Original Article

Childhood to Early-Midlife Systolic Blood Pressure Trajectories

Early-Life Predictors, Effect Modifiers, and Adult Cardiovascular Outcomes

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Abstract—Previous studies examining blood pressure change over time have modeled an average population trajectory. Recent research among older adults suggests there may be subgroups with different blood pressure trajectories. Identifying subgroups at risk of developing adult hypertension early in life can inform effective risk reduction efforts. We sought to identify different systolic blood pressure trajectories from childhood, their correlated risk factors, and early-midlife cardiovascular outcomes. Blood pressure data at ages 7, 11, 18, 26, 32, and 38 years from a longitudinal, representative birth cohort study (n=975) were used to identify 4 distinct trajectory groups via group-based trajectory modeling: normal (21.8%), high-normal (43.3%), prehypertensive (31.6%), and hypertensive (4.2%). The categories refer to blood pressure beginning at the age of 7 years and most recently measured at the age of 38 years. Family history of high blood pressure (OR [odds ratio], 43.23; 95% CI [confidence interval], 5.27–354.65), male sex (OR, 109.48; 95% CI, 26.82–446.96), being first born (OR, 2.5; 95% CI, 1.00–8.69) and low birth weight (OR, 2.79; 95% CI, 2.49–3.09) were associated with hypertensive group membership (compared with the normal group). Higher body mass index and cigarette smoking resulted in increasing blood pressure across trajectories, particularly for the higher blood pressure groups. Prehypertensive and hypertensive trajectory groups had worse cardiovascular outcomes by early midlife. Harmful blood pressure trajectories are identifiable in childhood, associated with both antecedent and modifiable risk factors over time, and predict adult cardiovascular disease risk. Early detection and subsequent targeted prevention and intervention may reduce the lifecourse burden associated with higher blood pressure. **(*Hypertension*. 2015;66:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05831.)** ● **Online Data Supplement**

Key Words: blood pressure ■ follow-up studies ■ hypertension ■ pediatrics ■ risk factor

High blood pressure in adulthood is a leading cause of morbidity and mortality, a major modifiable risk factor for cardiovascular disease, and associated with other cardiovascular risk factors, including impaired glucose tolerance, obesity, and dyslipidemia.[1] The standard approach of treating high blood pressure in middle and old-age can help mitigate these risks, but considerable burden remains. An approach that identifies those at greatest risk of developing high blood pressure much earlier in life could permit more effective risk reduction via earlier, age-appropriate prevention and intervention strategies.

In this context, universal routine screening to identify children at risk of developing high blood pressure in adulthood has been recommended by some organizations.[2,3] However, in 2013 the US Preventive Services Task Force concluded that current evidence was insufficient to assess the balance of benefits and harms of screening for primary hypertension in children and adolescents.[4] Proponents of universal screening note that blood pressure levels track from childhood to adulthood and that children with elevated blood pressure are more likely to develop hypertension in adulthood compared with children with low blood pressure.[5,6] Importantly, hypertension is often asymptomatic and elevated blood pressure is associated with organ damage and changes in cardiac structure in children.[7] However, critics of universal screening argue that (1)

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the correlations between child and adult blood pressure levels are too weak[8] (with blood pressure percentiles for children and adolescents used to define normative values not based on later cardiovascular risk)[9] and (2) that further research is needed examining the longitudinal association between childhood blood pressure, adult hypertension, and cardiovascular disease.[4]

Because of conflicting recommendations, clinicians need better information for medical decision-making around risk assessment and potential intervention options. Prospective-epidemiological studies can provide such information. Recent longitudinal research suggests that there may be subgroups with differential blood pressure trajectories among older populations.[5] If there is developmental heterogeneity in blood pressure trajectories over time then (1) it should be theoretically possible to identify early in life, groups of people at greatest risk of developing high or clinically significant blood pressure in adulthood and (2) the investigation of risk factors that differentiate between healthy and unhealthy trajectories is an important objective.

A burgeoning body of evidence points to a range of early-life predictors of high blood pressure in adulthood. These include intrauterine (eg, low birth weight,[10] being first born,[11] and maternal pregnancy hypertension[12]), postnatal (eg, not being breastfed),[13] familial (eg, family history of high blood pressure),[14] and psychosocial factors (eg, childhood low socioeconomic status).[15] Males are significantly more likely to have higher blood pressure than females from childhood to midlife.[16]

Identification of factors that modify high blood pressure development from childhood to adulthood may help clinicians to stage age-appropriate interventions. Excess body weight is an established risk factor for high blood pressure, and increases in body mass index (BMI) have been associated with higher blood pressure tracking from childhood to adulthood.[17] Other potentially modifiable risk factors include excess alcohol consumption[18] and cigarette smoking[19]; however, studies have mostly been cross sectional, or among older cohorts.

To date, researchers have commonly resorted to using assignment rules based on subjective categorization criteria (eg, 95th percentile) to test taxonomical theories about normal versus pathological development. In this study, advanced longitudinal methods were applied to test the hypothesis that blood pressure changes are best understood via the investigation of subgroups within the population that differ in their rate of blood pressure increase over time. Although relatively new to health research, advanced longitudinal statistical modeling techniques have been used to examine developmental trajectories for other health states.[20] We sought to identify early-midlife cardiovascular correlates of these developmental trajectories to help demonstrate broader clinical use. To the best of our knowledge, this is the first time that this type of modeling has been used to identify blood pressure trajectory groups from childhood to adulthood in a single longitudinal birth cohort study.

The aims of this research were to (1) identify latent groups of individuals sharing systolic blood pressure developmental trajectories from 7 to 38 years, (2) identify early-life predictors and potential modifiers of these trajectories, and (3) describe the association between trajectories and early-midlife cardiovascular risk indicators.

Methods

Participants are members of the Dunedin Multidisciplinary Health and Development Study, which has tracked the development of 1037 individuals born in 1972 to 1973 in Dunedin, New Zealand. The study design and inclusion criteria have been described elsewhere[21] (for details see the online-only Data Supplement).

This study used systolic blood pressure data measured at ages 7, 11, 18, 26, 32, and 38 years (all ages at which >1 measure of blood pressure was taken). Blood pressure was measured in a quiet room, using a cuff of appropriate size, with the Study member in a seated position, by medically trained assessors. Up to 18 years, a London School of Hygiene and Tropical Medicine blind mercury sphygmomanometer (Cinetronics Ltd, Mildenhall, United Kingdom) was used. Up to 38 years, a Hawksley random-zero sphygmomanometer (Hawksley and Sons Ltd, Sussex, United Kingdom) with a constant deflation valve was used. Systolic blood pressure was assessed as the first Korotkoff sound and based on the mean of either 2 or 3 measures taken at 5-minute intervals according to a standard protocol. Antihypertensive medication use information was collected at ages 26 (n=6), 32 (n=12), and 38 (n=26) years. Participants were coded as having a systolic blood pressure of 140 mm Hg for the assessment age they were on medication. Data were included if participants had blood pressure information at ≥3 ages (n=975), with information at a specific age subsequently excluded if a participant was pregnant (n=30 at the age of 26 years; n=26 at the age of 32 years; and n=8 at the age of 38 years; for details on the inclusion criteria based on blood pressure data see the online-only Data Supplement).

Early-Life Factors

Birth weight (g) and maternal pregnancy hypertension (diastolic blood pressure ≥90 mm Hg) data were taken from antenatal and perinatal hospital records. Birth order data (first born, second born, third born and higher) were obtained from parent report at the age of 3 years. Breastfeeding information was collected at the age 3 assessment and checked against validated health records.[22]

The collection of family history data about high blood pressure among study members' biological siblings, parents, and grandparents was conducted in 2003 to 2006 and is described elsewhere[23] (for details see the online-only Data Supplement).

Childhood socioeconomic status from birth to 5 years was based on parents' self-reported occupational status[24] (for details see the online-only Data Supplement).

Effect Modifiers From 7 to 38 Years

Height was recorded to the nearest millimeter using a portable stadiometer (Harpenden; Holtain, Ltd). Weight was measured to the nearest 0.1 kg using calibrated scales. Participants were weighed in light clothing. BMI was calculated in kilograms per square meter (weight [kg]/height [m^2]).[25]

Alcohol consumption at 7 and 11 years was coded as zero for all participants. At the age of 18 years, participants were asked how often they usually drank alcohol. At ages 26, 32, and 38 years, participants reported how many drinks (standard units) on average they consumed weekly.

No participants smoked daily at 7 or 11 years, so daily smoking was coded as zero. The current number of cigarettes smoked per day (for at least 1 month in the previous year) was recorded at ages 18, 26, 32, and 38 years.

Age 38 Cardiovascular Risk Indicators

Biomarkers were obtained for measurements of nonfasting total cholesterol (mmol/L), high-density lipoprotein cholesterol level (mmol/L), triglyceride level (mmol/L), and glycohemoglobin at the age of 38 years. Venipuncture was conducted at the same time each day (4:15–4:45 PM). Ninety-five percent of the sample consented to phlebotomy, with pregnant women at this age excluded from the analyses (for further details on biomarker assessment see the online-only Data Supplement).

Waist and hip girth were measured by averaging 2 measurements taken using a steel tape calibrated in centimeters with millimeter gradations. Waist girth was taken as the perimeter at the level of the noticeable waist and hip girth at the widest point of the hips.

A composite measure of metabolic abnormalities (excluding blood pressure) based on the US National Cholesterol Education Program Adult Treatment Panel III guidelines was created (online-only Data Supplement).[26] In brief, participants were considered to have met the criteria for the presence of metabolic abnormalities if they had 3 of 4 abnormalities.

Statistical Analysis

Group-based trajectory modeling was used to identify distinctive groups of individual trajectories in the population from ages 7 to 38 years. We used Proc Traj, a Statistical Analysis Software macro to estimate the model parameters[27] using a censored normal model appropriate for continuous normally distributed data.[28]

Several criteria[20,28] were used to determine the number of blood pressure trajectory groups and the trajectory shapes (eg, cubic in age; for details see the online-only Data Supplement). To determine the best model, 12 models were fitted.

We examined 2 types of covariates, early-life factors and effect modifiers (time-varying covariates). To examine the association between cardiovascular disease risk indicators at 38 years and blood pressure trajectories, we used analysis of variance for continuous measures and χ^2 statistics for categorical measures.

Results

A 4-trajectory group model with cubic specifications for all groups was identified. Figure shows the plotted predicted trajectory lines for each of the 4 groups designated as normal, high-normal, prehypertensive, and hypertensive, with 95% CIs based on predicted trajectory means. The means for all 4 groups significantly differed from each other at all ages, beginning at the age of 7 years. The normal group (21.8% of the sample population) and high-normal group (43.3%) had mean blood pressures in adulthood in the normal systolic blood pressure range (90–120 mm Hg). The prehypertensive group (31.6%) had a mean systolic blood pressure within the prehypertensive range (120–139 mm Hg) throughout adulthood. The hypertensive group (4.2%) had the highest mean blood pressure at the age of 7 years and displayed the steepest rise in blood pressure with mean blood pressure in the hypertensive range at the age of 38 years (≥140 mm Hg). Table S1 provides data on predictive values for prehypertension (≥120 mm Hg) and hypertension (≥140 mm Hg) at the age of 38 years based on prehypertensive and hypertensive group membership and blood pressure measured at each assessment age.

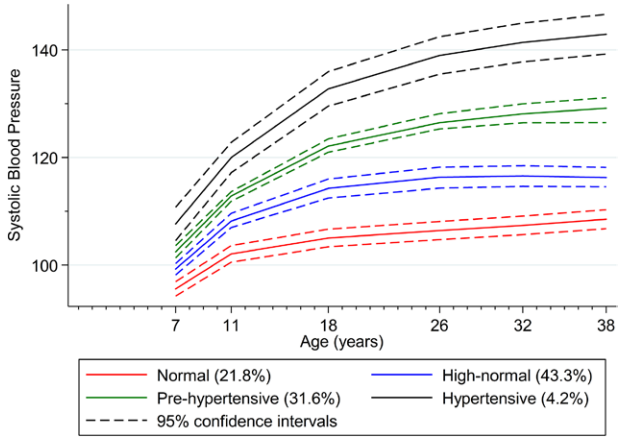

Figure. Plot of predicted trajectory lines with 95% confidence intervals for the 4 blood pressure trajectory groups identified in a general population longitudinal birth cohort.

Both early-life factors and effect modifiers were examined in relation to blood pressure trajectories (Tables 1–3). Tables 1 and 2 also provide data on the characteristics of participants for early-life factors based on trajectory group membership. Information on the physical characteristics of participants and effect modifiers over time based on group membership is presented in Table S2. Analyses were limited to 913 study members in the multivariable trajectory model because of some missing data among the covariates. There were a number of individuals assigned to different trajectory groups as a consequence of adding all covariates (early-life factors and effect modifiers), resulting in a 4% improvement in model fit (Bayesian Information Criterion=−17577.86 versus −18172.22).

In the fully adjusted model (including all covariates), males had significantly greater odds of being in the high-normal, prehypertensive, and hypertensive group compared with the normal group (Tables 1 and 2). Participants who had a higher proportion of relatives with high blood pressure had greater odds of being in the prehypertensive (OR, 6.15; 95% CI, 1.39–27.14) or the hypertensive group (OR, 43.23; 95% CI, 5.27–354.65) compared with the normal group. Study members whose mothers had pregnancy hypertension had greater odds of being in the prehypertensive group (OR, 3.59; 95% CI, 1.24–10.34) but not the hypertensive group (OR, 0.92; 95% CI, 0.15–5.51) when compared with the normal group. Participants who were first born had higher odds of being in the hypertensive group (OR, 2.95; 95% CI, 1.00–8.69) compared with the normal group, and study members with lower birth weights had increased odds of being in the hypertensive group (OR, 2.79; 95% CI, 2.49–3.09). No significant associations were found for early socioeconomic status or breastfeeding.

Increasing BMI was significantly associated with an upward shift in all 4 blood pressure trajectory groups (Table 3). Analyses were then undertaken to determine whether BMI had a greater effect on the trajectory levels of the high-normal, prehypertensive, or hypertensive groups compared with those in the normal group (ie, whether coefficients were significantly different by group). The effect of BMI over time was significantly different (ie, stronger) for 2 groups (the prehypertensive, χ^2=21.4; P<0.001 and hypertensive group, χ^2=9.0; P=0.002) when compared with the normal group. Increasing number of daily cigarettes was also significantly associated with an upward shift in trajectories for the high-normal and prehypertensive groups. No significant associations were found between trajectory groups and alcohol consumption.

Mean values for cardiovascular risk outcomes at the age of 38 years based on trajectory group membership are presented in Table 4. Significant mean differences were found between groups and cardiovascular risk indicators. After controlling for covariates, significant differences were found for waist/hip ratio (F[3, 868]=42.59; P<0.001), total cholesterol level (F[3, 849]=11.08; P<0.001), high-density lipoprotein cholesterol level (F[3, 849]=4.00; P=0.008), glycohemoglobin (F[3, 839]=3.35; P=0.02), triglyceride level (F[3, 849]=16.59; P<0.001), and the presence of metabolic abnormality (χ^2=8.22; P=0.04). In general, the higher the risk for high blood pressure, the greater the risk for other cardiovascular risk factors.

Table 1. Risk Factors for Blood Pressure Trajectory Group Membership: Univariate and Multivariable Analyses, Age 7 to 38 Years—Categorical Variables

	Univariate			Multivariable*		
Risk Factor	n (%)†	Odds Ratio	95% (CI)	n (%)†	Odds Ratio	95% CI
Maternal hypertension (vs no)						
Normal group	9 (4.9)	1.0	…	6 (3.9)	1.0	…
High-normal group	32 (7.9)	1.43	0.54–3.78	32 (8.0)	1.89	0.64–5.47
Prehypertensive group	32 (11.1)	2.57	1.11–5.95	38 (11.9)	3.59	1.24–10.34
Hypertensive group	5 (14.3)	2.50	0.62–10.06	2 (4.9)	0.92	0.15–5.51
First born (vs others)						
Normal group	61 (33.3)	1.0	…	53 (34.9)	1.0	…
High-normal group	113 (27.8)	0.78	0.47–1.30	113 (28.2)	0.98	0.53–1.82
Prehypertensive group	100 (34.7)	1.11	0.70–1.76	103 (32.3)	1.04	0.54–2.00
Hypertensive group	14 (40.0)	1.41	0.61–3.26	19 (46.3)	2.95	1.00–8.69
Male (vs female)						
Normal group	32 (17.5)	1.0	…	10 (6.6)	1.0	…
High-normal group	189 (46.4)	7.83	3.70–16.55	163 (40.6)	7.76	3.24–18.58
Prehypertensive group	216 (75.0)	35.33	16.56–75.41	260 (81.5)	47.66	19.73–115.13
Hypertensive group	33 (94.3)	113.34	22.09–581.41	37 (90.2)	109.48	26.82–466.96
Breastfeeding <4 wk (vs 4+ wk)						
Normal group	99 (54.1)	1.0	…	86 (56.6)	1.0	…
High-normal group	199 (48.9)	0.64	0.40–1.02	186 (46.4)	0.73	0.43–1.23
Prehypertensive group	147 (51.0)	0.84	0.54–1.29	172 (53.9)	0.96	0.55–1.67
Hypertensive group	14 (40.0)	0.47	0.20–1.06	15 (36.6)	0.49	0.20–1.20
Low socioeconomic status (vs others)						
Normal group	22 (12.0)	1.0	…	18 (11.8)	1.0	…
High-normal group	55 (13.5)	1.37	0.65–2.90	58 (14.5)	1.03	0.42–2.52
Prehypertensive group	32 (11.1)	1.08	0.53–2.19	34 (10.7)	0.98	0.36–2.65
Hypertensive group	6 (17.1)	2.08	0.71–6.12	5 (12.2)	0.72	0.17–3.12

CI indicates confidence interval.

*Model contains early-life factors (maternal hypertension, birth weight, birth order, sex, family history of high blood pressure, breastfeeding, and early childhood socioeconomic status) and effect modifiers (body mass index, alcohol consumption, and cigarette smoking).

†Number and percentage with risk factor in each trajectory group.

Discussion

The earliest age at which medical practitioners can identify young healthy individuals who are likely to develop high blood pressure in adulthood is not known. This article addresses this question and reports 4 new findings: (1) those at greatest risk of developing high blood pressure in adulthood had elevated blood pressure at 7 years and were distinguishable from those with normal blood pressure trajectories from childhood into early midlife; (2) several early-life risk factors that antedated our first blood pressure measurement at the age of 7 years were identified using trajectory modeling. These risk factors differentiated between groups of individuals on healthy and unhealthy trajectories; (3) BMI was a major effect modifier for all blood pressure trajectories over time, with effects strongest among the highest blood pressure groups. Cigarette smoking also modified trajectories for the high-normal and prehypertensive groups; and (4) blood pressure trajectories leading to prehypertension and hypertension in adulthood, while of concern in and of themselves, also predicted a range of other cardiovascular risk indicators in early midlife, including a composite index of metabolic abnormalities, indicating even greater clinical salience of these high-risk trajectories.

Against a background of conflicting evidence about the pros and cons of population-based screening for blood pressure risk, new evidence aiding clinical risk assessments earlier in the lifecourse is timely. By implementing a trajectory approach, we found that individuals destined to become prehypertensive and hypertensive by early midlife comprised approximately one third of this general population sample. Moreover, by using data collected over time we were able to better predict those individuals who developed prehypertension and hypertension in early midlife compared with measures of blood pressure taken at only 1 time point (eg, 7 years; Table S1), suggesting the importance of routine blood pressure measurements beginning in childhood.

Previous blood pressure research has linked risk factors measured early in life with high blood pressure at a single point in time later in life. This research goes beyond that by using group-based trajectory modeling to link risk factors

Table 2. Risk Factors for Blood Pressure Trajectory Group Membership: Univariate and Multivariable Analyses, Age 7 to 38 Years—Continuous Variables

	Univariate			Multivariable*		
Risk Factor	Mean (SD)	Odds Ratio	95% (CI)	Mean (SD)	Odds Ratio	95% CI
Birth weight, kg						
Normal group	3.37 (0.51)	1.0	…	3.41 (0.47)	1.0	…
High-normal group	3.39 (0.52)	1.14	0.73–1.78	3.39 (0.52)	0.77	0.46–1.30
Prehypertensive group	3.37 (0.52)	1.02	0.68–1.54	3.39 (0.54)	0.62	0.36–1.07
Hypertensive group	3.44 (0.58)	1.13	0.51–2.51	3.23 (0.48)	0.36	0.16–0.83
Proportion of relatives with high blood pressure						
Normal group	0.22 (0.16)	1.0	…	0.21 (0.16)	1.0	…
High-normal group	0.24 (0.20)	2.56	0.69–9.47	0.24 (0.19)	3.27	0.81–13.24
Prehypertensive group	0.27 (0.20)	6.38	1.91–21.32	0.27 (0.20)	6.15	1.39–27.14
Hypertensive group	0.34 (0.18)	31.79	4.41–202.00	0.34 (0.18)	43.23	5.27–354.65

CI indicates confidence interval.

*Model contains early-life factors (maternal hypertension, birth weight, birth order, sex, family history of high blood pressure, breastfeeding, and early childhood socioeconomic status) and effect modifiers (body mass index, alcohol consumption, and cigarette smoking).

to trajectories capturing the entire developmental course of blood pressure from ages 7 to 38 years. These included several established risk factors such as having a family history of high blood pressure, male sex, maternal pregnancy hypertension, and lower birth weight. Current data strongly support male sex and a family history of hypertension as important early-life risk factors and these are recommended as part of the US Preventive Services Task Force risk assessment for primary hypertension in children. The ORs for male sex and having a family history of high blood pressure were high but the CIs for the ORs were wide, possibly reflecting the small number of participants in these groups, particularly in the hypertensive group. Identifying the effects of pregnancy and in utero factors, such as low birth weight, can help to determine the development of cardiovascular risk indicators, including high blood pressure.[29] An association between maternal pregnancy hypertension and offspring's blood pressure most likely results from both a genetic transmission from parent to child plus in utero effects. A more recent finding was also replicated in our study; that is, first born children had higher odds of being in a trajectory group, resulting in hypertension compared with the normotensive group. Although there are no obvious mechanisms

Table 3. Effect Modifiers Influencing Blood Pressure Trajectory Level Within Each Group: Univariate and Multivariable Analyses, Age 7 to 38 Years

	Univariate			Multivariable*		
Risk Factor	Shift in Trajectory Per Unit Change in Variable	95% CI	*P* Value	Shift in Trajectory Per Unit Change in Variable	95% CI	*P* Value
Body mass index						
Normal group	0.53	0.41 to 0.65	<0.001	0.50	0.36 to 0.63	<0.001
High-normal group	0.92	0.78 to 1.05	<0.001	0.79	0.67 to 0.91	<0.001
Prehypertensive group	1.09	0.94 to 1.24	<0.001	1.04	0.89 to 1.18	<0.001
Hypertensive group	1.62	1.18 to 2.07	<0.001	1.70	1.25 to 2.15	<0.001
Average weekly alcohol consumption						
Normal group	0.02	−0.03 to 0.07	0.49	0.01	−0.06 to 0.08	0.72
High-normal group	0.08	0.03 to 0.13	0.002	0.02	−0.03 to 0.06	0.47
Prehypertensive group	−0.04	−0.10 to 0.03	0.30	−0.02	−0.06 to 0.03	0.49
Hypertensive group	0.00	−0.11 to 0.11	0.98	0.06	−0.11 to 0.23	0.47
No. of cigarette per day (in last month)						
Normal group	0.05	−0.05 to 0.15	0.33	0.07	−0.04 to 0.18	0.19
High-normal group	0.11	0.03 to 0.19	0.007	0.07	0.00 to 0.15	0.05
Prehypertensive group	0.01	−0.08 to 0.11	0.83	0.09	0.01 to 0.17	0.02
Hypertensive group	0.05	−0.11 to 0.22	0.52	0.23	−0.07 to 0.53	0.13

CI indicates confidence interval.

*Model contains early-life factors (maternal hypertension, birth weight, birth order, sex, family history of high blood pressure, breastfeeding, and early childhood socioeconomic status) and effect modifiers (body mass index, alcohol consumption, and cigarette smoking).

Table 4. Blood Pressure Trajectory Group Membership From Ages 7 to 38 Years and Cardiovascular Health-Related Outcome Measures and Risk Factors at 38 Years

	Univariate		Multivariable*	
Risk Factor	Mean	*P* Value†	Mean	*P* Value†
Waist/hip ratio, mm‡				
Normal group	0.809	<0.001	0.802	<0.001
High-normal group	0.848		0.847	
Prehypertensive group	0.885		0.887	
Hypertensive group	0.929		0.885	
Total cholesterol				
Normal group	4.90	<0.001	5.03	<0.001
High-normal group	5.14		5.07	
Prehypertensive group	5.44		5.46	
Hypertensive group	5.85		5.45	
High-density lipoprotein cholesterol				
Normal group	1.56	<0.001	1.54	0.008
High-normal group	1.47		1.47	
Prehypertensive group	1.38		1.40	
Hypertensive group	1.26		1.39	
Glycohemoglobin concentration				
Normal group	5.32	0.06	5.30	0.019
High-normal group	5.40		5.39	
Prehypertensive group	5.43		5.45	
Hypertensive group	5.52		5.36	
Triglyceride level				
Normal group	1.54	<0.001	1.58	<0.001
High-normal group	1.98		1.91	
Prehypertensive group	2.41		2.49	
Hypertensive group	3.05		2.24	
Composite index of metabolic abnormalities, %§				
Normal group	4.1	<0.001‖	6.3	0.04‖
High-normal group	8.6		10.1	
Prehypertensive group	14.9		13.5	
Hypertensive group	24.2		2.6	

*Model contains early-life factors (maternal hypertension, birth weight, birth order, sex, family history of high blood pressure, breastfeeding, and early childhood socioeconomic status) and effect modifiers (body mass index, alcohol consumption, and cigarette smoking).

†Analysis of variance.

‡The same pattern and strength of association was found when only waist circumference was used (data not shown).

§≥3 risk factors endorsed: (1) high waist circumference >880 mm (women) >1020 mm (men); (2) high-density lipoprotein cholesterol <40 mmol/L (men), <50 mmol/L (women), or cholesterol medication; (3) glycohemoglobin >5.7%; and (4) triglycerides >200/2.26 mmol/L, or cholesterol medication.

‖χ^2 statistic

underlying the link between being first born and having higher blood pressure, physical changes occur in the uterus during implantation and placentation in the first pregnancy. During later pregnancies, these changes are more apparent with increased efficiency of placental invasion of the uterine wall and subsequent improved nutrient flow to the fetus.[30] Higher blood pressure in later life may, therefore, be associated with a degree of in utero nutrient restriction of first borns compared with later borns.[31] Neither breastfeeding duration nor lower early childhood socioeconomic status were significantly associated with blood pressure trajectory group membership.

Knowledge about modifiable risk factors that alter blood pressure trajectories can help to determine intervention foci. This study showed that increasing BMI predicted an upward shift in blood pressure trajectory levels across the entire population. However, the impact of higher BMI was greatest among the higher blood pressure groups, suggesting excess body weight may be particularly problematic for individuals already on a trajectory toward developing higher blood pressure. Our results support recommendations for blood pressure screening of children and adolescents who are overweight and obese[32] and population-based strategies that focus on

maintaining a healthy weight. Similar to previous longitudinal studies,[19] we found that cigarette smoking was a significant risk factor and associated with an upward shift in trajectories for those in the high-normal and prehypertensive groups (≈75% of population). No statistically significant association was found for the hypertensive group; this may be because of small numbers in that group. Alcohol was not associated with shifts in trajectory levels in our study participants as they entered early midlife. Future research is required to ascertain if this lack of association persists at older ages.

To determine the predictive validity of the developmental blood pressure trajectory groups, early-midlife cardiovascular correlates of these trajectories were examined. Individuals in the higher blood pressure trajectory groups were more likely to have higher levels of known cardiovascular risk factors at the age of 38 years. These findings suggest that high systolic blood pressure in early life can serve as a generic risk indicator for poorer cardiovascular health more generally. These findings also support recommendations that routine screening for increased blood pressure in childhood may help to prevent subsequent cardiovascular disease in later life via age-appropriate intervention.[3,33] Further follow-up is needed to determine whether this will translate into decreased life expectancy and cardiovascular disease end points (eg, cardiac arrest and stroke).

There are several strengths and some limitations in this study. Few prospective studies exist with the breadth of data to investigate the range of determinants of blood pressure risk factor trajectories in this way. This representative population study has experienced low rates of attrition over almost 4 decades giving confidence in the observed associations. Early-life information was validated using hospital records and measures were created via multiple sources (eg, family history of high blood pressure). The limitations of this study must also be considered. First, despite having BMI information, we could not examine the association between physical activity and blood pressure because activity information was not collected at all time points. Second, although we were able to examine the effect that alcohol consumption and cigarette smoking had over time, frequency of use data were restricted to information collected at ages ≥18 years.

Perspectives

Millions die annually because of diseases directly associated with hypertension, and this number is rising. Intervening in early life to reduce high blood pressure may help increase life expectancy worldwide and reduce the associated burden of disease. The findings from this study suggest that groups of individuals who will develop high systolic blood pressure in early to mid-adulthood have elevated blood pressure in childhood, and that these individuals are more likely to be affected by cardiovascular disease–related comorbidity by age 38 years. In other words, estimating risk for future hypertension (and cardiovascular disease more generally) can be undertaken among children, long before systolic blood pressure rises to clinically detectable levels of prehypertension or hypertension in adulthood. Importantly, this research reinforces the importance of encouraging lifestyle changes including supporting the maintenance of a healthy body weight, particularly for those already on a high-risk blood pressure trajectory into adulthood.

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Disclosures

None.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252. doi: 10.1161/01.HYP.0000107251.49515.c2.
2. Expert Panel of Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescence: summary report. *Pediatrics*. 2011;128:S213–S256.
3. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, Jones DH, Kurtz T, Sheps SG, Roccella EJ; Council on High Blood Pressure Research Professional and Public Education Subcommittee, American Heart Association. Recommendations for blood pressure measurement in humans: an AHA scientific statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee. *J Clin Hypertens (Greenwich)*. 2005;7:102–109.
4. Moyer VA; U.S. Preventive Services Task Force. Screening for primary hypertension in children and adolescents: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;159:613–619. doi: 10.7326/0003-4819-159-9-201311050-00725.
5. Wills AK, Lawlor DA, Muniz-Terrera G, Matthews F, Cooper R, Ghosh AK, Kuh D, Hardy R; FALCon Study Team. Population heterogeneity in trajectories of midlife blood pressure. *Epidemiology*. 2012;23:203–211. doi: 10.1097/EDE.0b013e3182456567.
6. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. 2008;117:3171–3180. doi: 10.1161/CIRCULATIONAHA.107.730366.
7. Urbina EM, Khoury PR, McCoy C, Daniels SR, Kimball TR, Dolan LM. Cardiac and vascular consequences of pre-hypertension in youth. *J Clin Hypertens (Greenwich)*. 2011;13:332–342. doi: 10.1111/j.1751-7176.2011.00471.x.
8. Lurbe E. Childhood blood pressure: a window to adult hypertension. *J Hypertens*. 2003;21:2001–2003. doi: 10.1097/01.hjh.0000084791.15238.cc.
9. Chiolero A, Bovet P, Paradis G. Screening for elevated blood pressure in children and adolescents: a critical appraisal. *JAMA Pediatr*. 2013;167:266–273. doi: 10.1001/jamapediatrics.2013.438.
10. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens*. 2000;18:815–831.
11. Ayyavoo A, Savage T, Derraik JG, Hofman PL, Cutfield WS. First-born children have reduced insulin sensitivity and higher daytime blood pressure compared to later-born children. *J Clin Endocrinol Metab*. 2013;98:1248–1253. doi: 10.1210/jc.2012-3531.

12. Law CM, Barker DJ, Bull AR, Osmond C. Maternal and fetal influences on blood pressure. *Arch Dis Child*. 1991;66:1291–1295.
13. Martin RM, Ness AR, Gunnell D, Emmett P, Davey Smith G; ALSPAC Study Team. Does breast-feeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC). *Circulation*. 2004;109:1259–1266. doi: 10.1161/01.CIR.0000118468.76447.CE.
14. Munger RG, Prineas RJ, Gomez-Marin O. Persistent elevation of blood pressure among children with a family history of hypertension: the Minneapolis Children's Blood Pressure Study. *J Hypertens*. 1988;6:647–653.
15. Hardy R, Kuh D, Langenberg C, Wadsworth ME. Birthweight, childhood social class, and change in adult blood pressure in the 1946 British birth cohort. *Lancet*. 2003;362:1178–1183. doi: 10.1016/S0140-6736(03)14539-4.
16. Wang X, Poole JC, Treiber FA, Harshfield GA, Hanevold CD, Snieder H. Ethnic and gender differences in ambulatory blood pressure trajectories: results from a 15-year longitudinal study in youth and young adults. *Circulation*. 2006;114:2780–2787. doi: 10.1161/CIRCULATIONAHA.106.643940.
17. Burke V, Beilin LJ, Dunbar D. Tracking of blood pressure in Australian children. *J Hypertens*. 2001;19:1185–1192.
18. DeFrank RS, Jenkins CD, Rose RM. A longitudinal investigation of the relationships among alcohol consumption, psychosocial factors, and blood pressure. *Psychosom Med*. 1987;49:236–249.
19. Parikh NI, Pencina MJ, Wang TJ, Benjamin EJ, Lanier KJ, Levy D, D'Agostino RB Sr, Kannel WB, Vasan RS. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. *Ann Intern Med*. 2008;148:102–110.
20. Ostbye T, Malhotra R, Landerman LR. Body mass trajectories through adulthood: results from the National Longitudinal Survey of Youth 1979 Cohort (1981-2006). *Int J Epidemiol*. 2011;40:240–250. doi: 10.1093/ije/dyq142.
21. Poulton R, Moffitt TE, Silva PA. The Dunedin Multidisciplinary Health and Development Study: overview of the first 40 years, with an eye to the future. *Soc Psychiatry Psychiatr Epidemiol*. 2015;50:679–693. doi: 10.1007/s00127-015-1048-8.
22. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Poulton R. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet*. 2002;360:901–907. doi: 10.1016/S0140-6736(02)11025-7.
23. Melchior M, Moffitt TE, Milne BJ, Poulton R, Caspi A. Why do children from socioeconomically disadvantaged families suffer from poor health when they reach adulthood? A life-course study. *Am J Epidemiol*. 2007;166:966–974. doi: 10.1093/aje/kwm155.
24. Elley WB, Irving JC. Revised socio-economic index for New Zealand. *N Z J Educ Stud*. 1976;11:25–36.
25. Belsky DW, Caspi A, Goldman-Mellor S, Meier MH, Ramrakha S, Poulton R, Moffitt TE. Is obesity associated with a decline in intelligence quotient during the first half of the life course? *Am J Epidemiol*. 2013;178:1461–1468. doi: 10.1093/aje/kwt135.
26. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644.
27. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociolog Res Methods*. 2001;29:374–393.
28. Nagin DS. *Group-Based Modeling of Development*. Cambridge, MA: Harvard University Press; 2005.
29. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet*. 2002;360:659–665. doi: 10.1016/S0140-6736(02)09834-3.
30. Khong TY, Adema ED, Erwich JJ. On an anatomical basis for the increase in birth weight in second and subsequent born children. *Placenta*. 2003;24:348–353.
31. Gluckman PD, Hanson MA. Maternal constraint of fetal growth and its consequences. *Semin Fetal Neonatal Med*. 2004;9:419–425. doi: 10.1016/j.siny.2004.03.001.
32. Koebnick C, Black MH, Wu J, Martinez MP, Smith N, Kuizon B, Cuan D, Young DR, Lawrence JM, Jacobsen SJ. High blood pressure in overweight and obese youth: implications for screening. *J Clin Hypertens (Greenwich)*. 2013;15:793–805. doi: 10.1111/jch.12199.
33. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.

Novelty and Significance

What Is New?

- In a longitudinal birth cohort study of 1000 participants, we conducted trajectory modeling to identify 4 distinct developmental systolic blood pressure trajectory groups from ages 7 to 38 years.
- Groups at greatest risk of developing high blood pressure and related cardiovascular comorbidities (eg, higher total cholesterol) at the age of 38 years had higher blood pressure beginning at the age of 7 years compared with individuals in normal blood pressure trajectory groups.

What Is Relevant?

- Individuals in harmful developmental blood pressure trajectory groups were more likely to be male, have a family history of hypertension, be first born, and born lower birth weight; information that is useful for screening purposes.
- Higher body mass index and cigarette smoking over time resulted in increasing blood pressure levels, particularly for those individuals in higher blood pressure groups.
- Encouraging lifestyle changes (eg, weight reduction, the maintenance of a healthy body weight, and smoking cessation) may help to lower blood pressure levels over time, particularly for those individuals on a trajectory to developing hypertension.

Summary

Our findings suggest that it is possible to identify early in life, harmful blood pressure trajectories that are associated with both antecedent and modifiable risk factors over time, and predict cardiovascular disease risk in adulthood.

ONLINE SUPPLEMENT

CHILDHOOD TO EARLY MID-LIFE SYSTOLIC BLOOD PRESSURE TRAJECTORIES: EARLY LIFE PREDICTORS, EFFECT MODIFIERS, AND ADULT CARDIOVASCULAR OUTCOMES

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SHORT TITLE: Systolic blood pressure trajectories

Expanded Methods

Study population

Participants were members of the Dunedin Multidisciplinary Health and Development ('Dunedin') Study, a longitudinal investigation of the health and behavior of a complete birth cohort of consecutive births between April 1 1972 and March 31 1973 in Dunedin, New Zealand. The original cohort of 1037 children (52% male) represents the general population of New Zealand's South Island in the early 1970's[1]. To be eligible for inclusion participants had to be living in the greater Dunedin Metropolitan area three years after their birth at Queen Mary Maternity Hospital – the only maternity hospital in Dunedin at the time. The 9% who declined or were unable to participate were no different from the 91% who agreed to take part in terms of maternal prenatal complications, birthweight, neonatal complications, or family socioeconomic status. Day-long assessments have been conducted at ages 3, 5 (n=991, 96%), 7 (n=954, 92%), 9 (n=955, 92%), 11 (n=925, 90%), 13 (n=850, 82%), 15 (n=976, 95%), 18 (n=933, 97%), 21 (n=922, 97%), 26 (n=980, 96%), 32 (n=972, 96%) and most recently at age 38 years (in 2010-2012) when 95% (n=961) of the living Study members took part.

The Otago Ethics Committee approved each phase of the study. Study members gave informed consent before participating.

Childhood socioeconomic status (SES)

The six point scale used in our analyses to measure childhood SES is based on parental occupation and places each occupation into one of six categories (1=professional, 6=unskilled laborer) based upon the educational level and income associated with that occupation in data from the New Zealand census[2]. The variable created was based on childhood SES information collected at birth, ages 3 and 5 years to capture early life SES experiences, prior to the first measurement of blood pressure at 7 years. As previously reported, we distinguished three SES groups: high (groups 1 and 2 (e.g., manager, physician)), medium (groups 3 and 4 (e.g. secretary, electrician)), and low (groups 5 and 6 (e.g., cashier, textile machine operation))[3].

Family history of high blood pressure

Family history of high blood pressure (study members' biological siblings, parents and grandparents) information was obtained retrospectively at the age 32 assessments (n=937). Further, between 2003 and 2006 we interviewed the Study members' parents (mean age=58, range=47-83 years) to obtain maternal (n=935) and paternal (n=854) blood pressure history reports allowing construction of a familial liability blood pressure problems index which included siblings, parents and grandparents[4].

Age 38 cardiovascular indicators

Nonfasting total cholesterol (mmol/L), HDL cholesterol level (mmol/L) and triglyceride level (mmol/L) were measured using a colorimetric assay. Cholesterol was determined enzymatically by cholesterol oxidase and cholesterol esterase. The between day coefficient of variation for cholesterol ranged from 2.3 to 3.5 percent. HDL cholesterol level was also determined enzymatically by cholesterol oxidase and cholesterol esterase coupled with

polyethylene glycol (PEG) to the amino groups. Triglyceride level (mmol/L) was based on the hydrolysis of triglycerides to glycerol followed by oxidation to dihydroxyacetone phosphate and hydrogen peroxide. This was followed by the classical Trinder's reaction. The between day coefficient of variation for triglycerides ranged from 2.2 to 3.0 percent. Glycated hemoglobin levels (HbA1c) were measured in the serum and glycated hemoglobin concentration (expressed as a percentage of total hemoglobin) measured by ion exchange high performance liquid chromatography (Variant II: BioRad, Hercultes, Calif.) is a method certified by the US National Glycohemoglobin Standardization Program (http://www.missourie.edu/~diabetes/ngsp.html). The between day coefficient of variation for glycated hemoglobin ranged from 1.6 to 2.1 percent.

Study members were considered to have met the criteria for the presence of metabolic abnormalities if they had three of four abnormalities: 1) high waist circumference (≥88 cm for women, ≥102 cm for men), 2) low HDL cholesterol level (<50 mg/dL for women, <40 mg/dL for men), 3) high glycated hemoglobin (≥5.7%), and 4) high triglyceride level (≥200 mmol/L); and 10.5 percent were so designated.

Statistical analysis

Group based trajectory modelling (GBTM) was used to identify distinctive groups of individual trajectories in the population from ages 7 years to 38 years. Criteria that were used to determine the number of blood pressure trajectory groups and the trajectory shapes included (i) an *a priori* knowledge of systolic blood pressure development over time[5] (ii) tendency toward a parsimonious model (iii) the Bayesian Information Criterion (BIC) as a model fit statistic with larger values indicating better fit and (iv) each group having an average posterior probability of group membership exceeding 0.7.

Two types of covariates were examined, early life factors and effect modifiers (time-varying covariates). Early life factors were established before the first measurement of blood pressure and are displayed as the relative odds of being in a trajectory group (compared to a reference group) per unit change in the risk factor. Effect modifiers occur during the course of the trajectory and alter the trajectory itself. These are reported as coefficients and interpreted as showing how much higher or lower a trajectory is for each unit increase in the covariate[6].

Expanded Results

Despite the ability of trajectory modelling to handle missing data, we took a conservative approach by including participants' data if they had blood pressure information at three or more ages (n=975). To examine the effects of inclusion of these participants we then conducted a sensitivity analysis by including only those participants who had blood pressure information at five or more of the six ages (n=764). We found a similar pattern of results using the same four group model with cubic specifications with male gender, having a family history of high blood pressure, low birthweight and being first born being significantly associated with hypertensive group membership (compared to the normal group) ($p<.05$) and increasing body mass index and cigarette smoking being significant effect modifiers.

Supplemental Table 1 in the online-only Data Supplement contains information on the predictive values for prehypertension and hypertension at age 38 for (i) the prehypertensive and hypertensive blood pressure trajectory groups and (ii) blood pressure measured at each assessment from ages 7 to 32. Of those classified in the hypertensive trajectory group, 71.4%

were hypertensive (≥140 mmHg) at age 38 and 100% were either prehypertensive (≥120 mmHg) or hypertensive at age 38.

In terms of blood pressure measured at each individual assessment age, the results indicate poor accuracy[7] (area under the curve values between 0.6-0.7) at age 7 and at age 11, improving to fair accuracy (0.7-0.8) at ages 18, 26 and 32 for predicting those with prehypertension or hypertension at age 38. In general, positive predictive values for hypertension at age 38 based on cut-offs increased with age. Of those classified as hypertensive at age 32, 41.5% were classified as having hypertension at age 38.

References

1. Poulton R, Moffitt TE, Silva PA. The Dunedin Multidisciplinary Health and Development Study: Overview of the first 40 years, with an eye to the future. *Social Psychiatry and Psychiatric Epidemiology*. 2015;50:679-693.
2. Elley WB, Irving JC. Revised socio-economic index for New Zealand. *New Zealand Journal of Educational Studies*. 1976;11:25-36.
3. Poulton R, Caspi A, Milne BJ, Thomson WM, Taylor A, Sears MR, Moffitt TE. Association between children's experience of socioeconomic disadvantage and adult health: A life-course study. *Lancet*. 2002;360:1640-1645.
4. Melchior M, Moffitt TE, Milne B, Poulton R, Caspi A. Why do children from socioeconomically disadvantaged families suffer from poor health when they reach adulthood? A life-course study. *Am J Epidemiol*. 2007;166:966-974.
5. Wright JD, Hughes JP, Ostchega Y, Yoon SS, Nwankwo T. Mean systolic and diastolic blood pressure in adults aged 18 and over in the United States, 2001–2008. *National health statistics reports; no 35*. 2011.
6. Nagin DS. *Group-based modeling of development*. Cambridge: Harvard University Press; 2005.
7. Lüdemann L, Grieger W, Wurm R, Wust P, Zimmer C. Glioma assessment using quantitative blood volume maps generated by t1-weighted dynamic contrast-enhanced magnetic resonance imaging: A receiver operating characteristic study. *Acta Radiologica*. 2006;47:303-310.
8. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555-576.

Table S1: Area under the curve, values corresponding to membership in the prehypertensive and hypertensive systolic blood pressure trajectory groups or to cut off points for systolic blood pressure at ages 7 to 32, between groups at age 38 with or without (i) prehypertension (≥120 mmHg) or (ii) hypertension (≥140 mmHg)

		Prehypertension at age 38 (≥120 mmHg)					Hypertension at age 38 (≥140 mmHg)				
Systolic BP	Cut-off Points*	AUC†	Sensitivity	Specificity	PPV	NPV	AUC†	Sensitivity	Specificity	PPV	NPV
Trajectory groups‡											
Prehypertensive & Hypertensive			66.5%	92.2%	88.5%	75.3%		94.9%	69.9%	22.7%	99.3%
Hypertensive only			8.0%	100%	100%	54.6%		31.6%	98.8%	71.4%	93.9%
7 years		0.64					0.68				
	≥90th %tile		21.0%	90.1%	66.4%	55.2%		36.6%	86.8%	21.3%	93.4%
11 years		0.66					0.70				
	≥90th %tile		4.7%	98.8%	78.9%	51.9%		8.1%	97.6%	26.3%	91.1%
18 years		0.74					0.76				
	≥120 mmHg		73.4%	64.1%	64.3%	73.2%		89.0%	50.1%	14.9%	97.9%
	≥140 mm Hg		7.3%	99.5%	93.3%	54.9%		19.2%	97.8%	46.7%	92.5%
26 years		0.76					0.78				
	≥120 mmHg		61.5%	79.3%	73.2%	69.1%		81.8%	63.7%	17.7%	97.3%
	≥140 mm Hg		5.4%	99.3%	88.5%	53.3%		15.6%	98.2%	46.2%	92.4%
32 years		0.78					0.79				
	≥120 mmHg		65.3%	78.9%	74.3%	70.9%		79.2%	61.1%	16.2%	96.9%
	≥140 mm Hg		8.6%	99.1%	90.2%	53.8%		22.1%	97.0%	41.5%	92.9%

*Cut off points at ages 7 and 11 are based on the National High Blood Pressure Education Program Working Group[8] classifications for children according to gender and height percentile.

†Area under the curve (AUC) is based on continuous measures of blood pressure at ages 7, 11, 18, 26 or 32 (not cut-off points). Systolic blood pressure was based on the mean of either two or three measures taken at five minute intervals on one occasion.

‡Trajectory groups are based on blood pressure data collected at ages 7, 11, 18, 26, 32 and 38 years (n=975) and were identified using group-based trajectory modelling. The four groups identified were labelled (i) 'normal' (21.8% of the sample) (ii) 'high-normal' (43.3%) (iii)

‘prehypertensive’ (31.6%) and (iv) ‘hypertensive’ (4.2%). The same pattern for predictive values was found for trajectory groups based on blood pressure data at ages 7, 11, 18, 26 and 32 only (data not shown).

Table S2: Physical characteristics of participants and effect modifiers for developmental systolic blood pressure trajectory groups* over time

Factor	**Age**					
Trajectory group	Age 7	Age 11	Age 18	Age 26	Age 32	Age 38
Body mass index, mean (SD)†						
Normal	15.83 (1.30)	17.32 (2.11)	22.35 (2.76)	23.78 (4.06)	24.72 (4.51)	25.70 (5.1)
High-normal	15.76 (1.30)	17.39 (2.00)	22.56 (2.86)	24.67 (3.96)	25.86 (4.78)	26.79 (5.13)
Prehypertensive	15.94 (1.35)	17.62 (2.20)	23.08 (3.27)	25.86 (4.31)	27.08 (4.98)	28.31 (5.43)
Hypertensive	15.98 (1.28)	18.31 (2.49)	24.44 (3.88)	27.86 (5.65)	29.44 (5.39)	30.10 (5.52)
Height, mean (SD)						
Normal	1201.46 (53.74)	1419.00 (72.94)	1659.89 (85.54)	1667.87 (82.66)	1675.95 (86.15)	1675.13 (86.25)
High-normal	1208.78 (47.69)	1425.32 (60.65)	1696.11 (82.77)	1711.39 (89.44)	1717.29 (88.70)	1714.92 (89.19)
Prehypertensive	1216.30 (45.53)	1431.96 (55.83)	1732.66 (76.62)	1752.43 (78.93)	1758.83 (79.38)	1756.09 (78.50)
Hypertensive	1229.17 (45.85)	1447.46 (50.77)	1762.94 (63.73)	1777.80 (63.63)	1783.73 (67.10)	1780.29 (65.27)
Body weight, mean (SD)†						
Normal	22.93 (3.05)	35.04 (6.16)	61.70 (9.70)	67.14 (13.09)	69.77 (14.82)	72.38 (15.85)
High-normal	23.08 (2.85)	35.46 (5.79)	64.94 (9.51)	72.26 (12.47)	76.31 (14.85)	78.95 (15.87)
Prehypertensive	23.64 (2.87)	36.24 (5.95)	69.28 (10.60)	79.55 (14.05)	83.87 (16.00)	87.33 (17.31)
Hypertensive	24.10 (2.23)	38.36 (6.34)	75.72 (11.17)	87.76 (16.93)	93.31 (15.40)	95.05 (15.72)
Weekly alcohol drinks, mean (SD)						
Normal	-	-	1.51 (1.54)	7.05 (8.29)	8.89 (12.68)	8.82 (12.54)
High-normal	-	-	1.47 (1.42)	9.87 (13.73)	8.29 (12.95)	10.99 (19.72)
Prehypertensive	-	-	1.30 (1.27)	11.09 (16.58)	10.94 (14.42)	11.58 (13.83)
Hypertensive	-	-	1.57 (1.57)	10.10 (11.73)	8.48 (9.78)	12.48 (21.84)
Number of cigarettes daily, mean (SD)		-				
Normal	-	-	4.02 (6.88)	4.47 (7.33)	3.75 (6.98)	3.19 (6.57)
High-normal	-	-	3.87 (7.17)	4.50 (7.41)	3.80 (7.25)	3.02 (6.85)
Prehypertensive	-	-	3.23 (6.40)	4.06 (6.78)	4.14 (7.10)	3.33 (7.03)
Hypertensive	-	-	5.06 (11.66)	5.54 (9.54)	4.36 (9.72)	1.59 (6.11)

* Trajectory groups are based on blood pressure data collected at ages 7, 11, 18, 26, 32 and 38 years (n=975) and were identified using group-based trajectory modelling. Groups are based on data collected from n=913 participants using a model that contains both early life factors (maternal hypertension, birthweight, birth order, gender, family history of high blood pressure, breastfeeding, early childhood socioeconomic status) and effect modifiers (body mass index, alcohol consumption, cigarette smoking).

†Pregnant women excluded from analyses

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