had never smoked. Pack-years of smoking were calculated as intensity (i.e., the number of cigarette packs smoked daily) multiplied by the duration of daily smoking in years. Data on alcohol consumption,[23] physical activity,[24] and socioeconomic disadvantage[25] were also collected by questionnaires (details of methods are provided in Data S1). A physical activity index was calculated by combining the information on the frequency, intensity, and duration of physical activity for participants aged ≥9 years.[23] Data on anti-hypertensive medication use (yes/no) were collected in 2001 and 2007.

Statistical Analysis

The Bayesian relevant life course exposure model (BRLM)[26,27] was used to identify the relative contribution of BP measured in childhood, young- and mid-adulthood on arterial stiffness in mid-adulthood. Full methodological details of the BRLM have been published previously[28,29] and details about model formulation and diagnostics are shown in Data S2 and Figures S2 through S4. Briefly, the relative contribution of BP at each examined life stage to the development of large artery stiffness was estimated by relative weights, allowing BP to associate with large artery stiffness at different levels depending on the life stage at which it was measured. Based on the relative weights (i.e., the relative contribution) and their posterior distribution parameters, the association of BP with the observed outcomes could be contextualized into 1 of 3 life course models. Life course models include the accumulation life course model (where each life stage has the same importance), and subsets of the accumulation model: the sensitive period life course model (where different life stages have different importance); or the critical period life course model (where BP at only 1 life stage is considered important). BRLM also estimates an accumulated effect, representing the overall or total association of BP across each of the measured life stages, on large artery stiffness in mid-adulthood. Using the accumulated effect and the relative weights for BP, BRLMs could further determine the life stage specific effect. BRLM is fitted applying a non-informative Dirichlet prior for weights and a weakly informative Cauchy prior for the accumulated effect.

Missing BP values were interpolated using an individual growth curve model,[27] a 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 Data S3).[30] In this study, the best fitted individual growth curve model of BP (SBP, DBP, PP, and MAP) was one with a quartic age term and the inclusion of sex and height as modifiers. Life stage-specific values for BP were calculated as the mean values between ages 6 and 18 years for children, 21 and 30 years for young-adulthood, and 33 and 45 years for mid-adulthood. We also estimated the relative weights of SBP exposure between 0 and 27 years prior (3-year intervals) to when the outcomes of PWV and cD were measured (i.e., 2007).

Covariates were selected a priori because they have known associations with BP and large artery stiffness.[11,31] For continuous covariates, we averaged the repeated data measured over all study surveys to generate a lifetime-averaged value. We initially adjusted for sex and year of birth (model 1); then further adjusted for other covariates, including pack-years of smoking, lifetime-averaged values of alcohol consumption, BMI, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate (model 2).

We also considered a series of sensitivity analyses. First, we examined a model that additionally adjusted for anti-hypertensive medication. Second, because BRLM does not allow for interaction terms, the main analyses were stratified by sex to determine if the observed life course model was consistent by sex. Third, we refitted the models replacing the main exposure of SBP with other BP components (DBP, MAP, PP). Fourth, we conducted the BRLM with BP status as a categorical exposure variable. Childhood BP was classified as normal if SBP/DBP <120/80 mm Hg, high-normal if SBP/DBP ≥120/80 mm Hg, and <130/80 mm Hg, and hypertension if SBP/DBP ≥130/80 mm Hg.[32] Young- and mid-adulthood BP was classified using the 2018 European guidelines: optimal (<120/80 mm Hg), normal (<130/85 mm Hg), high-normal (130–139/85–90 mm Hg) and hypertension (≥140/90 mm Hg).[3] For the purpose of consistent BP classification from childhood to young and mid-adulthood, the categories of "optimal" and "normal" were combined and referred to as "normal" for BP measured in young and mid-adulthood. Fifth, given the BRLM does not allow for inclusion of time-varying covariates, we used an alternative approach that regressed SBP on BMI at each observed life stage and used the residuals from these regression models as primary exposure variables in the BRLMs. Sixth, we compared the observed outcome variables between the participants who indicated use of antihypertensive medications in 2001 or 2007 and those who did not indicate use of antihypertensive medications among the participants with normal current SBP (in 2007) using logistic regression adjusted for sex and baseline age. We further refitted the BRLMs among the participants with normal/elevated SBP (i.e., SBP<140 mm Hg) at the time-point when outcome variables were

measured, stratified by antihypertensive medications use. Seventh, given that type 2 diabetes associates with arterial stiffness, we repeated the analyses based on model 2, and additionally adjusted for the presence of type 2 diabetes.[33] Finally, we estimated the association of SBP across multiple time points measured 3 to 27 years before outcome assessment in 2007, stratified by SBP status in 2007.

Continuous variables were expressed as mean (SD) and categorical variables were presented as proportion and number of participants. The "rstan" package of R studio (Version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria) was used to fit the BRLM in the probabilistic programming language, Stan.[34] Stata (Version 16.1, StataCorp, College Station, USA) was used for all other analyses.

RESULTS

Participant Characteristics

Participant characteristics at each life stage are shown in Table 1. Of 1869 participants, 55.6% (n=1039) were female participants, 17.5% (n=327) were current smokers, 19.2% (n=358) were ex-smokers, and 9.1% (n=152) indicated having ever used hypertensive medication. Among the 1228 participants with normal current SBP (SBP <130 mm Hg in 2007) and who had data on use of antihypertensive medication, the proportion that indicated having ever used hypertensive medication (in either 2001 or 2007) was low (5.8%) (Table S2). The prevalence of type 2 diabetes was 1.7% (32/1856) during the observed life course. Outcome data on mid-adulthood PWV were available from 1583 participants and cD was available from 1858 participants. Mean (SD) PWV was 8.89 (1.61) m/s for male participants and 7.79 (1.26) m/s for female participants. For cD, the mean (SD) was 1.70 (0.59) %/10 mm Hg for male participants and 1.97 (0.72) %/10 mm Hg for female participants. Mean (SD) socioeconomic disadvantage score was 0.44 (0.59) from age 6 to 21 years and 0.002 (0.57) from age 24 to 45 years. Mean (SD) pack-years of smoking was 3.77 (7.34) packs (1 pack=20 cigarettes) smoked per day for 1 year among the studied sample.

Blood Pressure Across the Life Course and Arterial Stiffness in Mid-Adulthood

The total (accumulated) effect of exposure to SBP across the life stages on mid-adulthood PWV and cD is shown in Table 2. Higher cumulative exposure to SBP across the life stages was associated with higher PWV and lower cD in mid-adulthood, irrespective of covariate adjustment (Models 1 and 2, Table 2).

Figure 1 represents the relative weights of SBP measured at each life stage with mid-adult PWV and cD (posterior probability distributions are shown in Figure S5). Because the relative contribution was not completely from SBP in mid-adulthood, the association between SBP across the life course and large artery stiffness in mid-adulthood, assessed by either PWV or cD, was best described by a relaxed critical period life course model compared with a pure critical period model, with the highest contribution (i.e., relative weight) observed for the mid-adulthood life stage. The life stage specific effect of SBP supports this interpretation (Table 2).

Table 1. Characteristics of Study Participants at Different Life Stages

Characteristic	Childhood		Young adulthood		Mid-adulthood	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age, y	1869	15.0 (2.1)	1869	24.8 (1.5)	1869	37.2 (3.0)
Systolic blood pressure, mm Hg	1869	115.6 (10.4)	1869	118.0 (12.3)	1869	119.7 (13.3)
Diastolic blood pressure, mm Hg	1869	66.8 (5.4)	1869	70.6 (6.6)	1869	75.0 (7.8)
Mean arterial pressure, mm Hg	1869	85.4 (5.0)	1869	90.0 (6.7)	1869	92.7 (8.9)
Pulse pressure, mm Hg	1869	46.5 (7.2)	1869	47.9 (6.4)	1869	44.3(5.2)
Low-density lipoprotein cholesterol, mmol/L	1868	3.21 (0.76)	1309	3.14 (0.79)	1845	3.20 (0.78)
High-density lipoprotein cholesterol, mmol/L	1868	1.57 (0.28)	1315	1.38 (0.33)	1863	1.32 (0.31)
Triglycerides, mmol/L	1868	0.80 (0.30)	1316	1.15 (0.59)	1865	1.38 (0.85)
Body mass index, kg/m^2	1869	19.3 (2.8)	1250	23.4 (3.8)	1854	25.9 (4.6)
Physical activity index, unitless	1841	9.0 (1.7)	1666	8.7 (1.8)	1833	8.7 (1.7)
Heart rate, bpm	1867	75.1 (9.8)	1230	67.7 (9.3)	1845	67.8 (9.0)
Alcohol consumption, units/day*	NA	NA	629	0.74 (1.08)	1857	0.92(1.37)
Carotid artery distensibility, %/10 mm Hg	NA	NA	NA	NA	1858	1.85 (0.68)
Pulse wave velocity, m/s	NA	NA	NA	NA	1583	8.28 (1.52)

NA indicates not available at that life stage.
*One unit ≈14 g of alcohol.

Table 2. Association Between Systolic Blood Pressure and Markers of Large Artery Stiffness in Mid-Adulthood

	Pulse wave velocity (m/s)		Carotid distensibility (%/10 mm Hg)	
	Model 1* (n=1977)	Model 2* (n=1532)	Model 1* (n=1858)	Model 2* (n=1791)
	β† (95% CrI)	β† (95% CrI)	β† (95% CrI)	β† (95% CrI)
Accumulated effect	0.59 (0.51 to 0.63)	0.56 (0.49 to 0.63)	−0.18 (−0.22 to −0.15)	−0.13 (−0.16 to −0.10)
Life stages				
Childhood	0.01 (0.0004 to 0.05)	0.01 (0.0004 to 0.05)	−0.01 (−0.04 to −0.0004)	−0.01 (−0.03 to −0.0002)
Young adulthood	0.03 (0.001 to 0.10)	0.03 (0.001 to 0.10)	−0.02 (−0.06 to −0.001)	−0.1 (−0.04 to −0.0004)
Mid-adulthood	0.54 (0.47 to 0.62)	0.51 (0.43 to 0.59)	−0.15 (−0.19 to −0.12)	−0.11 (−0.14 to −0.07)

CrI indicates credible interval.

*Model 1 is adjusted for sex and year of birth. Model 2 is adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate.

†β values are for a 10 mm Hg higher systolic blood pressure.

Figure 2 and Table S3 show the relative weights of SBP at 3-year intervals from 0 to 27 years before outcome measurement. Of the total contribution of SBP on the observed outcomes, the highest contribution was attributed to the time-point of SBP measurement that was concurrent with PWV (relative weights, 43.0%, 95% credible interval [CrI], 13.0%, 68.9%) or cD (relative weights, 32.1%, 95% CrI, 6.6%, 57.9%) measurement.

Sensitivity Analyses

When hypertensive medication use was included in addition to model 2 covariates, the above results were essentially unchanged (data not shown). Sex-stratified analyses are shown in Table S4 and Figure S6. Although there were some differences in the life-stage specific effects and relative weights, mid-adulthood SBP still contributed most to the association with PWV and cD for both male and female participants. When we repeated the BRLM analyses for other components of BP, we found that the association between life course DBP, MAP, and PP with mid-adulthood large artery stiffness was also best described by a relaxed critical period life course model, with mid-adulthood measures contributing most to the total association (Table S5). The results using BP status as a categorical exposure variable are shown in Table S6. Cumulative exposure to elevated or hypertensive BP across the life course was associated with a 1.23 m/s higher PWV (95% CrI, 0.99 to 1.47) and a 0.26 %/10 mm Hg lower cD (95% CrI, −0.36 to −0.17) in mid-adulthood. Consistent with the data for the continuous BP measures, the highest contribution was attributed to having elevated or hypertensive BP in mid-adulthood. Among the participants with normal current SBP, those who indicated use of antihypertensive medication had higher PWV and lower cD than those that did not indicate use of hypertensive medication (mean [SD], PWV: 8.3 [1.3] m/s versus 7.9 [1.3] m/s, P=0.055; cD: 1.8 [0.8] %/10 mm Hg versus 2.0 [0.7] %/10 mm Hg, P=0.06) (Figure S7). When we refitted the BRLMs restricted to the subsample with normal/elevated current SBP (SBP <140 mm Hg in 2007), regardless of antihypertensive medication status, the relative contribution of SBP from earlier in life (i.e., SBP values measured 3 to 27 years prior) to the outcomes became higher and the relative contribution of current SBP (measured concurrent with the outcomes) became lower (Table S7). Among those participants with current SBP <140 mm Hg, the relative contribution attributed to previous SBP measures (i.e., SBP values measured 3 to 27 years before PWV measurement) among the participants who indicated use of hypertensive medication was higher than their counterparts who did not indicate use of hypertensive medication (the sum of relative weights of SBP measures 3 to 27 years before outcome measurement; PWV: 80.7% versus 67.3%; cD: 84.7% versus 80.6%) (Table S7). However, the sample size was low for this analysis and the credible intervals wide for our estimates. Accumulated SBP across multiple time points 3 to 27 years before outcome measurement associated with PWV and cD, regardless of SBP status when PWV and cD were measured (i.e., 2007) (Table S8). When we fitted the BRLMs using the residuals from the regression models that regressed BMI on SBP at each life stage as the main exposure, the results (Table S9) were similar to those shown in Table 2. When we repeated the analyses based on model 2 additionally adjusting for the development of type 2 diabetes, similar results were observed (data not shown).

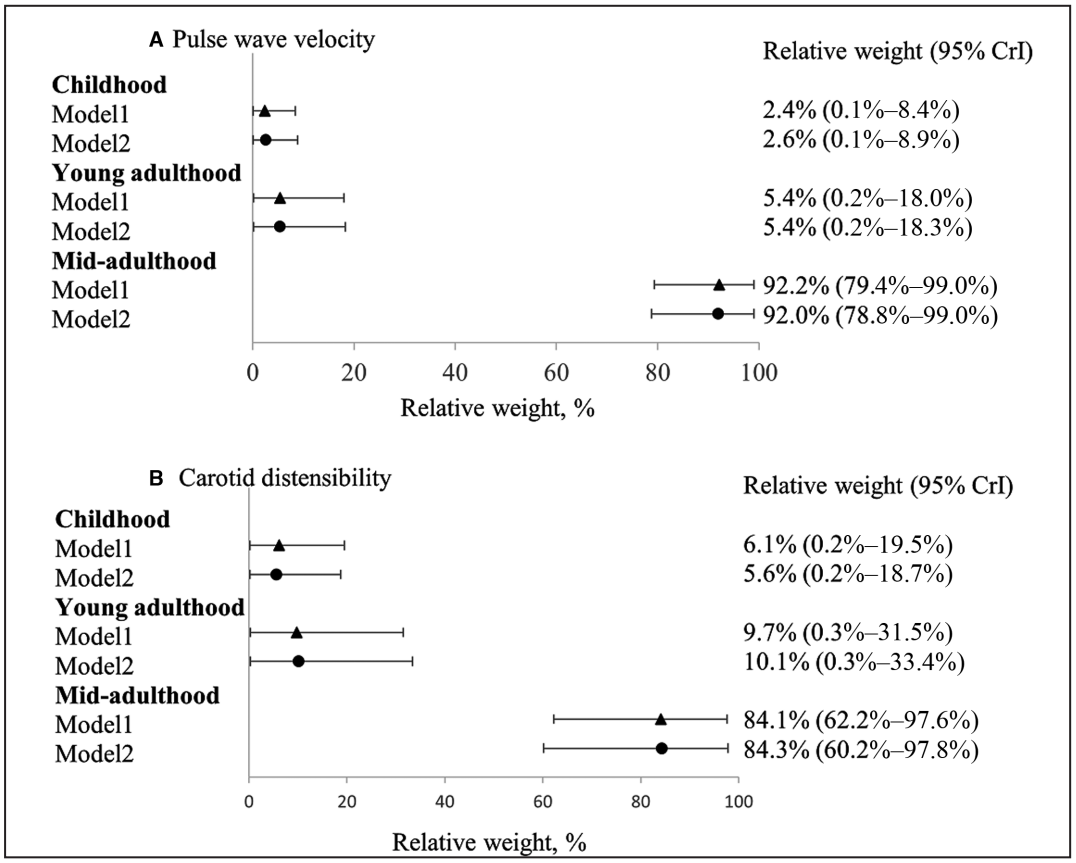

Figure 1. Relative weights and their 95% credible intervals of the association of systolic blood pressure in childhood, young- and mid-adulthood on pulse wave velocity (A) and carotid distensibility (B) in mid-adulthood.

Model 1 (triangles) adjusted for sex and year of birth. Model 2 (circles) adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate. CrI indicates credible interval. Relative weights are expressed for a 10 mm Hg higher systolic blood pressure at each life stage.

DISCUSSION

To our knowledge, this is the first study to use detailed life course modeling to determine the relative contribution of BP exposure from childhood to mid-adulthood (over 27 years) with markers of large artery stiffness in mid-adulthood. The key finding was that mid-adult SBP contributed most (from 84% to 92%) to large artery stiffness in mid-adulthood, with comparatively small contributions from childhood and young-adulthood SBP. Indeed, the relative contribution was greatest the nearer the SBP measurement occurred to the outcome measurement. Findings were consistent by sex, and with other BP components (DBP, MAP, PP), and using BP status as a categorical exposure. These data provide new information about the extent to which life course exposure to BP associates with mid-adulthood large artery stiffness.

Data from the Bogalusa Heart Study reported that the cumulative burden of SBP, calculated as the area under the curve of serial measurements from age 4 to 44 years, was associated with brachial-ankle PWV in adulthood, independent of lipids, BMI, smoking, and age (β for a 1-SD higher cumulative SBP, 0.299 m/s).[35] Although these data are consistent with ours in suggesting life course BP exposure matters to future arterial stiffness, their analyses did not consider the contributions of BP measured at discrete life stages, as we have done. Our finding that mid-adulthood is a critical period when exposure to excess BP is likely to have the greatest contribution to arterial stiffness is consistent with those from 2 time-point analyses in the YFS. Specifically, Aatola et al.[13] found that those with elevated BP status in childhood who were able to resolve to normal BP status by adulthood did not have a significantly increased risk of stiffer arteries than those with normal BP status in both childhood and adulthood.

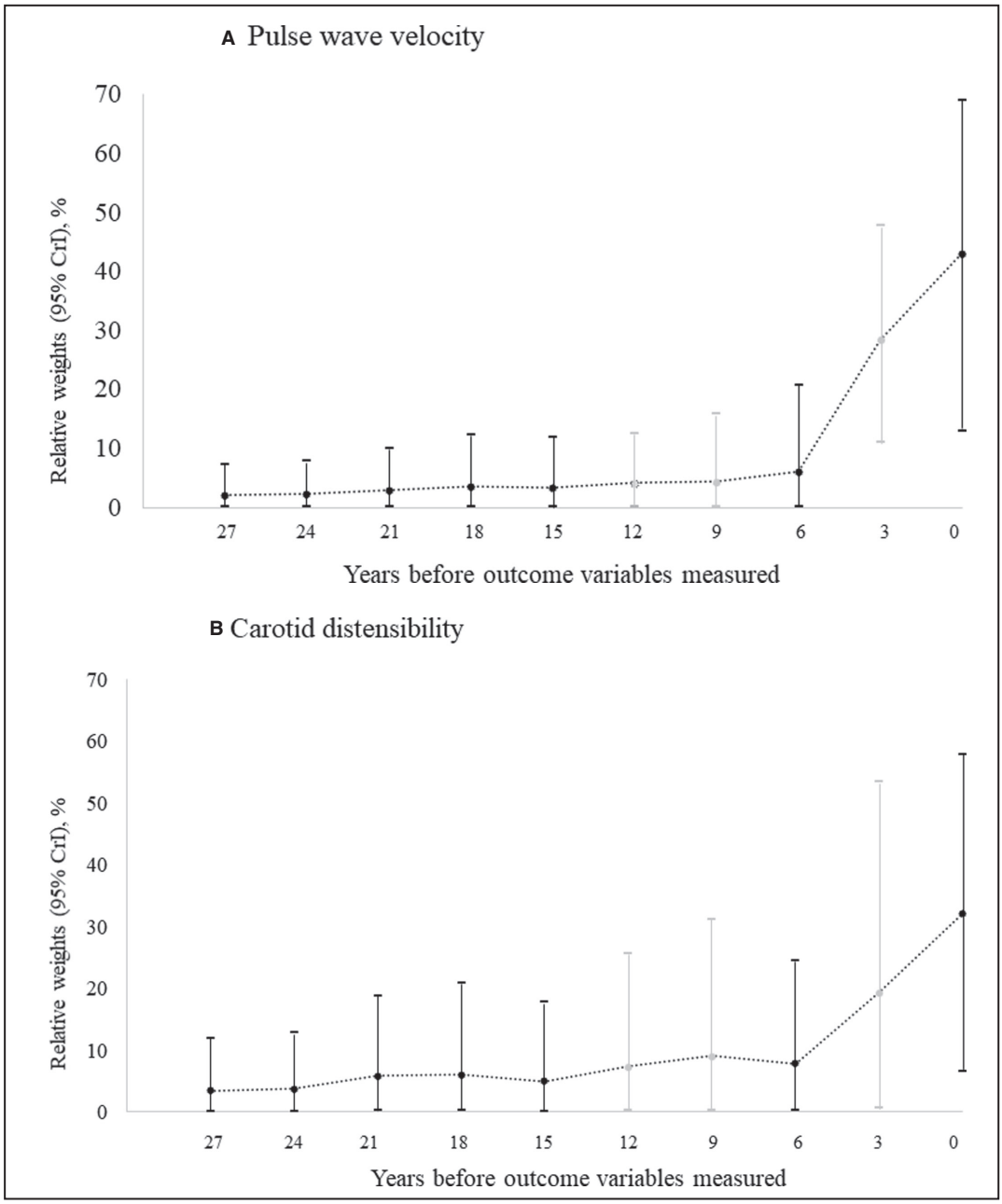

Figure 2. Relative weights and their 95% credible interval of the association of systolic blood pressure at 3-year intervals from 0 to 27 years before outcome measurement in mid adulthood: pulse wave velocity (A), and carotid distensibility (B).

The dots represent the relative weights, error bars indicate the 95% credible interval. Grey represents the estimates derived from the systolic blood pressure values interpolated by the individual growth curve model, black represents the use of a combination of original and interpolated systolic blood pressure measures. Values are from the model adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate. Dashed lines indicate the changing trend of the relative weights as the time point gets closer to when pulse wave velocity, and carotid distensibility were measured. CrI indicates credible interval. Relative weights are expressed for a 10 mm Hg higher systolic blood pressure at each 3-year age interval.

Along similar lines, those who developed incident elevated BP between childhood and adulthood had an increased risk of high adult arterial stiffness. Moreover, Juonala et al.[10] found that adjustment for current SBP measured in adulthood attenuated the association of childhood SBP with adult cD by ≈ 50%. In contrast to

the abovementioned analyses, our models were able to simultaneously account for associations between BP measured across multiple periods in the life course and years before outcome measurement to discern the contribution of different life stages of BP exposure. In the absence of randomized trials conducted over the lifecourse, our observations indicate that mid-adulthood might be a critical window when prevention or intervention of arterial stiffening might be optimized.

A consideration of the life course analysis is that it does not reflect the importance of *indirect* effects of exposure to early-life (childhood and young-adulthood) BP. For example, childhood BP tracks (or persists) with BP measured in middle-age,[21] and once elevated BP is developed it is difficult to reverse.[36] Indeed, ≈ 10% of elevated BP observed in adults is attributable to elevated childhood BP.[37] Moreover, SBP exposure time points before the outcome measures was associated with PWV and cD, regardless of SBP status at the time of outcome measurement (i.e., in 2007) (Table S8). Therefore, the modest estimates of the direct contribution of BP in early life to these outcomes should not be interpreted as downplaying the importance BP has at these earlier stages in life on determining the BP level obtained in mid-adulthood. Additionally, the analyses undertaken do not consider the rate of change or patterns of change in BP across the life course. The "horse-racing" hypothesis posits that the rate of change of risk factors, including BP, could provide predictive utility to the development of disease in later life, independent of its absolute levels at any given time point.[38] The Amsterdam Growth and Health Longitudinal Study showed that participants with stiffer arteries at age 36 years had modest differences in BP earlier in life (age 13 years), and these differences tended to become more pronounced with age, particularly during adulthood, than those with less stiff arteries.[39] These findings suggest that while we identify a critical period in the BP-arterial stiffness relationship in mid-adulthood that could serve to focus preventive efforts, the starting point needs to begin much earlier in life. Moreover, data from the Special Turku Coronary Risk Factor Intervention Project showed that participants with low arterial (carotid and aorta) distensibility in young adulthood had higher systolic BP already in infancy.[40] Public health messaging should continue to focus on maintaining healthy lifestyle choices that include regular exercise and dietary approaches to reduce BP that, based on our findings, might lower large artery stiffness in mid-adulthood.

The mechanism explaining our main finding of a mid-adulthood critical period in the association between BP and arterial stiffness is unclear. Given we observed exposure to SBP levels in the time points closest to measurement of large artery stiffness contributed most to the exposure-outcome association (Figure 2), one explanation is that a functional change in arterial stiffness is more dependent on current risk factor status.[10] Consistent with this explanation are data from intervention studies that show arterial stiffness is rapidly influenced by angiotensin-converting enzyme inhibitors[41] and nitrates.[42] Additionally, the temporal relationship between BP and arterial stiffness could be responsible for the critical period highlighted in this study. That is, changes in arterial stiffness underlying high BP levels differ between early and later life periods.[41] There is likely a unidirectional path from youth BP to follow-up arterial stiffness in contrast with reverse causality (i.e., bidirectional relationship) between BP and arterial stiffness that likely occur later in the lifecourse.[43]

Strengths of our study include the 27-year follow-up period, the relatively large sample size, the availability of 2 markers of large artery stiffness from 2 key arteries and the availability of standardized BP data measured from 3 life stages at up to 7 time points across the life course. Moreover, the analysis used a novel approach to investigate the relative contribution of BP at each life stage and the lifecourse hypothesis that best describes the exposure-outcome association. However, this study had limitations. The first is the impedance cardiography-derived PWV measurements, which is not the gold standard direct measure of carotid-to-femoral PWV. However, in previous studies, PWV values measured by the impedance cardiography method are in agreement with those measured from Doppler ultrasound.[19] Second, it was not possible to determine the contribution of BP measured before age 6 years in our cohort as these data were not available or not collected using standard procedures. However, previous data from a large consortium have suggested that risk factor measurements, including BP, beginning from the age of 9 years tend to exert a measurable difference in the odds of preclinical atherosclerosis.[44] Moreover, the "oldest" age was only age 45 years, we are therefore unable to discount that BP measures after this age in the life course might contribute differently to large artery stiffness measured later in life. The ongoing YFS will be able to provide these data once future follow-ups have been performed. Third, the present study adjusted for lifetime-averaged values for the covariates included in our models as the BRLM does not currently allow for the adjustment of time-varying covariates. Although it would be ideal to include life-stage specific covariates to account for time-varying confounding, results using lifetime-averaged values for the covariates or an approach that considered residuals of the primary exposure variable (covariates regressed on the primary exposure at each life stage) in the BRLMs returned similar results. (Table S9). Adjusting for lifetime-averaged values for covariates has been applied to other situations incorporating the BRLM approach to life course modeling.[26,27] Fourth, because PWV and cD are not available in childhood in the present study, we are unable to establish temporal associations between

BP and large artery stiffness. Fifth, we were unable to examine cardiovascular events in our sample. Instead, we used large artery stiffness, an established cardiovascular risk phenotype,[2] as the outcome of interest. Finally, bias because of 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.[45] There is the potential for bias in BP values including terminal digit preference and variability between observers as BP was measured with a standard mercury sphygmomanometer in 1980 and 1983. However, all BPs were measured by trained nurses and the interobserver reproducibility of BP was satisfactory (correlation coefficient, r: SBP: r=0.72 in 635 paired observations; DBP: r=0.51 in 633 paired observations).[16]

Perspectives

This study found that mid-adulthood BP has the highest contribution to mid-adulthood large artery stiffness, with a comparatively small contribution from BP in early life (childhood and young adulthood). These results suggest that while maintaining a lower BP level at each life stage is the priority, there is a critical age window for controlling high BP levels to reduce the risk of large artery stiffening. Future trials are needed to determine with more certainty when interventions aimed at preventing arterial stiffness by targeting BP could be most effectively implemented.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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SUPPLEMENTAL MATERIAL

Data S1. Additional information about assessment of alcohol consumption, physical activity index and socioeconomic disadvantage

Alcohol consumption

In 2001 and 2007, participants reported their consumption of 1/3 litre cans or bottles of beer, 1/3 litre glasses of wine, and 4 centiliter shots of liquor or strong alcohol during the past week. These amounts are comparable to approximately 14 g of alcohol (=1 unit). The total consumption of different beverages in the last week divided by seven was the daily alcohol consumption.[23] The average value for repeated data measured over all observed time-points was lifetime-averaged daily alcohol consumption and used in this study.

Physical activity index

Data on physical activity was self-reported by participants beginning of age 9 years or older at each study time-point. In 1980-1989, the questionnaire consisted of the variables regarding the frequency and intensity of leisure-time physical activity, participation in sports club training, participation in sport competitions, and habitual way of spending leisure time.[24] In the follow-ups from 1992 ahead, the physical activity questionnaire included five variables regarding the frequency and intensity of physical activity, frequency of vigorous physical activity, hours spent on vigorous physical activity, average duration of a physical activity session, and participation in organized physical activity.[24] The items were coded from 1 to 3 and summed to form a physical activity index with scores at each study time-point.[24] We then averaged the repeated data measured over all study surveys to generate lifetime-averaged value.

Socioeconomic disadvantage

For participants aged 6 to 21 years, socioeconomic disadvantage was determined by their parental education attainment (completed years of schooling for the parent with the highest education), the previous year's family gross income and parental unemployment. For

participants aged 24 to 45 years, socioeconomic disadvantage was determined by the number of years of participant's education (highest level of educational attendance or completed education), participant's annual gross income and participant's unemployment. Both parental and participant's unemployment is a binary variable (yes/no), and those who had ever been unemployed were categorized as unemployment (yes). Indicators regarding education and income were transformed into Z scores (mean=0, standard deviation [SD]=1). Unemployment variables were coded as -1 for ever unemployment and 0 otherwise. For each of the two age periods (i.e., between age 6 and 21 years and between age 24 and 45 years), the sum value of the corresponding three indicators was used to derive the socioeconomic disadvantage score, with a higher score indicating a higher socioeconomic disadvantage period.[25] The lifetime-averaged socioeconomic disadvantage score was the mean of socioeconomic disadvantage scores in these two age periods.

Data S2. Additional details regarding the Bayesian relevant life course exposure model

The Bayesian relevant life course exposure model (BRLM) considers a model of weighted exposure variable for each observed life stage.[28,29] BRLM assumes a weight for the exposure experienced during each life stage and the weight reflects the relative importance of exposure at each life stage at predicting the development of an outcome later in life. The relevant life course exposure is conceptualized as the product of the exposure metric and its corresponding weight over each life period, summed over all life periods. This technique: (i) does not require model/variable selection; (ii) incorporates the hierarchical nature of life course hypotheses; (iii) can be used for both continuous and categorical outcome variables.[28] The life-stage specific weight parameters are estimated using a Bayesian approach. Because in the BRLM the values of the weights inform the life course hypothesis, they are estimated from the data itself, and this allows the estimation of the lifetime effect of the exposure (i.e., the overall effect of relevant exposures accumulated over a person's lifetime). Once the posterior distribution of weights conditioned on a non-informative prior has been estimated using Bayesian inference, these weight distributions can be used to identify the life course hypothesis supported by the data by calculating a measure of the difference between the estimated and expected weight vectors (e.g., Euclidean distance) under a set number of life course hypotheses. The shortest Euclidean distance (Figure S2) identifies the life course hypothesis most supported by the data, without the need for model selection. There was little or no evidence to include prior beliefs on what life course model would best support these data. Therefore, BRLMs were fitted using a non-informative Dirichlet (1, 1, 1) prior for weights and a weekly informative Cauchy prior (0, 2.5) for the lifetime effect. In the present three life-stage (childhood, young-adulthood and mid-adulthood) study, the model assumptions included one accumulation life-course model (all weights =1/3), three critical life -course models (one of the three weights=100% and the other two=0), and one sensitive

model (weight in childhood = 5%, weight in young-adulthood = 20%, weight in mid-adulthood = 75%).

Model diagnostics

Convergence and mixing were assessed using trace plots and Rhat values, autocorrelation was assessed using autocorrelation function plots, identifiability of the parameters were examined using pairs plot, effectiveness of the sampler was assessed using effective sample size Neff metrics.[46] Pair plots display univariate histograms and bivariate scatter plots for selected parameter's estimates and allow to identify collinearity between variables (i.e., narrow bivariate plots) and the presence of multiplicative non-identifiability (i.e., banana-like shaped scatterplots). The effective Sample size Neff represents the amount by which autocorrelation within the chains increases uncertainty in posterior estimates. Diagnostics of the final fitted BRLM model (i.e., model 2) suggested adequate convergence, mixing, and effective sample size and no autocorrelation or identifiability issue (Figure S2 and Figure S3). Results were similar when SBP was replaced with other BP components (data not shown).

Data S3. Individual growth curve model

The individual growth curve (IGC)[30] model is an advanced multilevel regression model that quantifies changes in a variable over time at both the group (population average) and individual level. 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), allowing to estimate inter- and intra-individual changes in the response variable simultaneously. The IGC model also allows the user to specify a linear or non-linear growth trajectory of the response variable that is best supported by the data.

In this study, an IGC model was performed to determine blood pressure (BP) change over the observed life course (from age 6 to 49 years), herein referred to as BP trajectories. Moreover, we added sex and height to the model to determine how they modified the BP trajectory. Parameters (i.e., random intercept, random slope) were estimated using the maximum likelihood method, with models selected according to Akaike's information criterion (AIC) and the likelihood ratio test. After constructing the best fitted model, the individual level BP was extracted from the model and then used to interpolate over ages with missing data.[27] In this regard, the IGC model is a statistical technique that interpolates missing values in a set of observed data measured repeatedly based on the parameters of multilevel linear or non-linear curves. These parameters are determined by both the existing set of data points made within-individual and the mean growth trajectory of the whole sample.

First, an unconditional model was constructed to fit BP as a function of age, with each participant regarded as the random effect. Linear and higher power items of age were added into the analyses sequentially to explore linear and polynomial random intercept and random

slope. To avoid collinearity of age with its higher-order terms, we centred age to the mean (24.3 years). Then, we used the AIC or likelihood ratio test to compare increasingly complex models throughout the unconditional model analyses. After the best fitted unconditional model was determined, we introduced interaction terms of sex and all power terms of age, as well as height and all power terms of age into this model to test if sex and height modified the average BP level of participants' BP trajectories over time. The systolic BP trajectory in our study was best described by an IGC model with quartic age polynomial (age^4) random intercept, cubic age random slope and inclusion of sex and height as modifiers (which significantly improved model fit). The same conclusion was drawn on the optimal IGC model for diastolic BP, mean arterial pressure and pulse pressure. The "Lme4" package of R studio (Version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria) was used to perform the IGC modelling.

Table S1 Design of the Cardiovascular Risk in the Young Finns Study

Year	Age cohorts
1980	3 6 9 12 15 18
1983	6 9 12 15 18 21
1986	9 12 15 18 21 24
1989	12 15 18 21 24 27
1992	15 18 21 24 27 30
2001	24 27 30 33 36 39
2007	30 33 36 39 42 45
2011	34 37 40 43 46 49

Data from the age points highlighted in grey not included in this study.

Table S2. Proportion of participants with optimal, normal, and (or) elevated systolic blood pressure who had used antihypertensive medications

	Used antihypertensive medications year		
Systolic blood pressure (SBP)	2001	2007	2001 or/ and 2007*
2001 (6 years prior to the observed outcomes measured)			
Optimal (SBP<120 mmHg)	1.2% (12/1027)		
Normal or lower (SBP<130 mmHg)	1.9% (27/1418)		
Elevated or lower (SBP<140 mmHg)	2.1% (34/1603)		
2007(time-point when the observed outcomes measured)			
Optimal (SBP<120 mmHg)		3.6% (34/933)	4.3% (36/848)
Normal or lower (SBP<130 mmHg)		5.1% (69/1359)	5.8% (71/1228)
Elevated or lower (SBP<140 mmHg)		6.8% (112/1650)	7.8% (117/1493)

Abbreviation: SBP, systolic blood pressure.

*Used antihypertensive medications at any survey in 2001 or 2007; did not use antihypertensive medications indicate the participants who did not use antihypertensive medications in both 2001 and 2007.

Table S3. Relative weights of the association of systolic blood pressure in between 0 and 27 years in three-year increments before the outcomes were measured and arterial stiffness in mid-adulthood

Years before the outcome measured	Pulse wave velocity	Carotid distensibility
27	2.1% (0.1% to 7.3%)	3.5% (0.1% to 11.9%)
24	2.3% (0.1% to 7.9%)	3.7% (0.1% to 12.8%)
21	2.9% (0.1% to 10.1%)	5.8% (0.2% to 18.7%)
18	3.5% (0.1% to 12.2%)	6.0% (0.2% to 20.8%)
15	3.3% (0.1% to 11.9%)	5.1% (0.1% to17.8%)
12	4.2% (0.1% to 12.4%)	7.4% (0.2% to 25.7%)
9	4.4% (0.1% to 15.8%)	9.1% (0.2% to 31.1%)
6	6.0% (0.1% to 20.6%)	7.8% (0.2% to 24.4%)
3	28.4% (11.0% to 47.7%)	19.4% (0.7% to 53.5%)
0	43.0% (13.0% to 68.9%)	32.1% (6.6% to 57.9%)

Values are relative weights and their 95% credible interval. Values are from the model adjusted for adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate.

Table S4. Association between systolic blood pressure and markers of arterial stiffness in mid-adulthood, stratified by sex

	Pulse wave velocity (m/s)		Carotid distensibility (%/10mmHg)	
	Male (N=681)	Female (N=851)	Male (N=790)	Female(N=1001)
	β (95% CrI)	β (95% CrI)	β (95% CrI)	β (95% CrI)
Accumulated effect	0.58 (0.45 to 0.72)	0.56 (0.48 to 0.65)	-0.13 (-0.18 to -0.10)	-0.14 (-0.18 to -0.10)
Life stages				
Childhood	0.03 (0.001 to 0.10)	0.02 (0.001 to 0.07)	-0.01 (-0.04 to -0.0003)	-0.01 (-0.05 to -0.001)
Young adulthood	0.08 (0.002 to 0.26)	0.03 (0.001 to 0.10)	-0.03 (-0.09 to -0.001)	-0.02 (-0.08 to -0.001)
Mid-adulthood	0.47 (0.31 to 0.61)	0.51 (0.42 to 0.59)	-0.09 (-0.14 to -0.04)	-0.10 (-0.15 to -0.05)

Abbreviations: CrI, credible interval.

β values are per 10 mmHg increase in systolic blood pressure. Values are from the model adjusted for adjusted for year of birth, pack years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate.

Table S5. Association between blood pressure (diastolic blood pressure, mean arterial pressure and pulse pressure) and markers of arterial stiffness in mid-adulthood

	Pulse wave velocity (m/s)		Carotid distensibility (%/10mmHg)	
	β (95% CrI)	Relative weight (95% CrI)	β (95% CrI)	Relative weight (95% CrI)
Diastolic blood pressure	N=1532		N=1791	
Accumulated effect	0.76 (0.64 to 0.89)		-0.20 (-0.25 to -0.15)	
Life stages				
Childhood	0.10 (0.006 to 0.23)	12.7% (0.9% to 27.5%)	-0.02 (-0.07 to -0.001)	11.3% (0.5% to 30.3%)
Young adulthood	0.11 (0.005 to 0.30)	15.0% (0.6% to 39.5%)	-0.04 (-0.11 to -0.002)	22.0% (1.0% to 57.9%)
Mid-adulthood	0.55 (0.39 to 0.68)	72.4% (52.6% to 89.9%)	-0.13 (-0.19 to -0.07)	66.7% (34.3% to 91.8%)
Mean arterial pressure	N=1532		N=1791	
Lifetime effect	0.73 (0.62 to 0.84)		-0.20 (-0.24 to -0.15)	
Life stages				
Childhood	0.09 (0.005 to 0.21)	11.8% (0.7% to 26.8%)	-0.02 (-0.07 to -0.001)	12.3% (0.5% to 30.0%)
Young adulthood	0.07 (0.002 to 0.23)	10.1% (0.3% to 30.3%)	-0.03 (-0.09 to -0.001)	14.6% (0.5% to 43.9%)
Mid-adulthood	0.56 (0.45 to 0.66)	78.1% (59.7% to 94.3%)	-0.14 (-0.19 to -0.10)	73.1% (45.7% to 94.5%)
Pulse pressure	N=1532		N=1791	
Lifetime effect	0.41 (0.28 to 0.55)		0.01 (-0.06 to 0.07)	
Life stages				
Childhood	0.01 (0.0002 to 0.03)	2.2% (0.1% to 8.2%)	0.01 (-0.01 to 0.05)	39.2% (1.2% to 89.9%)
Young adulthood	0.02 (0.001 to 0.08)	5.8% (0.2% to 20.8%)	0.003 (-0.02 to 0.03)	29.4% (0.9% to 81.2%)
Mid-adulthood	0.38 (0.24 to 0.52)	92.0% (76.3% to 99.1%)	-0.001 (-0.04 to 0.02)	31.3% (0.8% to 88.0%)

Abbreviations: CrI, credible interval.

β values are per 10 mmHg increase in blood pressure. Values are from the model adjusted for adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglyceride, socioeconomic disadvantage, physical activity index, and heart rate.

Table S6. Association between elevated and/or hypertensive blood pressure and markers of arterial stiffness in mid-adulthood

	Pulse wave velocity (m/s)		Carotid distensibility (%/10mmHg)	
	β (95% CrI)	Relative weight (95% CrI)	β (95% CrI)	Relative weight (95% CrI)
Elevated or hypertensive BP[*]				
Accumulated effect	1.23 (0.99 to 1.47)		-0.26 (-0.36 to -0.17)	
Life stages				
Childhood	0.06 (0.002 to 0.19)	4.8% (0.2% to 14.7%)	-0.01 (-0.04 to -0.0003)	4.3% (0.1% to14.8%)
Young adulthood	0.28 (0.05 to 0.56)	23.0% (4.0% to 42.1%)	-0.04 (-0.12 to -0.001)	14.6% (0.5% to 41.1%)
Mid-adulthood	0.88 (0.65 to 1.11)	72.2% (53.6% to 91.2%)	-0.21 (-0.30 to -0.12)	81.2% (54.5% to 97.4%)
Hypertensive BP[†]				
Accumulated effect	1.40 (0.96 to 1.86)		-0.37 (-0.62 to -0.15)	
Life stages				
Childhood	0.14 (0.004 to 0.43)	9.6% (0.3% to 27.4%)	-0.06 (-0.18 to -0.002)	17.5% (0.6% to 58.8%)
Young adulthood	0.14 (0.004 to 0.47)	9.8% (0.3% to 29.7%)	-0.10 (-0.32 to -0.003)	27.4% (1.1% to 72.4%)
Mid-adulthood	1.10 (0.77 to 1.43)	80.6% (59.7% to 96.6%)	-0.21 (-0.36 to -0.06)	55.1% (79.2% to 91.3%)

Abbreviations: BP, blood pressure; CrI, credible interval.

Values are from the model adjusted for adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglyceride, socioeconomic disadvantage, physical activity index, heart rate.

[*] The categories of elevated and hypertensive BP were combined and then applied to the models. That is, systolic BP/diastolic BP ≥ 120/80 mmHg for childhood, systolic BP/diastolic BP ≥130/85 mmHg for young adulthood and mid-adulthood.

[†] Hypertensive BP was defined as systolic BP/diastolic BP ≥130/80 mm Hg for childhood, systolic BP/diastolic BP ≥ 140/90 mmHg for young adulthood and mid-adulthood.

Table S7. Relative weights of the association of systolic blood pressure in between 0 and 27 years in three-year increments before the outcomes were measured and arterial stiffness among the participants with normal/elevated current systolic blood pressure (systolic blood pressure <140 mmHg in 2007), stratified by taking antihypertensive medications and without antihypertensive medications

Years before the outcome measured	Pulse wave velocity		Carotid distensibility	
	With antihypertensive medications (n=99)	Without antihypertensive medications (n=1154)	With antihypertensive medications (n=111)	Without antihypertensive medications (n=1348)
27	6.5% (0.1% to 28.6%)	4.1% (0.1% to 13.9%)	5.9% (0.3% to 17.3%)	4.7% (0.1% to 16.5%)
24	6.7% (0.2% to 27.2%)	5.8% (0.2% to 18.3%)	6.9% (0.3% to 31.3%)	7.3% (0.2% to 23.4%)
21	7.7% (0.2% to 26.8%)	4.7% (0.1% to 15.6%)	8.9% (0.3% to 33.1%)	8.7% (0.2% to 27.3%)
18	9.3% (0.3% to 31.5%)	7.4% (0.2% to 24.8%)	11.0% (0.3% to 33.7%)	8.5% (0.2% to 28.6%)
15	9.1% (0.3% to 31.3%)	6.0% (0.2% to 20.9%)	10.0% (0.3% to 33.5%)	6.7% (0.2% to 23.6%)
12	10.1% (0.3% to 33.8%)	8.2% (0.2% to 28.9%)	11.1% (0.1% to 33.8%)	9.3% (0.3% to 31.8%)
9	10.7% (0.3% to 36.7%)	6.6% (0.1% to 22.1%)	8.0% (0.3% to 15.8%)	10.8% (0.3% to 35.2%)
6	9.7% (0.4% to 36.4%)	10.5% (0.3% to 35.9 %)	10.0% (0.1% to 33.6%)	9.5% (0.3% to 30.6%)
3	10.7% (1.0% to 38.6%)	13.8% (2.5% to 65.9%)	12.4% (11.0% to 34.3%)	15.4% (0.6% to 49.4%)
0	19.3% (1.0% to 40.9%)	32.7% (2.5% to 65.9%)	15.3% (1.0% to 34.1%)	19.4% (0.8% to 44.4%)

Values are relative weights and their 95% credible interval. Values are from the model adjusted for adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate.

Table S8. Association of systolic blood pressure in between 3 and 27 years in three-year increments before the outcomes and arterial stiffness, stratified by systolic blood pressure status at the same time-point when arterial stiffness was measured

Years before the outcome measured	Pulse wave velocity (m/s)				Carotid distensibility (%/10mmHg)			
	Normal SBP* (n=1134)		Elevated /high SBP* (n=398)		Normal SBP* (n=1321)		Elevated /high SBP* (n=470)	
	Lifetime effect β(95% CrI)	Relative weight (95% CrI),%	Lifetime effect β(95% CrI)	Relative weight (95% CrI),%	Lifetime effect β(95% CrI)	Relative weight (95% CrI), %	Lifetime effect β(95% CrI)	Relative weight (95% CrI), %
Lifetime	0.44 (0.31, 0.56)		0.58 (0.36, 0.79)		-0.07 (-0.10, -0.02)		-0.09 (-0.2, -0.02)	
27		3.3% (0.1% to 11.3%)		5.7% (0.2% to 19.0%)		7.6% (0.2% to 26.5%)		8.1% (0.2% to 27.2%)
24		5.1% (0.1% to 16.0%)		8.2% (0.3% to 25.8%)		8.2% (0.2% to 27.6%)		7.8% (0.2% to 27.1%)
21		4.3% (0.1% to 14.3%)		4.7% (0.1% to 17.2%)		11.9% (0.3% to 37.1%)		9.5% (0.3% to 32.0%)
18		6.3% (0.1% to 21.8%)		8.1% (0.2% to 28.6%)		10.5% (0.3% to 35.1%)		10.4% (0.2% to 34.6%)
15		5.1% (0.3% to 18.5%)		9.6% (0.3% to 32.9%)		9.1% (0.3% to 31.5%)		9.6% (0.3% to 33.1%)
12		7.5% (0.2% to 26.9%)		10.7% (0.3% to 36.5%)		11.3% (0.3% to 37.4%)		11.5% (0.3% to 37.7%)
9		9.9% (0.3% to 35.4%)		13.1% (0.1% to 22.1%)		12.5% (0.4% to 40.5%)		12.6% (0.4% to 40.8%)
6		17.9% (1.0% to 20.1%)		6.7% (0.4% to 42.5 %)		11.5% (0.4% to 36.4%)		12.9% (0.4% to 40.0%)
3		40.5% (1.7% to 78.2%)		33.0% (2.4% to 67.8%)		17.4% (0.6% to 50.6%)		17.6% (0.6% to 51.5%)

Abbreviations: CrI, credible interval; SBP, systolic blood pressure

β values are per 10 mmHg increase in SBP. Values are from the model adjusted for adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglyceride, socioeconomic disadvantage, physical activity index, heart rate.

* The categories of elevated and high SBP were SBP≥130 mmHg; The categories of normal SBP were SBP<130 mmHg.

Table S9. Association between systolic blood pressure and markers of arterial stiffness in mid-adulthood

	Pulse wave velocity (m/s)		Carotid distensibility (%/10mmHg)	
	β (95% CrI)	Relative weight (95% CrI)	β (95% CrI)	Relative weight (95% CrI)
Standard model*				
Accumulated effect	0.63 (0.50, 0.70)		-0.18 (-0.23 to -0.14)	
Life stages				
Childhood	0.01 (0.001 to 0.07)	3.0% (0.1% to 10.1%)	-0.02 (-0.06, -0.0007)	9.0% (0.4% to 31.9%)
Young adulthood	0.04 (0.001 to 0.14)	6.3% (0.2% to 21.0%)	-0.03 (-0.11 to -0.001)	15.5% (0.6% to 54.5%)
Mid-adulthood	0.58 (0.50 to 0.67)	90.7% (75.7% to 98.8%)	-0.12 (-0.18 to -0.01)	75.5% (36.7% to 94.0%)
Residual model†				
Accumulated effect	0.64 (0.50 to 0.70)		-0.20 (-0.24 to -0.15)	
Life stages				
Childhood	0.01 (0.001 to 0.05)	2.2% (0.1% to 8.0%)	-0.01 (-0.04 to -0.0002)	5.0% (0.1% to 17.4%)
Young adulthood	0.09 (0.01 to 0.33)	14.0% (0.2% to 49.4%)	-0.03 (-0.09 to -0.002)	18.2% (0.8% to 50.5%)
Mid-adulthood	0.54 (0.50, 0.70)	84.3% (50.0% to 95.6%)	-0.15 (-0.21 to -0.07)	77.0% (42.7% to 96.9%)

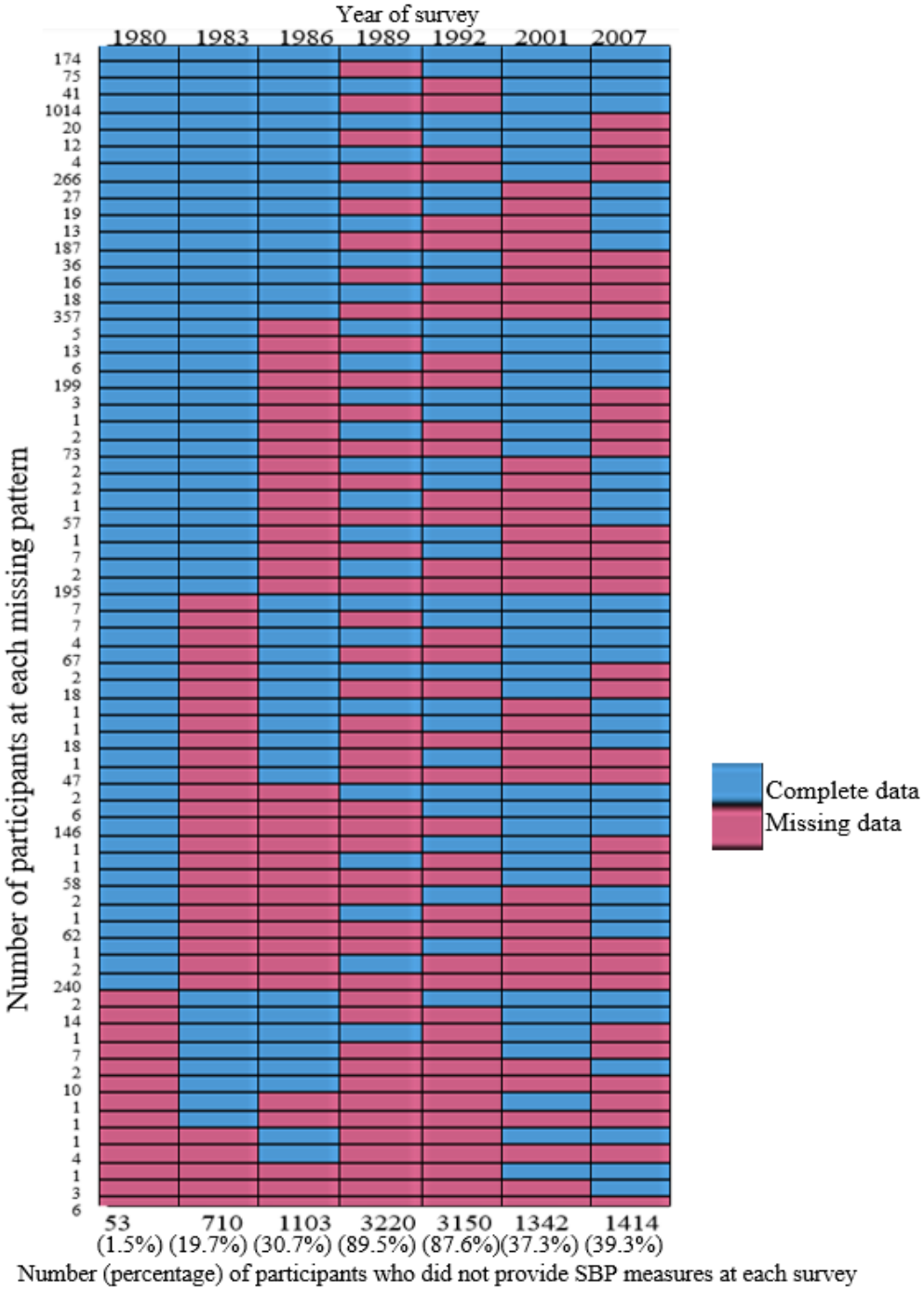
Abbreviations: CrI, credible interval.

β represents per 10 mmHg increase in systolic blood pressure.

* Standard model is adjusted for sex, year of birth, and lifetime-averaged values for body mass index, in which the mean of systolic blood pressure at each life stage is the primary exposure variable.

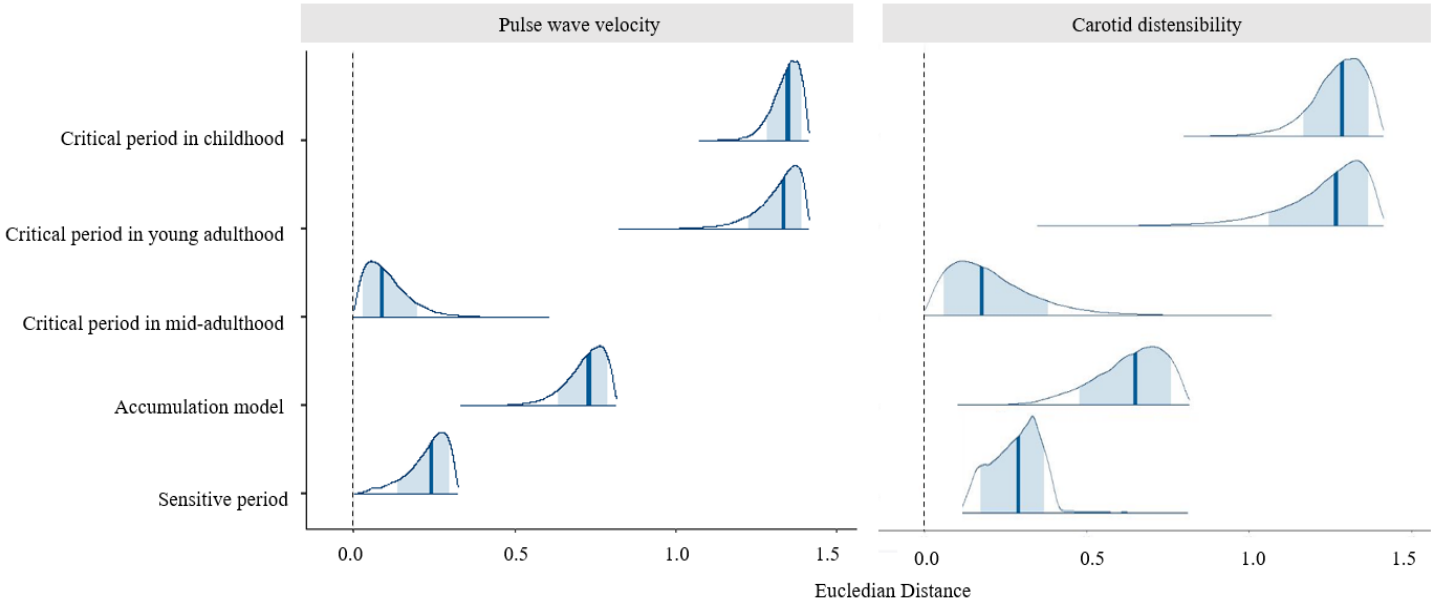
† Residual model is adjusted for sex, year of birth. Residual model uses the residuals from a regression analysis at each life stage as the primary exposure, in which systolic blood pressure regressed on body mass index.

Figure S1. Pattern of missing systolic blood pressure in the Cardiovascular Risk in Young Finns Study from 1980 to 2007.



Vertical axis represents the number of participants at each pattern of missing SBP from 1980 to 2007. For example, 174 participants had complete data across all surveys. Horizonal axis at the bottom represents the number (%) of participants did not provide SBP measurements at specific survey. For example, 53 participants did not have SBP measurements in 1980.

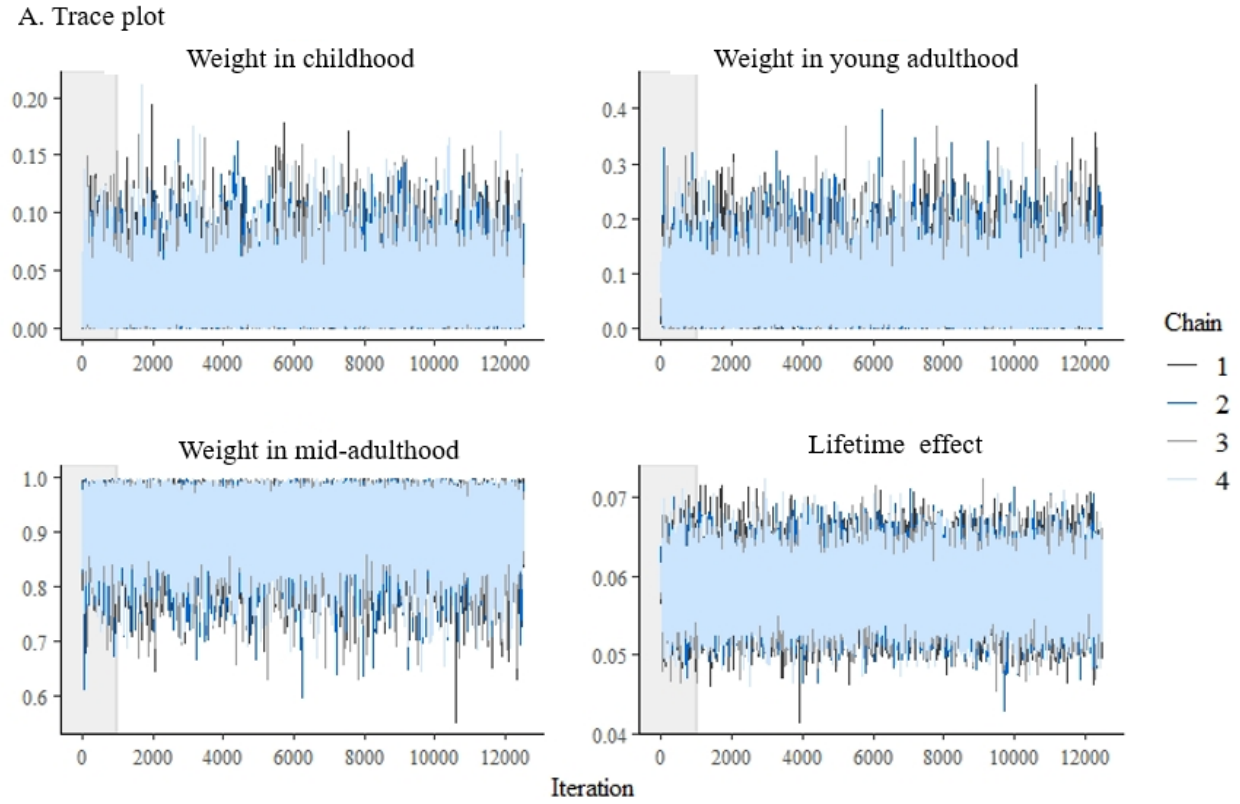
Figure S2. Median and 80% credible intervals of posterior distributions of Euclidean distance under three life-course scenarios.

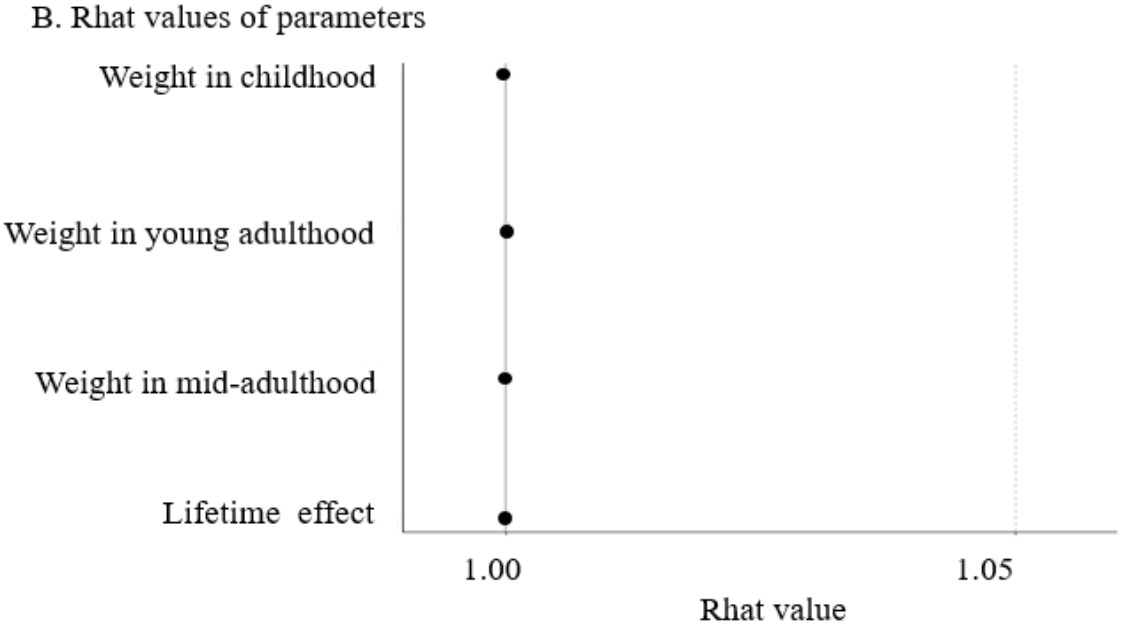


The vertical solid line represents the median, the blue area represents the 80% credible interval.

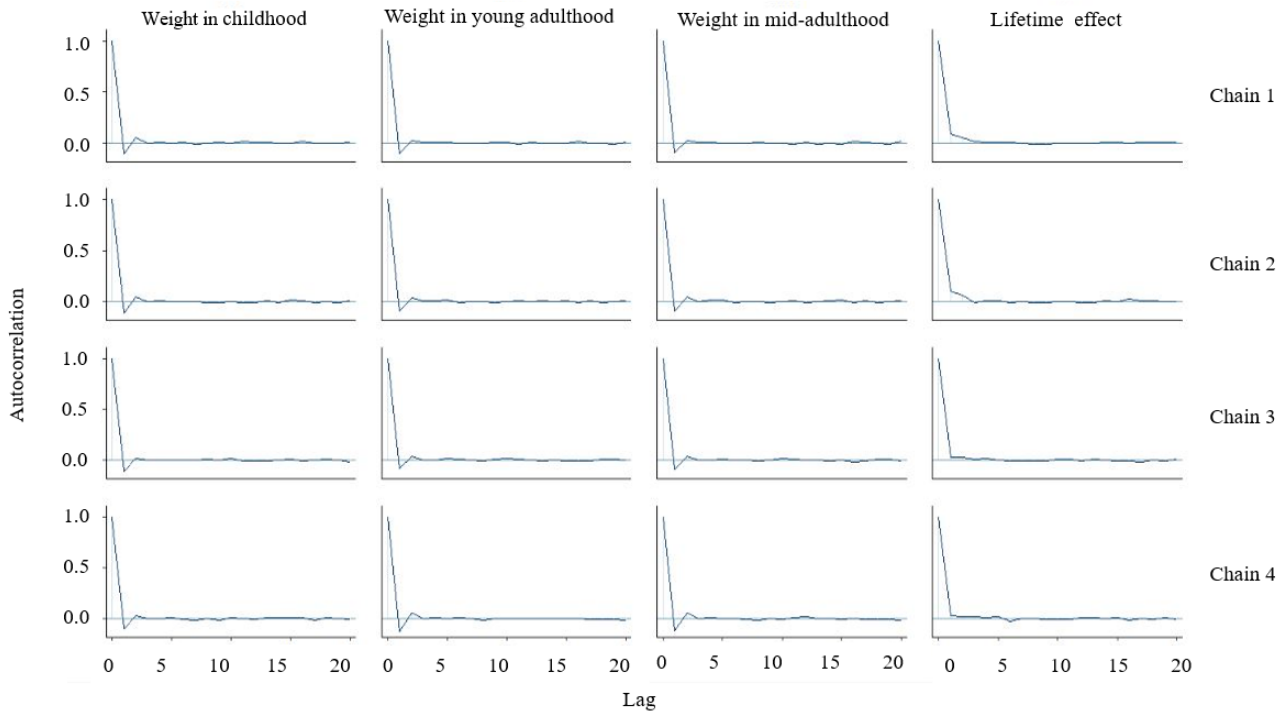
The Y axis shows the following reference vectors to estimated weights: critical period in childhood (weight in childhood=100%, weight in young adulthood=0, weight in mid-adulthood=0); critical period in young adulthood (weight in childhood=0, weight in young adulthood=100%, weight in mid-adulthood=0); critical period in mid-adulthood (weight in childhood=0, weight in young adulthood=0, weight in mid-adulthood=100%); accumulation model (weight in childhood=weight in young adulthood=weight in mid-adulthood=1/3); sensitive period (weight in childhood=5%, weight in young adulthood=20%, weight in mid-adulthood=75%).

Figure S3. Diagnostics of the Bayesian relevant life course exposure model for systolic blood pressure and pulse wave velocity.

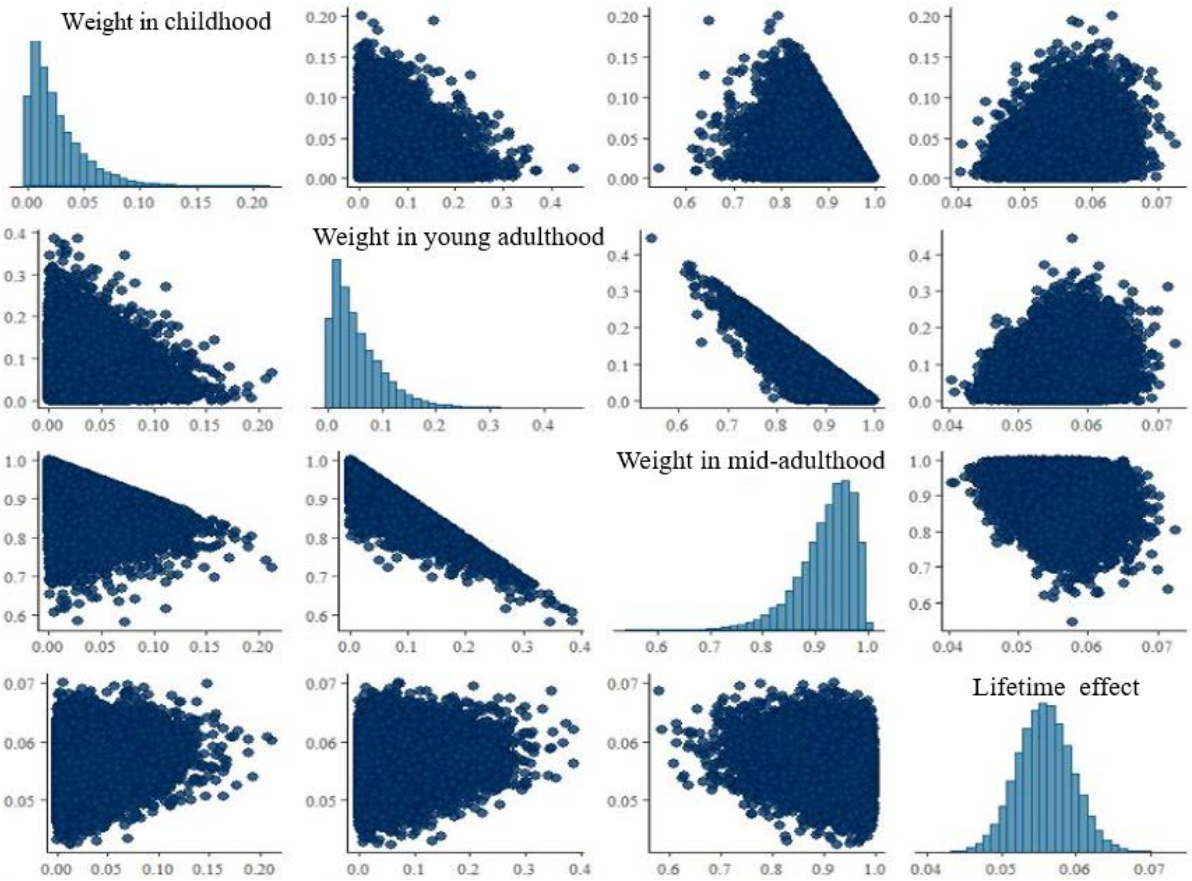




C. Autocorrelation function plots



D. Identifiability



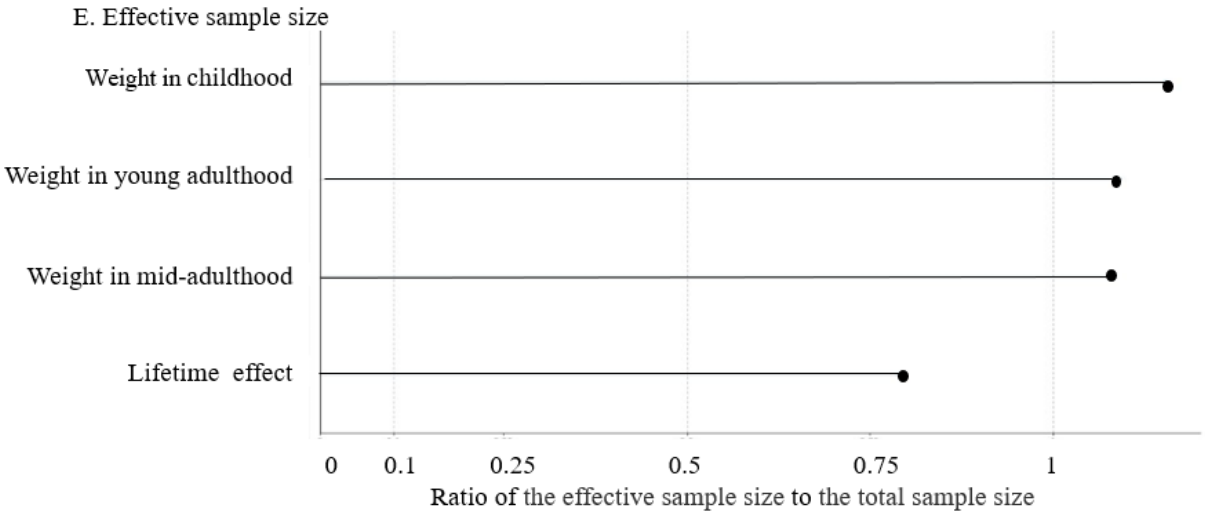
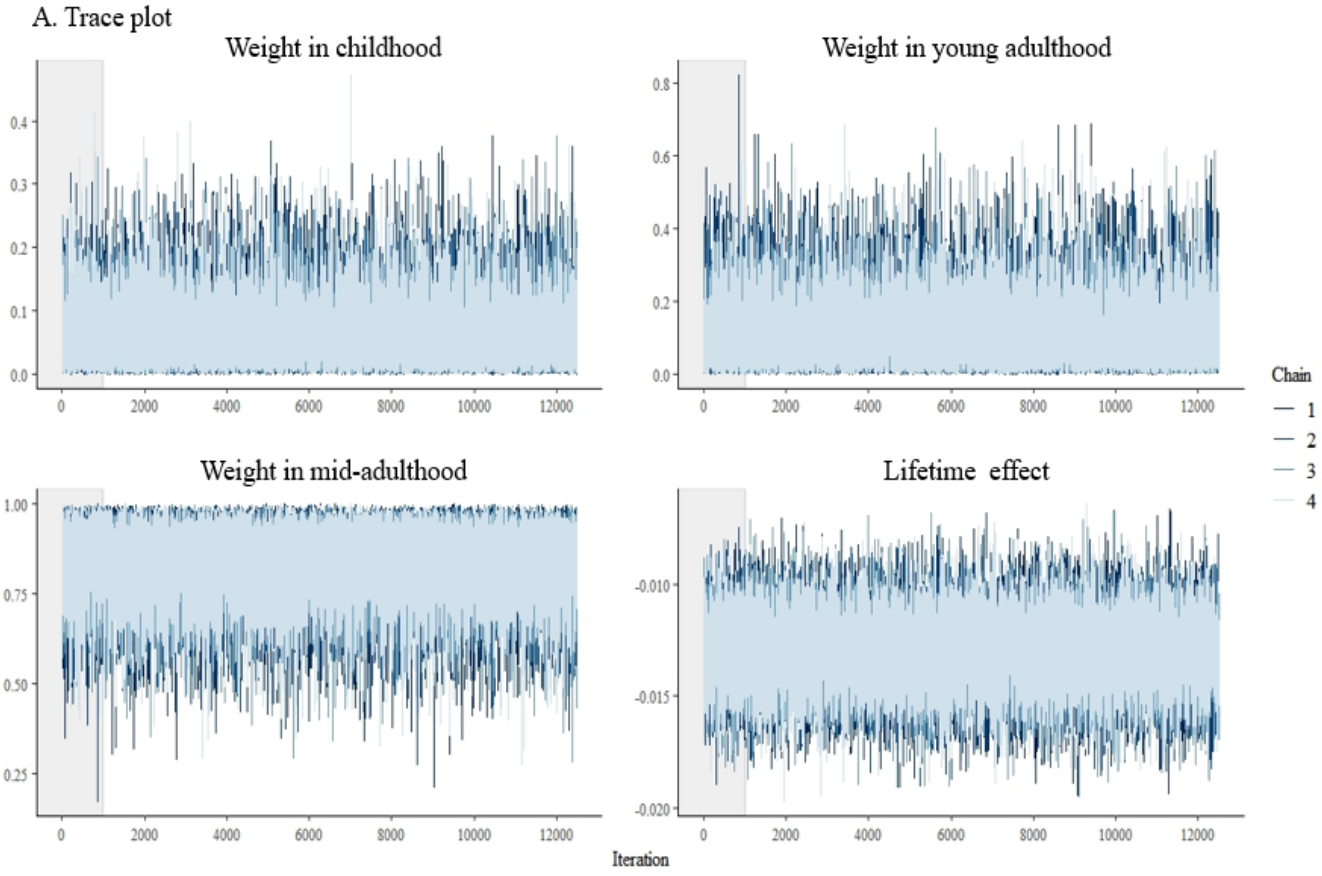
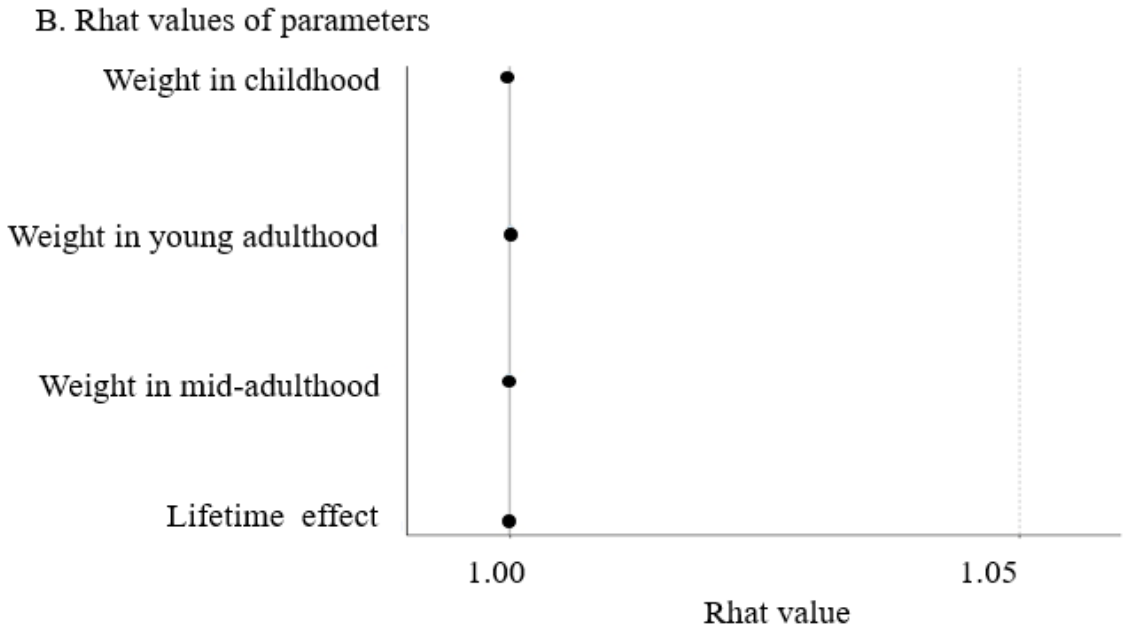
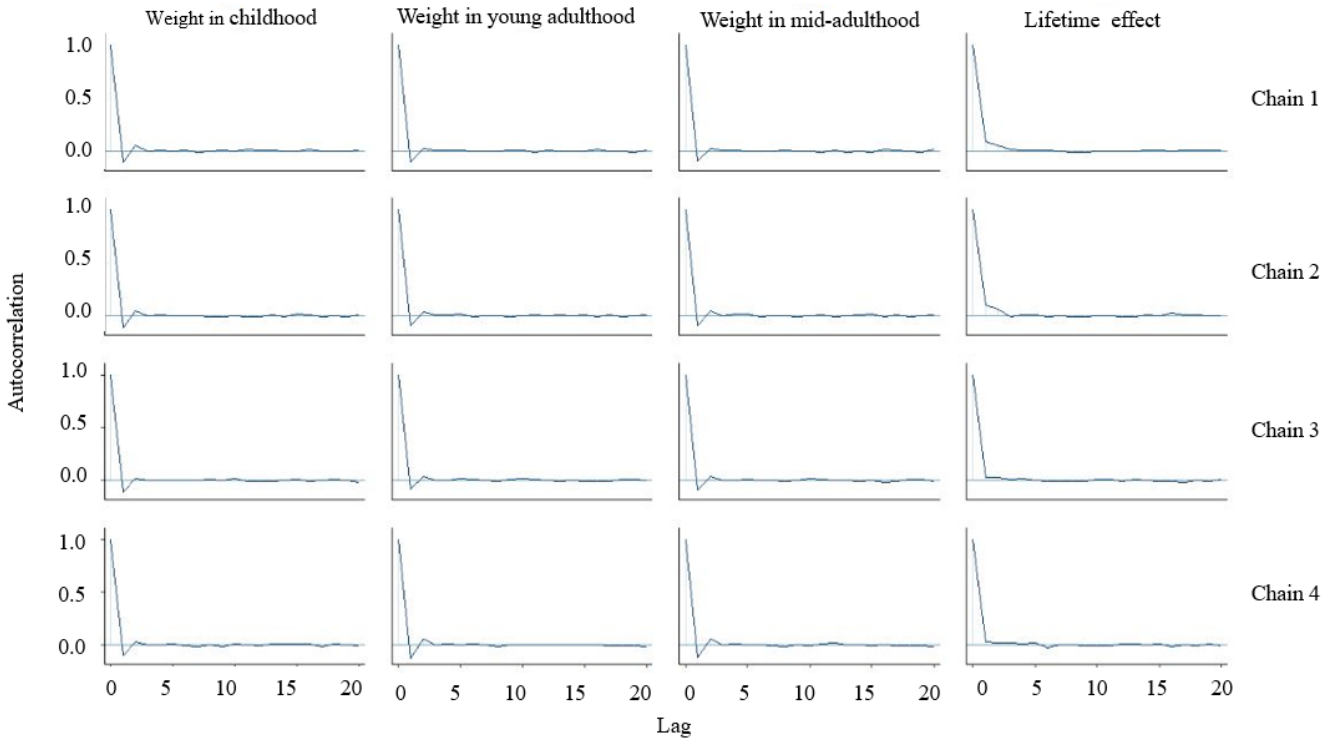

E. Effective sample size
Weight in childhood
Weight in young adulthood
Weight in mid-adulthood
Lifetime effect
0
0.1
0.25
0.5
0.75
1
Ratio of the effective sample size to the total sample size

Figure S4. Diagnostics of the Bayesian relevant life course exposure model for systolic blood pressure and carotid distensibility.

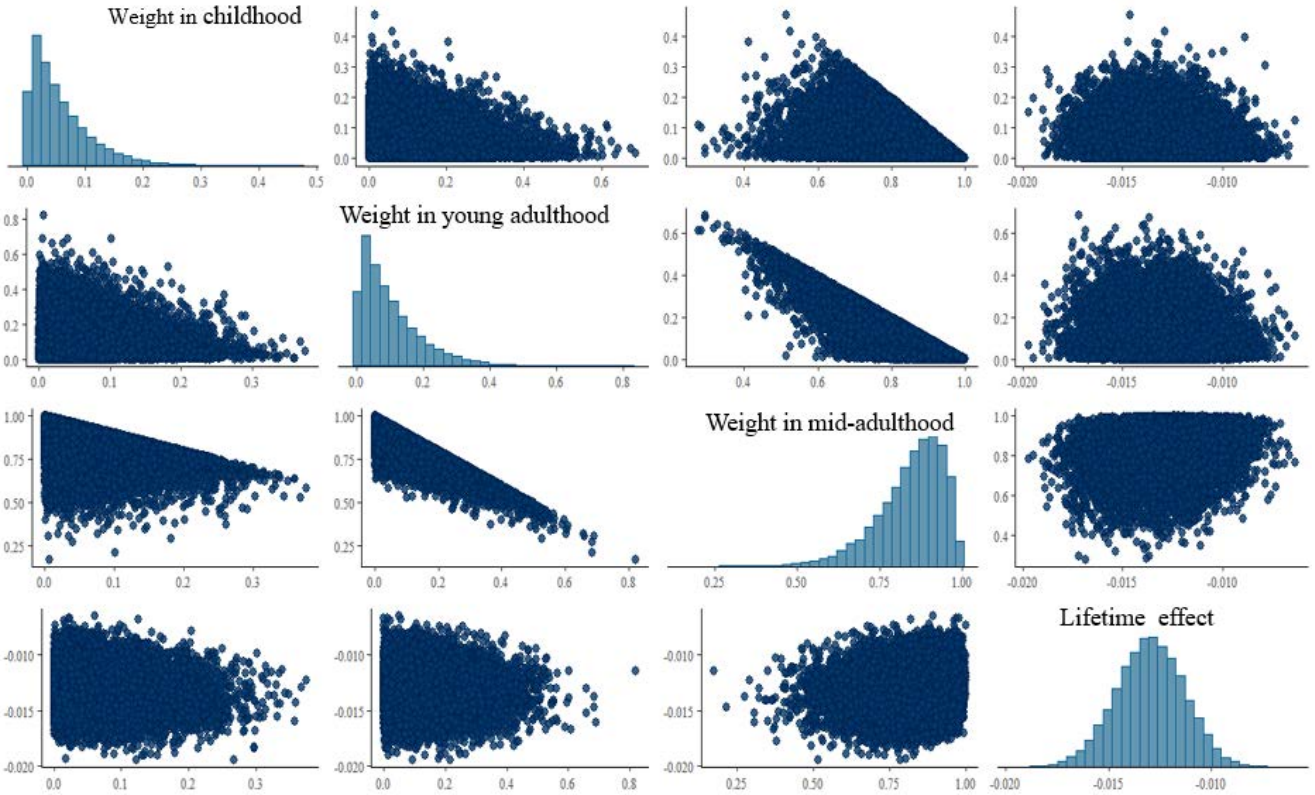




C. Autocorrelation function plots



D. Identifiability



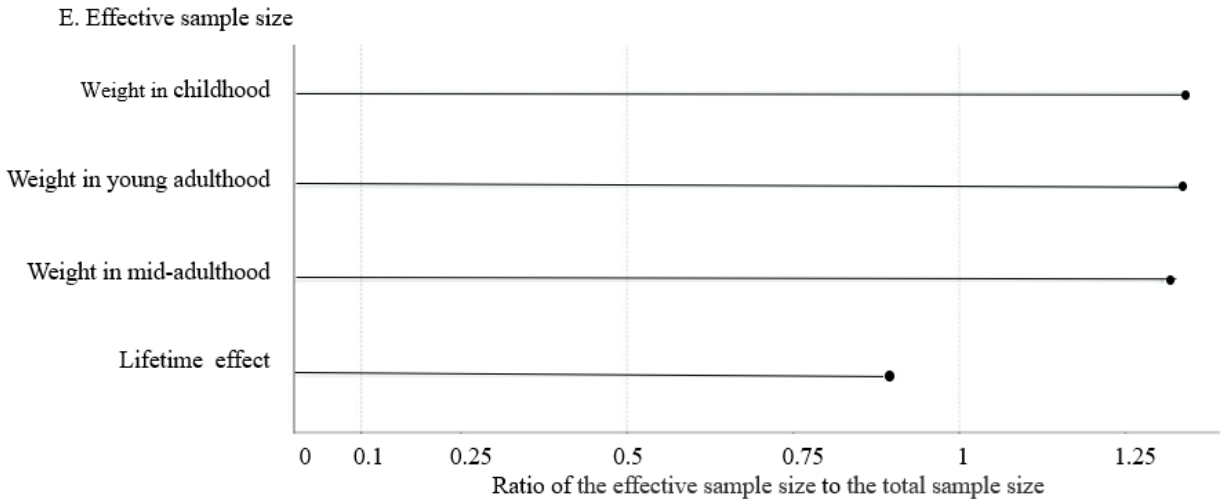
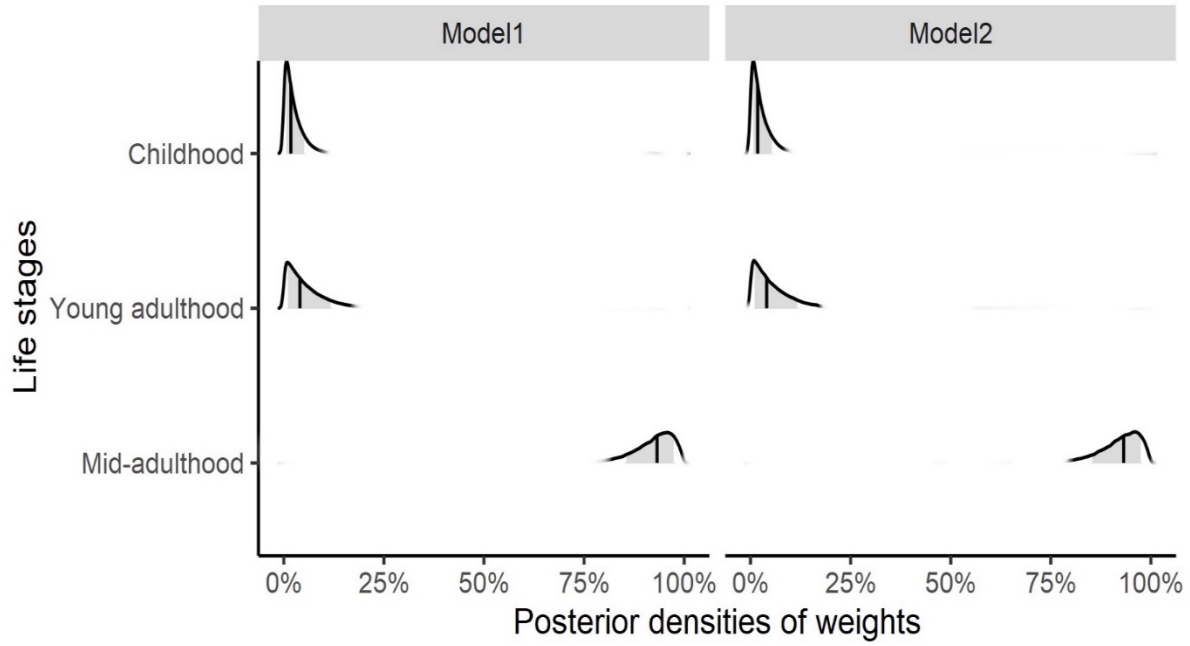
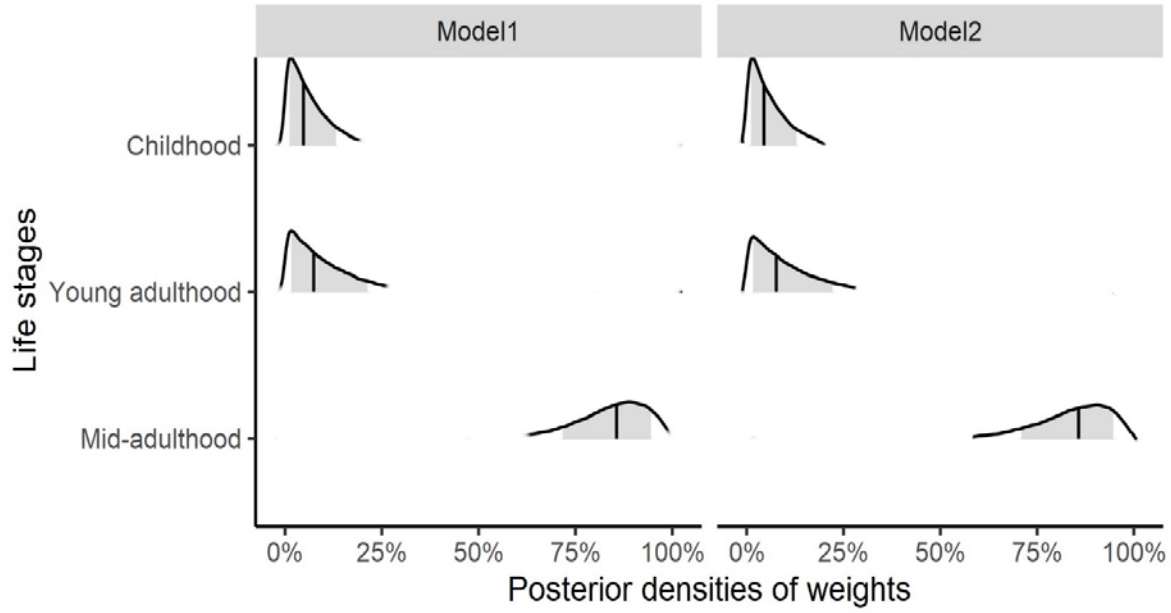

E. Effective sample size
Weight in childhood
Weight in young adulthood
Weight in mid-adulthood
Lifetime effect
0
0.1
0.25
0.5
0.75
1
1.25
Ratio of the effective sample size to the total sample size

Figure S5. Posterior densities of relative weights for exposure to systolic blood pressure in childhood, young adulthood and mid-adulthood for pulse wave velocity (A) and carotid distensibility (B) in mid-adulthood.

A. Pulse wave velocity

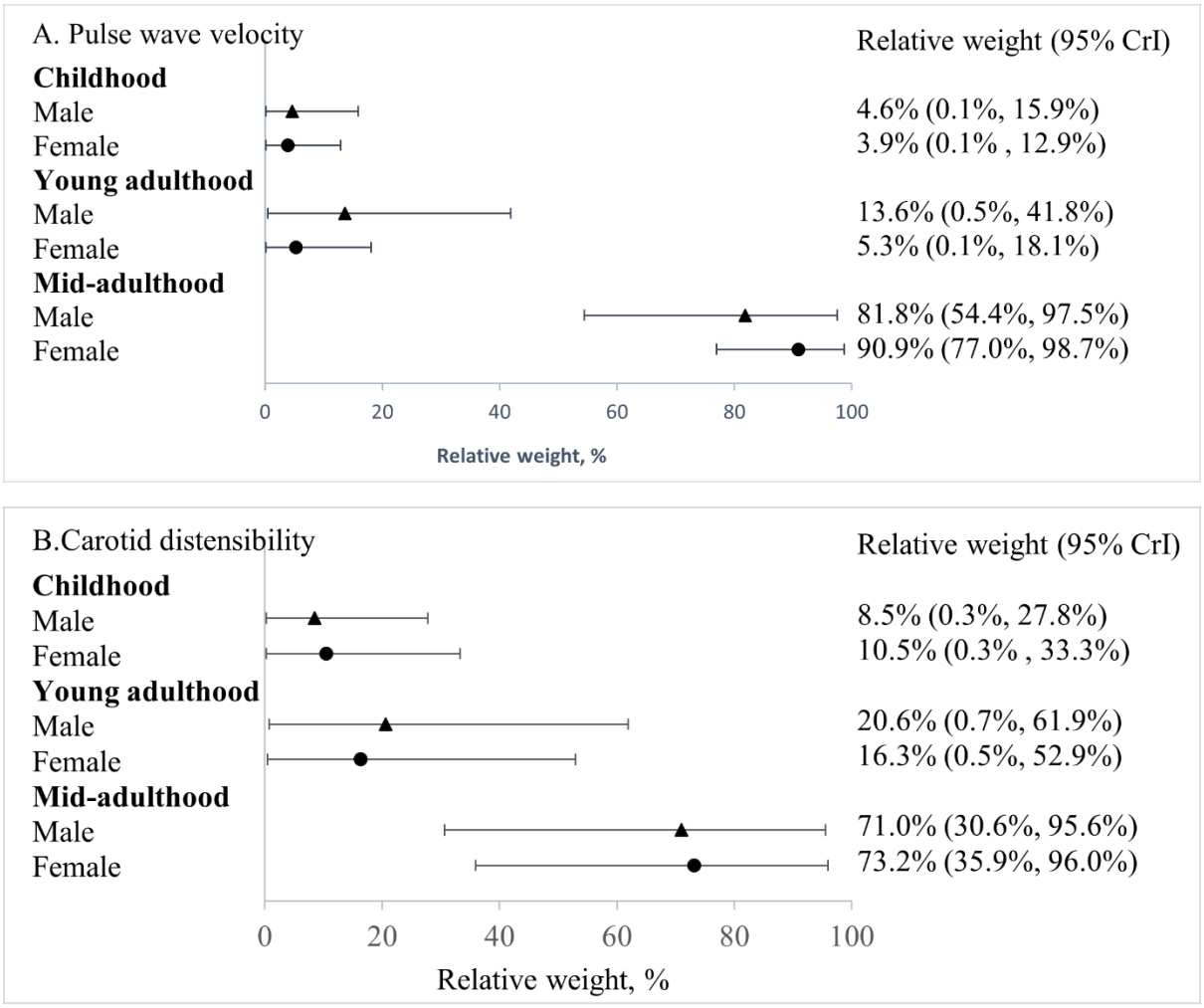


B. Carotid distensibility



The vertical solid line represents the median, the grey area represents the 80% credible interval. Model 1 is adjusted for sex and year of birth. Model 2 is adjusted for sex, year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate.

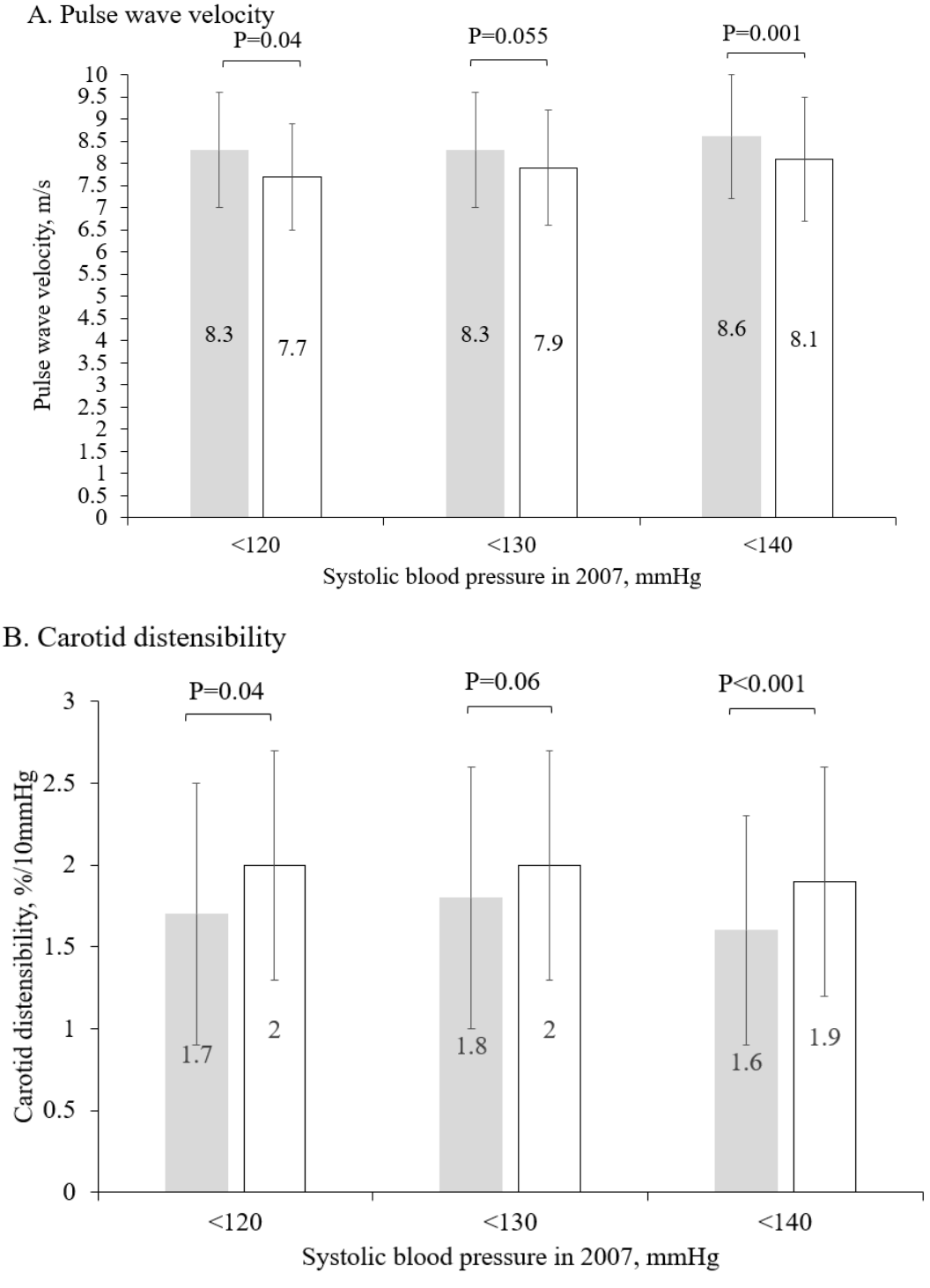
Figure S6. Relative weights and their 95% credible intervals of the association of systolic blood pressure in childhood, young adulthood and mid-adulthood on pulse wave velocity (A) and carotid distensibility (B) in mid-adulthood, stratified by sex.



Abbreviation: CrI, credible intervals.

The triangles represent the relative weight point estimates for males and the dots represent the relative weight point estimates for females; error bars and brackets indicate the 95% credible interval. Values are from the model adjusted for year of birth, pack-years of smoking, alcohol consumption, body mass index, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, socioeconomic disadvantage, physical activity index, and heart rate.

Figure S7. Comparisons of arterial stiffness between the participants with antihypertensive medications (either in 2001 or 2007) and those who without antihypertensive (neither 2001 nor 2007) medications, among the participants without hypertensive systolic blood pressure (<140 mmHg) in 2007 (concurrent with the arterial stiffness measurements).



Grey bars and the values inside represent the mean of pulse wave velocity (A) and carotid distensibility (B) among the participants taking antihypertensive medications. Blank bars and the values inside represent the mean of pulse wave velocity and carotid distensibility among the participants without antihypertensive medications. Error bars represent standard

deviations. P values were derived from the logistic regressions adjusted for sex and year of birth.