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Can Pediatric Hypertension Criteria Be Simplified? A Prediction Analysis of Subclinical Cardiovascular Outcomes from the Bogalusa Heart Study

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Abstract

Pre-hypertension and hypertension in childhood are defined by sex-, age- and height-specific 90th (or ≥120/80 mmHg) and 95th percentiles of blood pressure (BP), respectively, by the 2004 Fourth Report. However, these cut-offs are complex and cumbersome for use. This study assessed the performance of a simplified BP definition to predict adult hypertension and subclinical cardiovascular disease. The cohort consisted of 1,225 adults (530 males, aged 26.3–47.7 years) from the Bogalusa Heart Study with 27.1 years follow-up since childhood. We used 110/70 and 120/80 mmHg for children (age 6–11 years), and 120/80 and 130/85 mmHg for adolescents (age 12–17 years) as the simplified definition of childhood pre-hypertension and hypertension, respectively, to compare with the 2004 Fourth Report (the complex definition). Adult carotid intima-media thickness (CIMT), pulse wave velocity (PWV), and left ventricular mass were measured using digital ultrasound instruments. Compared to normal BP, childhood hypertensives diagnosed by the simplified definition and the complex definition were both at higher risk of adult hypertension with hazard ratio=3.1 (95% confidence interval=1.8–5.3) by the simplified definition and 3.2 (2.0–5.0) by the complex definition, high PWV with 3.5 (1.7–7.1) and 2.2 (1.2–4.1), high CIMT with 3.1 (1.7–5.6) and 2.0 (1.2–3.6), and left ventricular hypertrophy with 3.4 (1.7–6.8) and 3.0 (1.6–5.6). The results were confirmed by reclassification or receiver operating curve analyses. The simplified childhood BP definition predicts the risk of adult hypertension and subclinical cardiovascular disease equally as the complex definition does, which could be useful for screening hypertensive children to reduce risk of adult cardiovascular disease.

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Conflicts of Interest/Disclosures
None.

Author Contributions
Drs. Bo Xi and Wei Chen generated the hypothesis, directed implementation, and wrote the manuscript. Dr. Tao Zhang contributed to analytic strategy and statistical analyses. Dr. Shengxu Li edited the manuscript. Drs. Emily Harville, Lydia Bazzano and Jiang He supervised the field activities and data collection and edited the manuscript.

Keywords

Blood pressure; Children; Simplified definition; Subclinical cardiovascular disease; Prediction; Longitudinal study

Introduction

Childhood elevated blood pressure (BP) is a public health problem worldwide. [1] Elevated BP has been associated with risk of target organ damage in children.[2] In addition, BP in childhood is moderately correlated with BP in adulthood.[3] Children with elevated BP are more likely to develop subclinical atherosclerosis[4] and premature mortality, compared to those with normal BP,[5] although the absolute number developing adult CVD events for elevated BP children are much less than normal BP ones. It is important to identify children with elevated BP early in order to prevent target organ damage and identify secondary hypertension in childhood and later life, and lower the risk of cardiovascular disease (CVD) in adulthood.

Currently, BP measurements are recommended in clinical practice for children aged 3 years or older by both the American Academy of Pediatrics [6] and the European Society of Hypertension [7]. Pre-hypertension and hypertension in childhood are defined based on sex-, age-, and height-specific 90th and 95th BP percentiles, respectively, on three different occasions by the National High Blood Pressure Education Program (the Fourth Report). [6] However, these reference criteria lead to as many as 476 cut-off points for children and adolescents aged 1–17 years which are complex and cumbersome to use in clinical practice. Elevated BP is infrequently diagnosed in children even when routinely measured BP is available, partially because of the complexity of the BP percentile reference criteria.[8] Recently, several researchers have developed simplified tools to screen for elevated BP in children,[9] including the use of simplified mathematical formulas,[10, 11] simplified tables by age and/or sex,[12, 13] and height-specific simplified tables,[14] and BP to height ratio.[15, 16] However, these simplified methods are either still difficult to use or have low positive predictive values compared with the complex definition specific for sex, age and height percentiles.[17–19]

The International Diabetes Federation has recommended that systolic/diastolic BP (SBP/DBP) ≥130/85 mmHg should be used to define hypertension for adolescents.[20] We feel that ≥120/80 mmHg might be suitable to define hypertension for children aged 6–11 years based on the complex BP percentile tables (the Fourth Report). Most recently, the Systolic Blood Pressure Intervention Trial (SPRINT) suggests that reduction of SBP to <120 mmHg decreases risk of CVD and related mortality compared with the traditional reduction goal of <140 mmHg in adults.[21] Falkner and Gidding (2016) suggested normal (optimal) BP cut off could be <120/80 mmHg for adolescents ≥12 years and <110/70 mmHg for children <12 years for primordial prevention in pediatric population.[22] It is clear that these four cut-offs are much easier to remember and more user-friendly in clinical practice than the complex definition based on sex-, age-, and height percentiles. To our knowledge, no study has validated the performance of this simplified criterion in predicting CV risk in adulthood compared with the complex references.

We aimed to assess the performance of these simplified BP cut-offs in childhood to predict hypertension and subclinical CVD in adulthood utilizing the longitudinal cohort of the Bogalusa Heart Study.[23]

Methods

Subjects

The Bogalusa Heart Study, a series of long-term studies in a semi-rural biracial (65% white and 35% black) community in Bogalusa, Louisiana, was funded by Dr. Gerald Berenson in 1973. This study focuses on the early natural history of cardiovascular disease since childhood. The study cohort profile has been described in detail elsewhere.[23] In brief, between 1973 and 1988, eight cross-sectional surveys of children aged 4 to 17 years were conducted in Bogalusa, Louisiana. Children aged 4 and 5 years (n=57) were excluded as the sample size was small. A total of 1225 adults (43.3% men; age range=26.3–47.7 years) who participated in previous children surveys were examined between 2000 and 2010. The mean follow-up period was 27.1 years (range=19.1–36.5 years). This longitudinal cohort had data on cardiovascular risk factors from childhood to adulthood, and subclinical CVD including carotid intima-media thickness (CIMT), aorta–femoral pulse wave velocity (afPWV), left ventricular hypertrophy (LVH) in adulthood.

The number of children (number of visits) during the follow-up period in this longitudinal cohort was 236 (1), 333 (2), 310 (3), 197 (4), and 149 (≥5). The definitions of childhood pre-hypertension and hypertension were based on the Fourth Report and our simplified method cut-offs. For children experiencing more than one visits, BP value in the first visit was chosen to classify children as normotensives if BP values in all visits were below the cut-offs of both definitions; the first visit was chosen to classify children as pre-hypertensives or hypertensives if BP values in one or more visits during childhood were above the cut-offs of either definition. This sample selection strategy maximized the number of children with pre-hypertension and hypertension. For instance, using our selection approach, the number of children with hypertension was 59 based on the Fourth Report, and 50 according to our simplified method (Table 1). This approach is superior to the methods of choosing the first visit, choosing the last visit and random selection since a substantial proportion of hypertensive children were misclassified using these three selection methods, with only 25, 29 and 28 for the Fourth Report and 15, 33 and 23 for our simplified definition.

All subjects in this study gave informed consent for each survey, and for those under 18 years of age, consent of a parent/guardian was obtained in all children surveys. The protocol was approved by the institutional review board of the Tulane University Health Sciences Center.

General examinations

All examinations in both childhood and adulthood followed essentially the same protocols[23]. Height was measured twice with 0.1 cm accuracy, and weight was measured twice with 0.1

kg accuracy. The average values were used to calculate body mass index (BMI) as weight/height^2 (kg/m^2). Overweight and obesity was defined according to 85th and 95th percentile of CDC 2000 growth charts by sex and age.[24]

BP levels in both childhood and adulthood were measured on the right arm with appropriate cuff after at least 5 minutes resting for each participant using calibrated mercury sphygmomanometers between 8:00 am and 10:00 am. BP measurements were obtained with subjects sitting with back supported and feet on the floor. SBP was measured at the first Korotkoff phase, and DBP at the fifth Korotkoff (K5) phase for both children and adults. DBP at the fourth Korotkoff phase (K4) was also recorded for all children. For children with the K5 being "very low" (less than 20 mmHg) [25] recommended by the Fourth Report, the K4 was used as DBP. [6] For each participant, BP levels were measured by two trained observers (three replicates each). The mean values of the six readings were used for analysis. This is far more measurements than that would be obtained in a routine child health exam but the mean of six BP readings would be more stable and accurate. Adult hypertension was defined as ≥140/90 mmHg or taking antihypertensive medicine.

Subclinical CV structure and function

CIMT, afPWV and LVH in adulthood were measured using a Toshiba digital ultrasound instrument (Xario SSA-660A; Toshiba America Medical Systems, Tustin, California) following American Society of Echocardiography recommendations.[26] Details of CIMT, afPWV and LVH measurements have been described elsewhere. [27–29] In brief, the mean value of three sites of CIMT (the far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery) was determined using a 7.5-MHz linear array transducer.[27] Subclinical atherosclerosis was defined as values equal to or greater than the age-, sex-, and race-specific 80th percentile of CIMT. [30]

For afPWV, a 2.5 MHz nondirectional transcutaneous Doppler flow probe was positioned at the suprasternal notch, and another 7.5 MHz probe was positioned at the left femoral artery with the subject lying in a supine position. After the collection of the waveform data, the distance between the suprasternal notch and femoral arteries was measured with a caliper instrument to reduce the influence of body contours on the distance measured. af-PWV was calculated by dividing the distance traveled by the time differential between the two waveforms. Results from three data collection runs were averaged for each participant.[28] Arterial stiffness was defined as values at or above the age-, gender-, race- and heart-rate-specific 80th percentile of afPWV.[31]

LV dimensions were assessed by 2-dimensional guided M-mode echocardiography with 2.25- and 3.5-MHz transducers. Parasternal long- and short-axis views were used for measuring LV end-diastolic and end-systolic measurements in duplicate, and the mean was calculated. LV mass (LVM) was calculated from a necropsy-validated formula on the basis of a thick-wall prolate ellipsoidal geometry [29]. LV mass index (LVMI) was calculated as LVM/height$^{2.7}$ (g/m$^{2.7}$) to account for body size. The presence of LVH was defined by sex-specific cutoffs of LVMI >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men.[32]

Definition of elevated BP in childhood

Simplified BP definition—Pre-hypertension was defined as (SBP≥110 and/or DBP≥70 mmHg) and (SBP<120 and DBP<80 mmHg) for children aged 6–11 years, and (SBP≥120 and/or DBP≥80 mmHg) and (SBP<130 and DBP<85 mmHg) for adolescents aged 12–17 years. Hypertension was defined as SBP≥120 and/or DBP≥80 mmHg for children, and SBP≥130 and/or DBP≥85 mmHg for adolescents. There was no child at baseline using anti-hypertensive drugs.

Complex BP definition—Pre-hypertension and hypertension were defined as ≥ 90th percentiles (or ≥120/80 mmHg) and <95th percentiles, and ≥ 95th percentiles by sex, age and height based on BP references of the Fourth Report, respectively.[6]

Statistical analysis

The differences in baseline and follow-up variables between children and adolescents were tested using generalized linear model (GLM) (for continuous) or Chi-squared test (for categorical). Multi-variable adjusted Cox regression analyses were conducted to examine the performance of the childhood simplified definition as compared to the traditional complex definition in predicting adult hypertension, subclinical atherosclerosis, arterial stiffness and LVH, with adjustment for sex, age, race, and childhood BMI. We also performed sensitivity analyses according to sex, age group, BMI, categories and height categories. We calculated net reclassification improvement (NRI) to determine the extent to which the simplified definition (vs. the complex definition) improves the predictive ability. [33, 34] In addition, we used receiver operating characteristic curve (ROC) analysis to calculate the sensitivity, specificity, positive predictive value, negative predictive value, and area under curve (AUC) of two definitions of pediatric elevated BP (including pre-hypertension and hypertension) in predicting adult hypertension and subclinical CVD outcomes. All data analyses were performed using R 3.1.3. Two tailed-*P* values <0.05 were considered statistically significant.

Results

Participant characteristics

Table 1 shows the baseline and follow-up characteristics of study participants by age group. The number (percentage) of children with normal BP, pre-hypertension and hypertension was 998 (81.5%), 168 (13.7%), and 59 (4.8%), respectively, based on the complex definition, and 950 (77.5%), 225 (18.4%), and 50 (4.1%), respectively, based on the simplified method. At baseline, adolescents aged 12–17 years were more likely to have elevated BP than children aged 6–11 years. In adulthood, older participants had higher CIMT and afPWV, and had higher prevalence of hypertension than younger participants.

Consistence of two BP definitions in childhood

The Kappa correlation coefficient between the simplified definition and complex definition was 0.86 (95% CI: 0.89–0.91), with only 77 subjects being non-overlapping using two definitions (complex definition: n=52 for normal BP, n=10 for pre-hypertension, and n=15 for hypertension; simplified definition: the corresponding figures were 4, 67, and 6, respectively).

Association between elevated BP defined by two criteria in childhood and risk of adult outcomes

Participants with pre-hypertension or hypertension in childhood defined using either definition were at higher risk of adult hypertension and subclinical CVD outcomes including arterial stiffness, subclinical atherosclerosis and LVH compared to children with normal BP (Table 2). The strengths of the associations were similar using either the simplified definition or the complex definition. For instance, for the outcome of any subclinical CVD in adulthood, the hazard ratio (HR) was 3.21 (95%CI 2.07–4.96) and 2.20 (95%CI 1.47–3.30) for children with hypertension compared to those with normal BP, using two definitions, respectively (Table 2).

We performed sensitivity analyses to test the robustness of our findings. First, we used K4 for DBP, and the results were much similar to those using K5 (Table S1). In addition, K5 < 20 mmHg might be too low for us to decide for use of K4, we performed a sensitivity analysis using K4 to replace K5 when K5 < 30 mmHg. The results were very similar (data not shown). Second, we examined subgroups by sex, age (6–11 vs. 12–17 years), BMI categories (normal weight vs. overweight) and height categories (<50th percentile vs. ≥50th percentile specific for age and sex). The performance of the simplified BP definition was similar to that of the complex definition in predicting adult hypertension, high afPWV, high CIMT and LVH in each subgroup (Tables S2–S6). Third, we further adjusted for other covariates in adulthood (e.g., physical activity, smoking and alcohol consumption) in Cox regression models, and the results did not change substantially (data not shown). Fourth, when examining association with subclinical CV risk, we performed a sensitivity analysis after exclusion of adults taking anti-hypertensive (n=115) or lipid-lowering drugs (n=44), and obtained similar results.

Performance of two criteria in childhood for predicting adult outcomes using reclassification method and ROC analysis

The simplified BP definition also performed equally well compared with the complex BP definition in predicting hypertension and subclinical CVD in adulthood using reclassification method (Table S7) or ROC analysis (Table S8). There was no significant difference in NRI (all P>0.05) or AUC (all P>0.05) between the two definitions.

Discussion

Currently, pre-hypertension and hypertension are usually defined by sex-, age-, and height-specific 90th and 95th percentile of BP in children and adolescents.[6, 35] However, these percentile cut-offs are difficult to remember and use in practice. Simplifying these percentiles would allow convenient and effective screening and identification of elevated BP in childhood, which might be useful for early prevention of CVD in adulthood. In the present study, the Kappa correlation coefficient was 0.86, which confirmed that compared to the complex definition, our choices of simplified cut-offs of elevated BP were reasonable. In addition, we demonstrated that a simplified definition (110/70 and 120/80 mmHg for children, and 120/80 and 130/85 mmHg for adolescents, to define pre-hypertension and hypertension, respectively) performed similarly compared to the traditional complex BP references (the Fourth Report) in predicting adult hypertension and subclinical CVD outcomes measured as arterial stiffness, subclinical atherosclerosis and LVH. With a similar predictive power, the simplified definition can be more convenient and useful for screening high risk subjects in practice.

In adults, 120/80 and 140/90 mmHg are widely accepted as the optimal cut-offs of pre-hypertension and hypertension, respectively. The choice of these cut-offs is mainly based on the predictive value of BP for CVD outcomes. However, data are limited linking specific BP levels in children or adolescents to CVD outcomes in later life. The definition of pediatric elevated BP is mainly based on the distribution of BP levels using statistical methods, as well as the assumption that the upper limits of BP ranges in general children are probably not ideal. [22, 36] In addition, age and height are considered in establishing childhood BP percentiles because BP changes with two variables during normal growth and development. However, these childhood BP percentiles are arbitrary to some extent as they were established using the statistical method rather than linking BP levels in childhood to health outcomes in childhood or adulthood.

In 1977, the first US BP percentiles were established with only sex and age factored in.[37] In 1996 and 2004, besides sex and age, height was introduced into BP percentiles [6, 38] since height is an important factor influencing childhood BP.[39] However, the introduction of height into childhood BP percentiles made it more complex and difficult to use for health professionals in clinical practice. Although our proposed simplified definition does not take into account sex, age and height, they performed equally well (if not better) in predicting adult hypertension and subclinical CVD outcomes compared with the traditional complex BP references. Our findings suggest that the complex definition might be unnecessary to adjust for height.

The current longitudinal study cohort followed from childhood to adulthood provided an opportunity to assess the performance of pediatric BP cutoffs by prediction analyses. However, this study has certain limitations. First, the small number of blacks did not allow us to perform subgroup analysis by race. Second, the cohort is still too young (mean age=37.3 years) to have clinical CVD events such as coronary heart disease and stroke. Thus, we used surrogate endpoints of PWV, CIMT and LVH for prediction analysis. Other subclinical indices such as endothelial function may be a more mechanistically related surrogate index of CVD. Unfortunately, endothelial function data were not available in this cohort. Third, many medical organizations recommend that children aged 3 years and above should be included, but we provided simplified BP cut-offs for children aged 6–17 years only. Further studies are necessary to bridge this gap. Fourth, in children aged 6–11 years, a big discrepancy in the prevalence rates of pre-hypertension (11.3% vs 3.7%) was seen by using the two definitions in the present study. Further studies with sufficient sample size are necessary to determine the optimal cut-off for this age group.

Perspectives

The present study suggests that compared to the much more complex definition of the Fourth Report, our simplified BP cut-offs performed equally well to predict hypertension and subclinical CVD in adulthood. Our findings support the use of the simplified definitions to screen and identify children and adolescents with elevated BP in order to prevent CVD risk in adulthood. Further future cohort studies are needed to confirm our findings in different populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

To our knowledge, this is the first study using 110/70 and 120/80 mmHg for children (age 6–11 years), and 120/80 and 130/85 mmHg for adolescents (age 12–17 years) as the simplified definitions of childhood pre-hypertension and hypertension, respectively, to compare with the complex definitions in predicting adult hypertension and cardiovascular outcomes.

What Is Relevant?

The simplified childhood BP definition predicts the risk of adult hypertension and subclinical cardiovascular disease equally as the complex definition does. The simplified pediatric BP cut-offs could be convenient and useful for screening children at high risk and for targeting early life interventions to reduce the risk of developing cardiovascular disease (CVD) in later life.

Summary

The present study suggests that compared to the much more complex definition of the Fourth Report, our simplified BP cut-offs performed equally well to predict hypertension and subclinical CVD in adulthood. Our findings support the use of the simplified definitions to screen and identify children and adolescents with elevated BP in order to prevent CVD risk in adulthood.

Table 1

Baseline and follow-up characteristics of study participants by age group

Variable	Total	Children (6–11 years)	Adolescents (12–17 years)	*P* value*
No. of subjects	1225	737	488	
Whites, n (%)	849 (69.3)	508 (68.9)	341 (69.9)	0.772
Males, n (%)	531 (43.4)	305 (41.4)	226 (46.3)	0.100
Baseline				
Age, years	10.9 ± 3.3	8.6 ± 1.7	14.4 ± 1.6	<0.001
Height, cm	142.9 ± 19.3	130.1 ± 11.8	162.2 ± 10.3	<0.001
BMI, kg/m^2	18.4 ± 4.0	16.9 ± 3.0	20.6 ± 4.2	<0.001
SBP, mmHg	103.0 ± 13.1	97.1 ± 10.1	111.8 ± 12.2	<0.001
DBP-K4	63.8 ± 9.8	59.7 ± 8.3	69.9 ± 8.6	<0.001
DBP-K5, mmHg	48.6 ± 12.4	44.8 ± 10.5	54.3 ± 13.0	<0.001
Overweight, n (%)	127 (10.4)	81 (11.0)	46 (9.4)	
Obesity, n (%)	105 (8.6)	62 (8.4)	43 (8.8)	0.671
Pre-hypertension, n (%)-simplified definition	225 (18.4)	83 (11.3)	142 (29.1)	
Hypertension, n (%)-simplified definition	50 (4.1)	20 (2.7)	30 (6.2)	<0.001
Pre-hypertension, n (%)-complex definition	168 (13.7)	27 (3.7)	141 (29.0)	
Hypertension, n (%)-complex definition	59 (4.8)	26 (3.5)	33 (6.8)	<0.001
Follow-up				
Age, years	37.3 ± 4.5	34.9 ± 3.8	40.8 ± 2.7	<0.001
Height, cm	169.5 ± 9.5	169.0 ± 9.3	170.3 ± 9.7	0.009
BMI, kg/m^2	29.5 ± 7.1	29.3 ± 7.2	29.8 ± 6.8	0.202
SBP, mmHg	117.4 ± 14.6	115.3 ± 13.8	120.5 ± 15.3	<0.001
DBP, mmHg	79.2 ± 10.2	77.8 ± 10.0	81.2 ± 10.2	<0.001
afPWV, m/s	5.4 ± 1.3	5.3 ± 1.3	5.7 ± 1.4	<0.001
CIMT, mm	0.82 ± 0.17	0.79 ± 0.13	0.87 ± 0.20	<0.001
LVMI, g/m$^{2.7}$	35.6 ± 11.2	35.1 ± 11.0	36.2 ± 11.4	0.107
Hypertension, n (%)	271 (22.1)	131 (17.8)	140 (28.7)	<0.001
High PWV, n (%)	213 (20.0)	129 (20.0)	84 (20.0)	1.000
High CIMT, n (%)	228 (20.0)	124 (18.2)	104 (22.8)	0.065
LVH, n (%)	138 (12.4)	75 (11.2)	63 (14.3)	0.144
Any of high PWV, CIMT or LVH, n (%)	452 (44.1)	262 (42.5)	190 (46.5)	0.231

Continuous variables are expressed as mean ± SD

*Difference between children and adolescents

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; afPWV, aorta–femoral pulse wave velocity; CIMT, carotid intima-media thickness; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy

Table 2

Hazard ratio and 95% confidence interval for adult hypertension and subclinical CVD outcomes associated with childhood pre-hypertension and hypertension as predictors by the two definitions

Outcome	Childhood Pre-hypertension					
	Simplified definition			Complex definition		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Adult hypertension	2.82	2.04–3.89	<0.001	2.91	1.99–4.26	<0.001
High PWV	2.66	1.82–3.89	<0.001	2.55	1.58–4.12	<0.001
High CIMT	2.79	1.96–3.97	<0.001	3.03	1.99–4.61	<0.001
LVH	1.92	1.19–3.10	0.007	2.45	1.40–4.28	0.002
Any subclinical CVD	2.55	1.97–3.31	<0.001	3.03	2.20–4.18	<0.001
	Childhood Hypertension					
	Simplified definition			Complex definition		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Adult hypertension	3.11	1.83–5.26	<0.001	3.17	1.99–5.04	<0.001
High PWV	3.51	1.74–7.07	<0.001	2.22	1.21–4.07	0.010
High CIMT	3.07	1.70–5.56	<0.001	2.03	1.15–3.58	0.015
LVH	3.41	1.70–6.84	0.001	2.97	1.57–5.61	0.001
Any subclinical CVD	3.21	2.07–4.96	<0.001	2.20	1.47–3.30	<0.001

CVD, cardiovascular disease; PWV, pulse wave velocity; CIMT, carotid intima-media thickness; LVH, left ventricular hypertrophy

Sex, age, race, and childhood BMI were included in the models for adjustment.