Utility of Different Blood Pressure Measurement Components in Childhood to Predict Adult Carotid Intima-Media Thickness

The i3C Consortium Study

Juha Koskinen,* Markus Juonala,* Terence Dwyer, Alison Venn, Janina Petkeviciene, Indrė Čeponienė, Lydia Bazzano, Wei Chen, Matthew A. Sabin, Trudy L. Burns, Jorma S.A. Viikari, Jessica G. Woo, Elaine M. Urbina, Ronald Prineas, Nina Hutri-Kähönen, Alan Sinaiko, David R. Jacobs, Jr, Julia Steinberger, Stephen Daniels, Olli Raitakari, Costan G. Magnussen

See Editorial Commentary, pp 296–298

Abstract—Childhood blood pressure (BP) levels predict adult subclinical atherosclerosis. However, the best childhood BP component for prediction has not been determined. This study comprised 5925 participants aged 3 to 18 years from 6 cohorts who were followed into adulthood (mean follow-up 25.8±6.2 years). Childhood BP was measured by using a standard mercury sphygmomanometer in all cohorts. Study-specific carotid intima-media thickness ≥90th percentile was used to define subclinical atherosclerosis. Per SD change in the predictor, childhood systolic BP (SBP; age- and sex-adjusted odds ratio [95% CI], 1.24 [1.13–1.37]), mean arterial pressure (1.10 [1.07–1.13]), and pulse pressure (1.15 [1.05–1.27]) were associated with increased adulthood intima-media thickness. In age- and sex-adjusted analyses, area under the receiver operating characteristic curves for SBP (*C* value [95% CI], 0.677 [0.657–0.704]) showed significantly improved prediction compared with diastolic BP (0.669 [0.646–0.693], *P*=0.006) or mean arterial pressure (0.674 [0.653–0.699], *P*=0.01). Pulse pressure provided a *C* value that was not different from SBP (0.676 [0.653–0.699], *P*=0.16). Combining different BP components did not improve prediction over SBP measurement alone. Based on the associations with adult carotid intima-media thickness, cut points for elevated SBP were 105 mm Hg for 3- to 6-year-old boys, 108 mm Hg for 3- to 6-year-old girls, 108 mm Hg for 7- to 12-year-old boys, 106 mm Hg for 7- to 12-year-old girls, 123 mm Hg for 13- to 18-year-old boys, and 115 mm Hg for 13- to 18-year-old girls. Our analyses suggest that several childhood BP measurement components are related to adulthood carotid intima-media thickness. Of these, SBP provided the best predictive ability. **(*Hypertension*. 2019;73:335-341. DOI: 10.1161/HYPERTENSIONAHA.118.12225.)** • Online Data Supplement

Key Words: arterial pressure ■ atherosclerosis ■ blood pressure ■ epidemiology ■ pediatrics

Among adults, elevated carotid artery intima-media thickness (cIMT) is associated with cardiovascular disease (CVD) and stroke.[1] Data from the International Childhood Cardiovascular Cohort Consortium have shown childhood blood pressure (BP) levels to associate with adult cIMT measured >20 years later. Among the 4210 participants from 4

Received October 11, 2018; first decision October 25, 2018; revision accepted November 11, 2018.

From the Research Centre of Applied and Preventive Cardiovascular Medicine (J.K., O.R., C.G.M.) and Department of Medicine (M.J., J.S.A.V.), University of Turku, Finland; Heart Center, Kymenlaakso Central Hospital, Kotka, Finland (J.K.); Division of Medicine (M.J., J.S.A.V.) and Department of Clinical Physiology and Nuclear Medicine, University of Turku (O.R.), Turku University Hospital, Finland; Murdoch Childrens Research Institute, Parkville, Victoria, Australia (M.J.); George Institute, University of Oxford, United Kingdom (T.D.); Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia (A.V., C.G.M.); Faculty of Public Health, Medical Academy (J.P.) and Department of Cardiology, Medical Academy (I.C.), Lithuanian University of Health Sciences, Kaunas; Department of Epidemiology and Department Biostatistics and Bioinformatics, Tulane University Health Sciences Center (L.B.) and Department of Epidemiology, Tulane Center for Cardiovascular Health (W.C.), Tulane University, New Orleans, LA; Royal Children's Hospital, Parkville, Australia (M.A.S.); Department of Pediatrics, University of Melbourne, Parkville, Australia (M.A.S.); Department of Epidemiology, College of Public Health, University of Iowa (T.L.B.); Division of Biostatistics and Epidemiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, OH (J.G.W.); The Heart Institute, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, OH (E.M.U.); Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (R.P.); Department of Pediatrics, University of Tampere School of Medicine and Tampere University Hospital, Finland (N.H.-K.); Department of Pediatrics (A.S.) and Division of Epidemiology and Community Health, School of Public Health (D.R.J.), University of Minnesota, Minneapolis; Department of Pediatrics, University of Minnesota Masonic Children's Hospital (J.S.); and Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora (S.D.).

*These authors contributed equally to this work.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.118.12225.

Correspondence to Juha Koskinen, Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Kiinamyllynkatu 10, FI 20520, Finland. Email jkkosk@utu.fi

cohort studies, elevated BP (either systolic or diastolic ≥90th percentile for age, sex, and height) that persisted from childhood into adulthood was associated with a nearly 2-fold higher risk of developing high cIMT compared with those who had normal BP levels at both time points.[2]

BP is a well-established risk factor in childhood for future preclinical atherosclerosis, but uncertainty exists about the relative importance of various BP components in predicting risk.[3,4] Systolic BP (SBP) is influenced by cardiac contractility while diastolic BP (DBP) by cardiac relaxation. Pulse pressure (PP), the difference between SBP and DBP, represents the force that the heart generates each time it contracts and may also reflect arterial stiffness.[5] Mean arterial pressure (MAP) represents an average arterial pressure during a single cardiac cycle and is estimated from SBP and DBP readings. In the Framingham Heart Study, combining PP with MAP, and SBP with DBP, produced models that were superior to single BP components for predicting subsequent CVD.[3]

In this study, we used data from 5925 individuals in 6 prospective cohort studies that have followed participants from childhood into adulthood. The objective of the study was to examine the utility of various BP components and their combinations in childhood for predicting future high cIMT.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Sample

Detailed study characteristics and examination methods for the 6 cohorts have been previously described.[6–12] Although loss to follow-up varied by cohort, previous analyses have suggested the representativeness of the cohorts has largely been maintained.[6,8,13,14] In total, 5925 participants who had available BP data from childhood (ages 3–18) and ultrasound data from adulthood (ages 19–51) were included in this study. Mean follow-up period was 25 years. Locally appointed ethics committees reviewed and approved the individual cohort studies that we analyzed, and participants in those studies (or their legal guardians) provided written informed consent. The present analysis conformed to the Declaration of Helsinki.

BP Measurements

BP at baseline was measured by using a standard mercury sphygmomanometer in all cohorts. Summary of the methods in different cohorts is shown in Table S1 in the online-only Data Supplement. PP was defined as follows: SBP-DBP. The MAP was defined as follows: (SBP+(DBP×2))/3. Diastolic IV was used to calculate PP IV and diastolic V to calculate PP V. Diastolic IV and V were used to calculate MAP IV and MAP V, respectively.

Ultrasound Measurements

B-mode ultrasound studies of the left carotid artery were performed at follow-up examinations using standardized protocols in each study. Details of the ultrasound data and protocols have been described elsewhere.[6,12,15,16] In the YFS (Young Finns Study), to assess intraindividual reproducibility of ultrasound measurements, 57 subjects were reexamined 3 months after the initial visit. The average absolute difference and SD between measurements was 0.05±0.04 mm. In BHS (Bogalusa Heart Study), 75 participants underwent repeat ultrasound examinations 10 to 12 days after their initial visit to determine intraindividual reproducibility. The average absolute difference and SD between measurements for all cIMT segments was 0.05±0.03 mm. In the Insulin Study, reproducibility of the cIMT showed a mean difference (±SD) of 0.02±0.03 for analysis separated by 1 week. In the Muscatine Study, a 4.4% random sample underwent repeat cIMT studies during a second visit, a mean of 107 days later, to assess intraindividual reproducibility. The mean absolute difference for all cIMT segments was 0.06 mm. In CDAH study (Childhood Determinants of Adult Health study), intraindividual reproducibility for replicate maximum cIMT measurements was assessed in a random sample of 30 participants. The average absolute difference and SD between measurements was 0.02±0.04 mm. In the Kaunas Study, 50 measurements of cIMT were assessed by a second investigator with between-observer coefficient of variation 4%.

Definition of High cIMT in Adulthood

cIMT values are strongly related with age and sex.[9] In addition, methods to measure cIMT differed between the cohorts. Therefore, to take into account these issues, we first calculated age- and sex-specific percentile points for each individual's cIMT values separately in each cohort. In line with our prior reports, high cIMT in adulthood was then defined as ≥90th percentile based on these age-, sex-, and study-specific percentile points.[2] In sensitivity analyses, similar results were found using cut points corresponding to the 80th cIMT percentiles (data not shown).

Statistical Methods

The normality assumption of the residuals was assessed by examining histograms of the residuals and normal probability plots. The residuals were normally distributed. No significant interaction effects were observed between sex and BP measures with continuous ultrasound variables, indicating that the associations of risk markers and ultrasound variables were similar between sexes. Additionally, because of differences in the range of risk factor levels among the cohorts, and changes reflecting secular trends, the analyses were performed by calculating age-, sex-, and study-specific z scores for each childhood BP measurement and for adulthood high cIMT. Therefore, data from males and females were combined in all models. Differences between study groups were assessed by fitting ANOVA models. Age- and sex-adjusted logistic regression models were used to examine the associations for the BP measurements with adult preclinical atherosclerosis (high cIMT). The ability of individual and combined BP measures to predict high cIMT in adulthood was assessed using area under the curve (AUC) receiver operating characteristic curves (ROC), category-free net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Calibration was assessed by using the Hosmer-Lemeshow (H-Lχ2) goodness of fit test. Differences in AUC between age- and sex-adjusted models were estimated with the use of the DeLong algorithm.[17] IDI represents an averaged measure with reduced variability, and thus a more conservative significance level of $P \leq 0.01$ was used in the present study.[18] In addition, NRI is designed to quantify improvement in performance, and hence its magnitude is more important than statistical significance.[19] Thus, caution in interpreting statistical significance levels for IDI and NRI is recommended. The optimal cut points were defined from the receiver operating characteristic curve by calculating sensitivity and specificity and deriving the distance from the perfect point at the upper-left corner of the receiver operating characteristic plot where 1−Specificity=0 and Sensitivity=1. Optimal cutoff, that is, distance to (0,1) was defined by the equation: $\sqrt{(1-\text{Sensitivity})^2+(1-\text{Specificity})^2}$. Sensitivity describes the probability of correctly classifying the participant as having high cIMT (≥90th percentile); specificity describes the probability of correctly classifying the participant as having normal cIMT (<90th percentile). Except for the IDI analyses mentioned above, statistical significance was inferred as a P value of ≤0.05. Statistical analyses were performed with SAS 9.4.

Results

Clinical Characteristics

Table 1 shows clinical characteristics of the 5925 study participants at baseline in childhood. Age, SBP, DBP, MAP,

Table 1. Baseline Characteristics in the 6 Study Cohorts

Variable	YFS (N=2554) Mean±SD	BHS (N=1300) Mean±SD	CDAH (N=695) Mean±SD	Muscatine (N=721) Mean±SD	Insulin* (N=294) Mean±SD	Kaunas* (N=361) Mean±SD	*P* Value†	All (N=5925)
Age, y	11±4	10±3	13±2	13±3	14±2	13±0.3	<0.0001	12±4
Sex (male %)	54	57	54	52	47	54	0.44	54
Systolic blood pressure, mm Hg	112±11	100±10	109±13	115±14	108±9	114±12	<0.0001	109±13
Diastolic IV blood pressure, mm Hg	75±10	62±8	78±12	75±9.3	…	…	<0.0001	72±11
Diastolic V blood pressure, mm Hg	68±10	45±12	66±12	68±10	56±13	55±11	<0.0001	62±15
Mean arterial pressure IV, mm Hg	88±9	75±8	81±10	89±10	…	…	<0.0001	
Mean arterial pressure V, mm Hg	83±9	63±10	81±10	83±10	73±10	75±9	<0.0001	76±12
Pulse pressure IV, mm Hg	38±11	55±13	43±13	40±11	…	…	0.0003	
Pulse pressure V, mm Hg	45±11	54±13	42±13	48±13	51±13	59±14	<0.0001	48±13
Body mass index, kg/m^2	17.8±3.0	17.7±3.6	18.6±2.9	19.8±3.5	22.7±5.1	18.9±3.1	<0.0001	18.4±3.6

BHS indicates Bogalusa Heart study; CDAH, Childhood Determinants of Adult Health study; and YFS, Young Finns study.
*In the Insulin and Kaunas studies diastolic IV blood pressure was not measured.
†Group comparisons among study cohorts.

and PP were different among study cohorts. No sex differences were observed between study cohorts. Absolute cIMT values at different percentiles from each cohort are shown in Table S2.

Association of Childhood BP Components With High cIMT in Adulthood

SBP, MAP IV, and PP (IV and V) were associated with subsequent high cIMT. Age- and sex-adjusted results are shown in Table 2. When the models were further adjusted for childhood body mass index, the associations remained statistically significant for SBP (odds ratio for 1 SD change [95% CI], 1.17 [1.05–1.29]; *P* value 0.003), PP V (1.14 [1.04–1.25]; *P* value 0.004), and PP IV (1.11 [1.01–1.23]; *P* value 0.03) but not for MAP V (1.04 [0.94–1.14]; *P* value 0.50). Additionally, adjusting for length of follow-up, all results remained essentially similar (data not shown).

In age-stratified analyses (Table S3) among participants who were 3 to 11 years-old at baseline, SBP (1.20 [1.01–1.41]), PP V (1.21 [1.04–1.41]), and PP IV (1.20 [1.02–1.40]) were associated with high cIMT in adulthood. Among participants who were 12 to 18 years-old, SBP (1.28 [1.14–1.44]), MAP V (1.14 [1.02–1.27]), MAP IV (1.19 [1.06–1.34]), PP V (1.17 [1.05–1.29]), and PP IV (1.17 [1.05–1.31]) were associated with high cIMT in adulthood.

Differences in Individual and Combined BP Measurements in Childhood Predicting High cIMT in Adulthood

Table 3 shows C statistics for individual BP measures in predicting high cIMT compared with the C statistic for SBP, which outperformed all individual BP measures except for PP V and PP IV. Detailed analysis between SBP and PP V, and between SBP and PP IV showed no statistical differences in NRI values (0.041, *P* value 0.37 and 0.089, *P* value 0.06, respectively) or in IDI values (0.001, *P* value 0.04 and 0.002, *P*=0.02, respectively). When compared with other main cardiovascular risk factors in childhood, the predictive ability of SBP did not significantly differ from that of body mass index (AUCs [95% CI] 0.677 [0.657–0.704] versus 0.681 [0.659–0.703], *P*=0.37). SBP provided better predictive value (0.677 [0.657–0.704]) compared with total cholesterol (0.668 [0.645–0.692], *P* for difference 0.02).

In age-stratified analyses (Table S4) among participants who were 3 to 11 years-old no differences between BP measures were detected in predicting cIMT in adulthood. Among participants who were 12 to 18 years-old, SBP outperformed DBP IV, DBP V, MAP V, and MAP IV (*P*<0.04). No differences were observed between SBP and PP V and PP IV.

Next, we assessed the differences between individual and combined BP measurements in models to predict high cIMT in adulthood (Table 4). No difference was observed between DBP IV and DBP V measures or between SBP and SBP+DBP V. Similar results were observed when DBP IV was used

Table 2. Associations of Childhood Blood Pressure Measures (Age, Sex, and Study Specific) With High cIMT in Adulthood (Age-, Sex-, and Study-Specific ≥90th Percentile)

Blood Pressure Measurement	OR (95% CI)	*P* Value
Systolic blood pressure	1.24 (1.13–1.37)	<0.0001
Diastolic IV	1.07 (0.97–1.17)	0.16
Diastolic V	1.01 (0.92–1.10)	0.88
MAP IV*	1.10 (1.07–1.13)	0.006
MAP V†	1.08 (0.98–1.19)	0.11
PP IV*	1.15 (1.05–1.27)	0.0027
PP V†	1.11 (1.08–1.13)	0.0004

Age- and sex-adjusted univariate logistic regression models were performed for each blood pressure measure. OR and 95% CI are for a 1-SD increase. cIMT indicates carotid artery intima-media thickness; MAP, mean arterial pressure; OR, odds ratio; and PP, pulse pressure.
*Diastolic IV was used in the MAP IV and PP IV models.
†Diastolic V was used in the MAP V and PP V models.

Table 3. Utility of Single Measures of Childhood Blood Pressure (Age-, Sex-, and Study-Specific) to Predict High Adult cIMT

Blood Pressure Measurement	AUC (95% CI)	*P* Value for Difference
Systolic blood pressure	0.677 (0.657–0.704)	Reference
Diastolic IV	0.670 (0.647–0.694)	0.004
Diastolic V	0.669 (0.646–0.693)	0.006
MAP IV*	0.674 (0.653–0.699)	0.01
MAP V†	0.672 (0.648–0.648)	0.003
PP IV*	0.676 (0.653–0.699)	0.16
PP V†	0.673 (0.651–0.694)	0.21

AUC indicates area under the curve; cIMT, carotid artery intima-media thickness; MAP, mean arterial pressure; and PP, pulse pressure.

*Diastolic IV was used in the MAP IV and PP IV models.

†Diastolic V was used in the MAP V and PP V models.

instead of DBP V (data not shown). PP V and PP V+MAP V outperformed MAP V alone in predicting high cIMT. No difference was observed between MAP V+PP V and SBP+DBP V in predicting high cIMT. Similar results were obtained when MAP V was replaced with MAP IV, and PP V was replaced with PP IV (data not shown). No difference was observed between SBP and MAP V+PP V (*P* always >0.31 for AUC difference, IDI, and NRI values). Goodness of fit indicated by the Hosmer-Lemeshow χ^2 was acceptable (always <10) for all models examined.

We also examined the predictive value of childhood SBP for high adult cIMT stratified by study cohort (Figure). For YFS, AUC (95 % CI) was 0.740 (0.708–0.772), for BHS 0.649 (0.603–0.696), for CDAH 0.650 (0.593–0.701), for the Muscatine Study 0.648 (0.579–0.717), for the Insulin Study 0.574 (0.479–0.669), and for the Kaunas study 0.646 (0.568–0.723). Finally, we created cut points for elevated SBP values in different age and sex groups based on the associations with adult cIMT (Table 5).

Discussion

The findings from a large longitudinal 6-cohort international study show that a single measurement of SBP during childhood/adolescence, was better, or an equally accurate alternative, to other BP components or their combinations in predicting the development of subclinical atherosclerosis, as represented by high cIMT, a mean of 25 years later. In addition, this study confirms the value of a simple measurement of SBP in the clinical setting.

Although it is known that BP in childhood is predictive of BP in adulthood, data relating BP levels in childhood to later cardiovascular events is currently lacking. In a cohort study of Swedish male conscripts, BP at the age of 18 was associated with CVD mortality later in adulthood.[20] In addition, childhood BP has been associated with different markers of subclinical atherosclerosis, such as cIMT and arterial pulse wave velocity.[21,22] The present study expands on these data by comparing the utility of different childhood BP components and their combinations in predicting future cIMT, a marker of subclinical atherosclerosis.

Table 4. Utility of Different Blood Pressure Measurement Components and Their Combinations in Childhood to Predict Adult High cIMT (Age-, Sex-, and Study-Specific ≥90th Percentile)

Method for Prediction	Blood Pressure Measurement	*P* for Difference
AUC (95% CI)	Diastolic V: 0.669 (0.646–0.693) Diastolic IV: 0.670 (0.647–0.694)	0.37
IDI	Diastolic V vs diastolic IV: 0.0012	0.002
NRI	Diastolic V vs diastolic IV: 0.05	0.25
AUC (95% CI)	Systolic: 0.677 (0.657–0.704) Systolic+diastolic V: 0.678 (0.655–0.700)	0.32
IDI	Systolic vs systolic+diastolic V: 0.0001	0.78
NRI	Systolic vs systolic+diastolic V: 0.007	0.12
AUC (95% CI)	Systolic: 0.677 (0.657–0.704) Systolic+PP V*: 0.678 (0.655–0.700)	0.40
IDI	Systolic vs systolic+PP V*: 0.0001	0.70
NRI	Systolic vs systolic+PP V*: 0.072	0.10
AUC (95% CI)	PP V*: 0.673 (0.651–0.694) PP V*+MAP V*: 0.677 (0.655–0.699)	0.09
IDI	PP V* vs PP V*+MAP V*: 0.002	0.005
NRI	PP V* vs PP V+MAP V*: 0.066	0.15
AUC (95% CI)	MAP V*: 0.667 (0.645–0.689) PP V*+MAP V*: 0.677 (0.655–0.699)	0.005
IDI	MAP V* vs PP V*+MAP V*: 0.035	0.001
NRI	MAP V* vs PP V*+MAP V*: 0.15	0.011
AUC (95% CI)	PP V*+MAP V*: 0.677 (0.655–0.699) Systolic+diastolic V: 0.678 (0.656–0.700)	0.25
IDI	PP V*+MAP V* vs systolic+diastolic V: 0.0003	0.23
NRI	PP V*+MAP V* vs systolic+diastolic V: 0.014	0.76

AUC indicates area under the curve; cIMT, carotid intima-media thickness; IDI, integrated discrimination index; MAP, mean arterial pressure; NRI, net reclassification index; and PP, pulse pressure.

*Diastolic V was used in the MAP V and PP V models

Questions remain about the utility of single versus combined BP measurement components in predicting cardiovascular health. Most pediatric patients with elevated BP are found to have isolated systolic hypertension.[23] Then with increasing age, there is a gradual shift to DBP as the major predictor of risk, then to SBP and to PP. PP, an indicator of arterial stiffness,[5] has been shown to be useful in predicting CVD events in the elderly.[24] A follow-up of participants in the Multiple Risk Factor Intervention Trial concluded that CVD risk assessment was improved in 35- to 57-year-old males by considering both SBP and DBP jointly compared with SBP, DBP, or PP separately.[25] Results from the Framingham Heart Study confirmed the importance of combining BP components, such as SBP and DBP, or PP and MAP, to improve stratification of CVD risk in adult populations.[3]

BP tracks from childhood into adulthood, with persons with elevated childhood BP having a higher probability of adult hypertension than those with normal BP.[26] In the present study, we found that prediction of cIMT was significantly better with SBP than with DBP. This is consistent

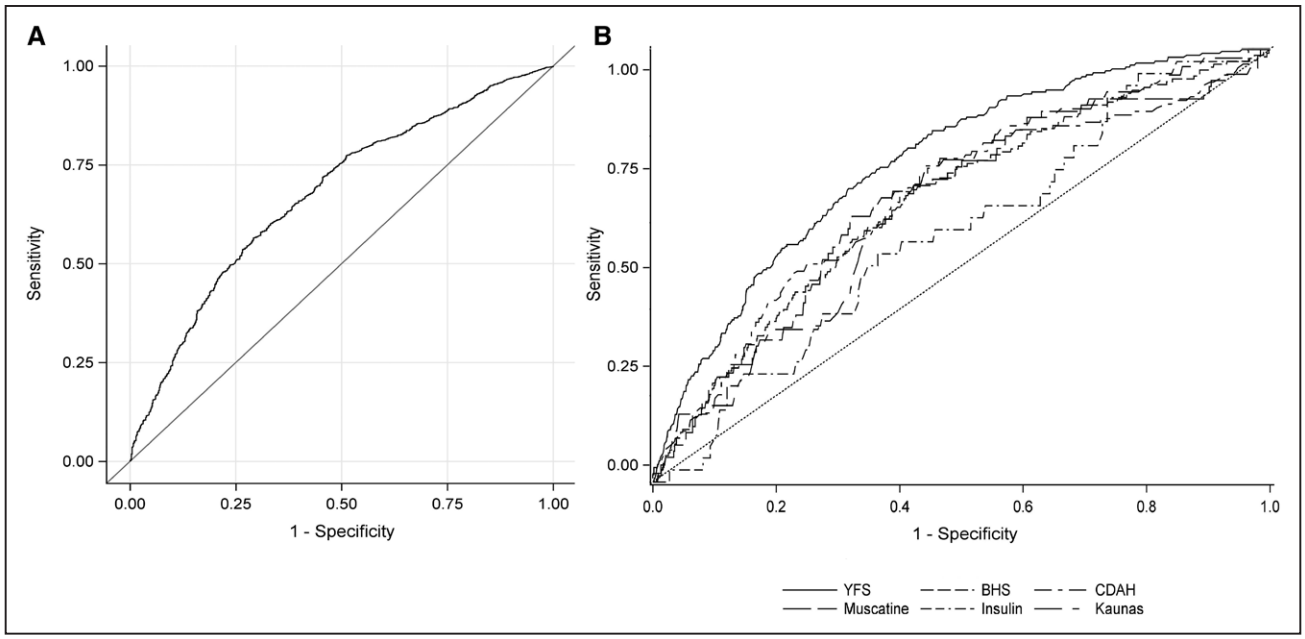

Figure. Receiver operating characteristic curves for childhood systolic blood pressure in predicting adult high carotid intima-media thickness, (**A**) combined in all cohorts, (**B**) by cohort (BHS indicates Bogalusa Heart study; CDAH, Childhood Determinants of Adult Health study; and YFS, Young Finns study).

with results from the YFS and CDAH studies showing that child-to-adult tracking correlations were higher for SBP compared with DBP.[26–28] Measurement of DBP is complicated by the presence of 2 diastolic Korotkoff phases (fourth and fifth phase) in many children and adults. The recommendations for the assessment of DBP among children have varied. Previously, the fourth Korotkoff phase (muffling of sound) was a recommended method in assessing DBP.[4] Although the fourth Korotkoff phase has been shown to have less interobserver variability and a stronger correlation with adult hypertension,[28] the most recent recommendations (since the 1996 Working Group report[29]) have supported the use of the fifth Korotkoff phase (disappearance of sound) for all children and adolescents.[30] The present study supports the present recommendations by showing no significant differences between the fourth and fifth Korotkoff phases in predicting future cIMT.

Concerning clinical practice implications of the present study, we provided cut points for elevated childhood BP levels in different age and sex groups, based on the prediction of adult cIMT (Table 5). Sensitivity (42%–80%) and specificity (27%–73%) were not very high for these childhood cutoffs. However, they are comparable with NCEP and NHANES cut points for elevated LDL (low-density lipoprotein)-cholesterol in childhood predicting subsequent high cIMT.[31]

The main strength of this study is the large database from all 6 studies that included similar lifestyle and biological risk factors in childhood and followed the cohorts into adulthood. The study also has certain limitations. First, there were no replicate measures that might have modified our results, with BP measurements taken only at a single time point in childhood and in adulthood. However, in the YFS, single childhood measurements were nearly as informative as repeated measurements in determining associations between childhood and adult measurements.[6] Additionally, when individual SBP and DBP were studied, SBP was found to be associated with cIMT, but the correlations between DBP and cIMT in adulthood were weaker, and a higher number of DBP measurements did not improve prediction of cIMT.[32] In the present study, BP was measured 2 to 6 times during one visit. It has been reported that BP tracking was slightly higher with multiple BP measurements per visit, but the tracking correlations were not improved with >2 measurements.[28] Second, because the study cohorts are comprised of young adults at follow-up, we are not able to study associations between risk factors and definite cardiovascular events. Instead, we have used cIMT as a surrogate end point. Therefore, the risk stratification groupings are not based on absolute risk of CVD events (as in adult risk score systems) but on high cIMT (≥90th percentile). We observed that childhood BP levels predict cIMT in young

Table 5. Optimal Cut Points for Childhood Systolic BP Predicting High cIMT in Adulthood, Including Sensitivity and Specificity

Sex	Age, y	N	Optimal Cutoff for Systolic BP,* mm Hg	Sensitivity, %	Specificity, %
Males					
	3–6	657	105	53	50
	7–12	1152	108	45	66
	13–18	888	120	53	56
Females					
	3–6	833	108	52	60
	7–12	1371	106	50	50
	13–18	1024	115	38	63

BP indicates blood pressure; and cIMT, carotid intima-media thickness.

*Optimal distance to (0,1) was defined by the equation: $\sqrt{(1-\text{Sensitivity})^2+(1-\text{Specificity})^2}$.

adulthood. In older adults cIMT has been shown to predict subsequent CVD events,[1] but there is paucity of knowledge about the predictive utility of young adulthood cIMT measurements for future CVD with the exception of data from the Carotid Atherosclerosis Progression Study indicating an equivalent or higher relative risk of a combined end point (myocardial infarction, stroke, or death) among younger (<50 years) versus older (≥50 years) adults.[32]

Our data, based on 6 large population-based prospective cohorts, confirm that youth with elevated SBP are at increased risk of adult high cIMT measured, on average, 25 years later. Moreover, prediction using SBP alone is at least equivalent to any other individual or combined BP measurement, suggesting that in the pediatric setting, the prediction of future subclinical atherosclerosis can be best achieved using childhood SBP measurements.

Perspectives

This finding is clinically important because prehypertension and hypertension are substantially underdiagnosed in the pediatric setting. Additionally, uncertainty exists about the relative importance of various BP components in predicting risk. The findings from the present study address these important areas and confirm the value of a simple measurement of SBP in the clinical setting.

Sources of Funding

This study was supported by a grant from the US National Institutes of Health (NIH/National Heart, Lung and Blood Institute [NHLBI]) number R01 HL121230 and the Australian National Health and Medical Research Council Project Grant (APP1098369 and APP211316). C.G. Magnussen was supported by a National Heart Foundation of Australia Future Leader Fellowship (100849). The Young Finns has been financially supported by the Academy of Finland (grants 126925, 121584, 124282, 129378, 117787, and 41071), the Social Insurance Institution of Finland; Kuopio, Tampere, and Turku University Hospital Medical Funds, Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research, Finnish Cultural Foundation, Sigrid Juselius Foundation, Yrjö Jahnsson Foundation. J. Koskinen was supported by Turku University foundation (11–2259), Emil Aaltonen Foundation and Urmas Pekkala Foundation. The Muscatine Study was supported by a Specialized Center of Research (SCOR) in Atherosclerosis grant from the NHLBI HL-14230, by RR-00059 from the General Clinical Research Centers Program, NCRR, NIH, and by the following NHLBI (NHLBI) R01s HL-48050, HL-54730, and HL-61857. The Kaunas Cardiovascular Cohort Study was supported by research grants from the Research Council of Lithuania (LIG-01/2012).

Disclosures

None.

References

1. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467. doi: 10.1161/CIRCULATIONAHA.106.628875
2. Juhola J, Magnussen CG, Berenson GS, et al. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: the International Childhood Cardiovascular Cohort Consortium. *Circulation*. 2013;128:217–224. doi: 10.1161/CIRCULATIONAHA.113.001614
3. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:243–250. doi: 10.1161/CIRCULATIONAHA.108.797936
4. Freedman DS, Foltz JL, Berenson GS. Differences between the fourth and fifth Korotkoff phases among children and adolescents. *Am J Hypertens*. 2014;27:1495–1502. doi: 10.1093/ajh/hpu064
5. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T; American Heart Association Council on Hypertension. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension*. 2015;66:698–722. doi: 10.1161/HYP.0000000000000033
6. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277–2283. doi: 10.1001/jama.290.17.2277
7. Dwyer T, Magnussen CG, Schmidt MD, Ukoumunne OC, Ponsonby AL, Raitakari OT, Zimmet PZ, Blair SN, Thomson R, Cleland VJ, Venn A. Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care*. 2009;32:683–687. doi: 10.2337/dc08-1638
8. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650–1656. doi: 10.1056/NEJM199806043382302
9. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation*. 2001;104:2815–2819.
10. Moran A, Jacobs DR Jr, Steinberger J, Steffen LM, Pankow JS, Hong CP, Sinaiko AR. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. *Circulation*. 2008;117:2361–2368. doi: 10.1161/CIRCULATIONAHA.107.704569
11. Rasmussen-Torvik LJ, Pankow JS, Jacobs DR Jr, Steinberger J, Moran A, Sinaiko AR. Development of associations among central adiposity, adiponectin and insulin sensitivity from adolescence to young adulthood. *Diabet Med*. 2012;29:1153–1158. doi: 10.1111/j.1464-5491.2012.03726.x
12. Ceponiene I, Klumbiene J, Tamuleviciute-Prasciene E, Motiejunaite J, Sakyte E, Ceponis J, Slapikas R, Petkeviciene J. Associations between risk factors in childhood (12-13 years) and adulthood (48-49 years) and subclinical atherosclerosis: the Kaunas Cardiovascular Risk Cohort Study. *BMC Cardiovasc Disord*. 2015;15:89. doi: 10.1186/s12872-015-0087-0
13. Dwyer T, Sun C, Magnussen CG, et al. Cohort profile: the International Childhood Cardiovascular Cohort (i3C) Consortium. *Int J Epidemiol*. 2013;42:86–96. doi: 10.1093/ije/dys004
14. Sinaiko AR, Jacobs DR Jr, Steinberger J, Moran A, Luepker R, Rocchini AP, Prineas RJ. Insulin resistance syndrome in childhood: associations of the euglycemic insulin clamp and fasting insulin with fatness and other risk factors. *J Pediatr*. 2001;139:700–707. doi: 10.1067/mpd.2001.118535
15. Magnussen CG, Fryer J, Venn A, Laakkonen M, Raitakari OT. Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: agreement between measurements from two ultrasound machines. *Ultrasound Med Biol*. 2006;32:1323–1329. doi: 10.1016/j.ultrasmedbio.2006.05.009
16. Dengel DR, Jacobs DR, Steinberger J, Moran AM, Sinaiko AR. Gender differences in vascular function and insulin sensitivity in young adults. *Clin Sci (Lond)*. 2011;120:153–160. doi: 10.1042/CS20100223
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
18. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172; discussion 207. doi: 10.1002/sim.2929
19. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11–21. doi: 10.1002/sim.4085
20. Sundström J, Neovius M, Tynelius P, Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. *BMJ*. 2011;342:d643. doi: 10.1136/bmj.d643
21. Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, Chen W, Srinivasan SR, Daniels SR, Kähönen M, Laitinen T, Taittonen L, Berenson GS, Viikari JS, Raitakari OT. Influence of age on associations between

childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation*. 2010;122:2514–2520. doi: 10.1161/CIRCULATIONAHA.110.966465

22. Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Hulkkonen J, Laitinen T, Taittonen L, Lehtimäki T, Raitakari OT, Kähönen M. Lifetime risk factors and arterial pulse wave velocity in adulthood: the cardiovascular risk in young Finns study. *Hypertension*. 2010;55:806–811. doi: 10.1161/HYPERTENSIONAHA.109.145102
23. Sorof JM, Poffenbarger T, Franco K, Bernard L, Portman RJ. Isolated systolic hypertension, obesity, and hyperkinetic hemodynamic states in children. *J Pediatr*. 2002;140:660–666. doi: 10.1067/mpd.2002.125228
24. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J; MRFIT Research Group. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 2002;287:2677–2683. doi: 10.1001/jama.287.20.2677
25. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96:308–315.
26. Juhola J, Magnussen CG, Viikari JS, Kähönen M, Hutri-Kähönen N, Jula A, Lehtimäki T, Åkerblom HK, Pietikäinen M, Laitinen T, Jokinen E, Taittonen L, Raitakari OT, Juonala M. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the cardiovascular risk in Young Finns Study. *J Pediatr*. 2011;159:584–590. doi: 10.1016/j.jpeds.2011.03.021
27. Kelly RK, Thomson R, Smith KJ, Dwyer T, Venn A, Magnussen CG. Factors affecting tracking of blood pressure from childhood to adulthood: the Childhood Determinants of Adult Health Study. *J Pediatr*. 2015;167:1422.e2–1428.e2. doi: 10.1016/j.jpeds.2015.07.055
28. Chen X, Wang Y, Appel LJ, Mi J. Impacts of measurement protocols on blood pressure tracking from childhood into adulthood: a metaregression analysis. *Hypertension*. 2008;51:642–649. doi: 10.1161/HYPERTENSIONAHA.107.102145
29. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. *Pediatrics*. 1996;98:649–658.
30. 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. doi: 10.1542/peds.114.2.S2.555
31. Magnussen CG, Venn A, Thomson R, Juonala M, Srinivasan SR, Viikari JS, Berenson GS, Dwyer T, Raitakari OT. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in Young Finns study, the Bogalusa Heart study, and the CDAH (Childhood Determinants of Adult Health) study. *J Am Coll Cardiol*. 2009;53:860–869. doi: 10.1016/j.jacc.2008.09.061
32. Oikonen M, Nuotio J, Magnussen CG, Viikari JS, Taittonen L, Laitinen T, Hutri-Kähönen N, Jokinen E, Jula A, Cheung M, Sabin MA, Daniels SR, Raitakari OT, Juonala M. Repeated blood pressure measurements in childhood in prediction of hypertension in adulthood. *Hypertension*. 2016;67:41–47. doi: 10.1161/HYPERTENSIONAHA.115.06395

Novelty and Significance

What Is New?

- In the present international, multicenter study, we assessed and compared the predictive ability of childhood blood pressure components (systolic, diastolic, mean arterial, and pulse pressure) in predicting carotid intima-media thickness in adulthood. In addition, we provided age- and sex-specific cut points for clinical practice.

What Is Relevant?

- We found that children with elevated systolic blood pressure are at increased risk of adult subclinical atherosclerosis 25 years later. Moreover, prediction using systolic blood pressure alone is at least equivalent to any other individual or combined blood pressure measurements.

Summary

Systolic blood pressure alone in childhood could provide a simple way to predict future subclinical atherosclerosis.