Simplified Definitions of Elevated Pediatric Blood Pressure and High Adult Arterial Stiffness

WHAT’S KNOWN ON THIS SUBJECT: Elevated blood pressure (BP) has long-term influence on the atherosclerotic process. The relative predictive ability of the standard BP definition endorsed by the National High Blood Pressure Education Program and the recently proposed 2 simplified definitions has not been studied.

WHAT THIS STUDY ADDS: Simplified pediatric BP tables predict risk of high adult arterial stiffness as well as the complex table does. These simple screening tools could be used for identifying pediatric subjects at risk and for intervening to improve adult cardiovascular outcomes.

abstract

OBJECTIVE: The ability of childhood elevated blood pressure (BP) to predict high pulse wave velocity (PWV), a surrogate marker for cardiovascular disease, in adulthood has not been reported. We studied whether elevated pediatric BP could predict high PWV in adulthood and if there is a difference in the predictive ability between the standard BP definition endorsed by the National High Blood Pressure Education Program and the recently proposed 2 simplified definitions.

METHODS: The sample comprised 1241 subjects from the Cardiovascular Risk in Young Finns Study followed-up 27 years since baseline (1980, aged 6–15 years). Arterial PWV was measured in 2007 by whole-body impedance cardiography.

RESULTS: The relative risk for high PWV was 1.5 using the simple 1 (age-specific) definition, 1.6 using the simple 2 (age- and gender-specific) definition, and 1.7 using the complex (age-, gender-, and height-specific) definition (95% confidence interval: 1.1–2.0, \( P = .007 \); 1.2–2.2, \( P = .001 \); and 1.2–2.2, \( P = .001 \), respectively). Predictions of high PWV were equivalent for the simple 1 or simple 2 versus complex definition (\( P = .25 \) and \( P = .68 \) for area under the curve comparisons, \( P = .13 \) and \( P = .35 \) for net reclassification indexes, respectively).

CONCLUSIONS: Our results support the previous finding that elevated BP tracks from childhood to adulthood and accelerates the atherosclerotic process. The simplified BP tables could be used to identify pediatric patients at increased risk of high arterial stiffness in adulthood and hence to improve the primary prevention of cardiovascular diseases. Pediatrics 2013;132:e70–e76

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KEY WORDS
blood pressure, pediatrics, prehypertension, screening, stiffness

ABBREVIATIONS
AUC—area under receiver-operating characteristic curve
BP—blood pressure
CVD—cardiovascular diseases
NHBPEP—National High Blood Pressure Education Program
NPV—negative predictive value
NRI—net reclassification improvement
PPV—positive predictive value
PWV—pulse wave velocity

Dr Aatola analyzed and interpreted the data, performed statistical analysis, and drafted the initial manuscript; Dr Magnussen analyzed and interpreted the data, performed statistical analysis, and critically reviewed and revised the manuscript; Dr Koivistoinen analyzed and interpreted the data, performed statistical analysis, and critically reviewed and revised the manuscript; Drs Hutri-Kähönen, Viikari, and Lehtimäki acquired the data, handled funding and supervision, and reviewed and revised the manuscript; Dr Juonala acquired the data, analyzed and interpreted the data, and critically reviewed and revised the manuscript; Drs Raitakari conceived and designed the research, acquired the data, handled funding and supervision, and critically reviewed and revised the manuscript; Dr Kähönen conceived and designed the research, acquired the data, handled funding and supervision, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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(Continued on last page)
Previous reports have shown that the atherosclerotic process begins in youth, and elevated blood pressure (BP) accelerates it.1–4 Because of the epidemic of overweight and obesity in youth, the prevalence of hypertension is increasing.5,6 Early modification of risk factors, especially elevated BP and obesity, to prevent the progression of atherosclerosis is among the major contemporary challenges in the primary prevention of cardiovascular diseases (CVD).

Previous studies have shown that BP tracks from childhood to adulthood, and subjects having elevated BP in childhood and adolescence are at increased risk of developing hypertension in adulthood.7–9 These data indicate that elevated BP is established early in life, hence the prehypertension and hypertension are able to be identified already in youth, underlying the potential to reduce risks and optimize health outcomes as they relate to hypertensive diseases.

In the most recent guidelines issued by the National High Blood Pressure Education Program (NHBPEP), BP screening was recommended at all pediatric visits for health care from age 3 years.10 The NHBPEP guidelines provide decision-based cut-points to allow clinicians and pediatric health providers to define youth as normal, prehypertensive (formerly high normal, >90th percentile) and hypertensive (>95th percentile), according to age, gender, and height percentiles. Considering there are 7 height percentiles, 2 measures (systolic and diastolic BP), and 17 age groups (1–17 years) for boys and girls, the NHBPEP tables contain 478 threshold values for the definition of pediatric prehypertension alone, the same amount for definition of pediatric hypertension. This complex definition could at least partly explain the poor diagnosis of prehypertension and hypertension in children and adolescents reported previously.11,12 As a solution for this problem, Kaelber and Pickett13 and Mitchell et al12 recently proposed new screening tables. Kaelber and Pickett reduced the number of threshold values to 64 (2 measures and 16 age groups for boys and girls) by omitting height percentiles and separate cut-points to denote hypertension.13 Mitchell et al introduced a table with only 10 threshold values (2 measures and 5 age groups in increments of 3 years).12 Those values were near the lowest prehypertensive BP value in the NHBPEP table and were set to end in either 0 or 5. Both these simplified tables are proposed to use as a screening tool, which can more quickly and easily be used to identify pediatric patients whose BP levels need additional evaluation.

Arterial stiffness is a surrogate marker for CVD and, assessed as pulse wave velocity (PWV), is generally accepted as an independent predictor of cardiovascular events and all-cause mortality.14,15 Increased PWV was also added to the list of markers of subclinical organ damage and prognostic factors in the European guidelines for management of arterial hypertension.16 We and others have shown that childhood systolic BP is an independent predictor of PWV in adulthood.17–19 These previously mentioned findings strengthen the hypothesis that elevated pediatric BP accelerates the arterial stiffening and atherosclerotic process. However, to the best of our knowledge, no information has been published concerning the ability of the childhood elevated BP definitions to predict arterial stiffness in adulthood. Therefore, the aim of the current study was to evaluate and compare the utility of these 3 definitions to predict high adult PWV using participants of the prospective Cardiovascular Risk in Young Finns Study.

METHODS

Subjects

The Cardiovascular Risk in Young Finns Study is an ongoing multicenter follow-up study of atherosclerosis precursors in Finnish children and adolescents. The first cross-sectional study was conducted in 1980 for 3596 subjects aged 3 to 18 years.20 They were randomly selected from the Finnish national population register. Although data were available for participants aged 3 years in 1980 (n = 577), they were not included in the analyses because BP measures were collected using an ultrasound device. Measures from youth aged 18 years (n = 537) were not included in the analyses because the cut-points are identical for all 3 definitions. In 2007, 1289 subjects had PWV measurements taken. The subjects with incomplete childhood data (n = 19), subjects with type 1 (n = 9) or type 2 (n = 8) diabetes, and female patients who were pregnant (n = 12) were excluded. Therefore, 1241 subjects were included in the analysis. Study flowchart is shown in Fig 1. We repeated the analysis after excluding participants taking lipid-lowering (n = 24) or antihypertensive medications (n = 76), with essentially similar results. All subjects gave written informed consent, and the study was approved by local ethics committees.

Clinical Measurements

At baseline and follow-up, height was measured using a Seca stadiometer with 0.5 cm accuracy. BP was measured with a standard mercury sphygmomanometer in 1980 and a random zero sphygmomanometer (Hawksley & Sons Ltd, Lansing, United Kingdom) in 2007. All measurements were taken on the right arm after the participant had been seated for 5 minutes. Cuff size was chosen according to arm circumference. Systolic BP was recorded for Korotkoff’s first phase. Diastolic BP was recorded at both Korotkoff’s fourth and fifth phases. Korotkoff’s fifth phase results have been
used in the analyses because in 1980 in all age groups, diastolic BP was better achieved with Korotkoff’s fifth phase (no missing values in this study population) than Korotkoff’s fourth phase (absent in 2.5% of subjects). This was consistent with results reported previously by Uhari et al. Readings to the nearest integer of millimeters of mercury were performed 3 times on each participant. The mean of these 3 measurements was used in the analyses.

**Definition of Elevated BP Levels in Childhood**

**Simple 1 Definition**
Participants were defined according to age-specific (increments of 3 years) cut-points proposed by Mitchell et al. The cut-points are near the lowest prehypertensive (≥90th percentile) BP value in the NHBPEP tables and are set to end in 0 or 5.

**Simple 2 Definition**
Participants were defined according to age- and gender-specific BP cut-points proposed by Kaelber and Pickett. The cut-points correspond to the lower limit of height (5th percentile) in the prehypertensive BP range (≥90th percentile) for a given age and gender in the NHBPEP tables.

**Complex Definition**
Participants were defined according to age, gender, and height percentiles for prehypertensive youth BP issued by the NHBPEP.

**Arterial PWV Studies**
We used a whole-body impedance cardiography device (CircMon, JR Medical Ltd, Saku Vald, Estonia) to determine PWV. CircMon includes a whole-body impedance cardiography channel, distal impedance plethysmogram channel, and an electrocardiogram channel. When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in the whole-body impedance signal and, subsequently, in the distal plethysmogram signal from a popliteal artery at knee joint level. The measurement is triggered by the R wave of the electrocardiogram. The PWV can be determined from the distance and the time difference between the 2 recording sites. The repeatability index and the reproducibility index were good (99% and 87%, respectively). A detailed description of the method, the validation study, and reference values have been reported previously. High PWV was defined as values at or above the age-, gender-, and heart-rate-specific 80th percentile.

**Statistical Methods**
The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed with the use of age- and gender-adjusted regression analysis for continuous variables, the $\chi^2$ test for categorical variables and the $t$ test to examine differences in age. Age- and gender-adjusted logistic regression was used to estimate relative risks and 95% confidence intervals of adult high PWV according to the 3 definitions for elevated pediatric BP.

The ability of each definition to predict high adult PWV was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under receiver-operating characteristic curves (AUC), and estimates of risk reclassification; statistics that are in line with criteria put forward by the American Heart Association. Sensitivity was calculated as true-positives/(true-positives + false-negatives) × 100; specificity as true-negatives/(true-negatives + false-positives) × 100; NPV as true-negatives/(true-negatives + false-negatives) × 100; and PPV as true-positives/(true-positives + false-positives) × 100. AUC was determined.
from the logistic model and represents an estimate of the probability that the model assigns a higher risk to those who have the outcome (high PWV) compared with those who do not have the outcome. Differences in AUC between the simplified and complex definitions were estimated using the DeLong algorithm. Net reclassification improvement (NRI) was also calculated to determine the extent to which the complex (vs simple 1 or simple 2) definition reclassified participants to a risk status that better reflected their final outcome (case or control). The proportions of participants reclassified to either higher- or lower-risk categories are presented. Risk classification is improved if an individual with the outcome in adulthood (case) is placed in a higher risk category in youth or if an individual without the outcome in adulthood (control) is moved to a lower risk category in youth. The NRI is the sum of improvements in the reclassification of both case and control participants. Analyses were performed with the SPSS for Windows (Release 20.0.0, SPSS Inc, IBM Corporation, Armonk, NY) and Stata (Release 10, StataCorp LP, College Station, TX). Statistical significance was inferred at a 2-tailed $P < .05$.

**RESULTS**

The baseline (1980) characteristics of study participants ($n = 1241$) and nonparticipants ($n = 1241$) are shown in Table 1. There were more boys among nonparticipants ($P < .0001$), and they were slightly younger ($P = .01$). There was no difference in height, systolic BP, or diastolic BP. The prevalence of elevated BP in childhood was the same in the both groups according to the simple 1, simple 2, and complex definition ($P = .10, P = .11$, and $P = .33$, respectively).

Table 2 shows the characteristics of study participants in baseline and follow-up by PWV status in adulthood.

**TABLE 1**: Baseline Characteristics of Study Participants and Nonparticipants (Subjects Missed Follow-up or Excluded) in 1980

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants</th>
<th>Nonparticipants</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>1241</td>
<td>1241</td>
<td></td>
</tr>
<tr>
<td>Gender, female, $n$</td>
<td>687 (55.4)</td>
<td>583 (47.0)</td>
<td>$&lt; .0001$</td>
</tr>
<tr>
<td>Age, y</td>
<td>10.7 ± 3.3</td>
<td>10.4 ± 3.2</td>
<td>.01</td>
</tr>
<tr>
<td>Height, cm</td>
<td>145 ± 19</td>
<td>143 ± 19</td>
<td>.59</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>112 ± 10</td>
<td>112 ± 11</td>
<td>.07</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>68 ± 9</td>
<td>68 ± 9</td>
<td>.07</td>
</tr>
<tr>
<td>Prevalence of elevated BP, simple 1 definition, $n$</td>
<td>689 (53.9)</td>
<td>710 (57.2)</td>
<td>.10</td>
</tr>
<tr>
<td>Prevalence of elevated BP, simple 2 definition, $n$</td>
<td>717 (57.8)</td>
<td>756 (60.9)</td>
<td>.11</td>
</tr>
<tr>
<td>Prevalence of elevated BP, complex definition, $n$</td>
<td>536 (43.2)</td>
<td>560 (45.1)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). Comparison between participants and nonparticipants were performed using age- and gender-adjusted regression analysis for continuous variables, $\chi^2$ tests for categorical variables, and $t$ test to examine differences in age.

There was no difference in gender, age, or height between low- and high-PWV groups in the baseline. Those having high adult PWV had higher systolic and diastolic BP values ($P = .02$ and $P = .004$, respectively) and higher prevalence of elevated BP in childhood according to the simple 1, simple 2, and complex BP definition ($P = .007$, $P = .001$, and $P = .0005$, respectively). In the follow-up the BP differences were more evident, and the absolute differences in the prevalence of elevated BP ($23.1\%$ vs $48.6\%$, $P < .0001$) and in PWV ($7.7$ m/s vs $9.9$ m/s, $P < .0001$) were remarkable.

Subjects having elevated BP in childhood were at increased risk of high PWV in adulthood (Table 3). The magnitude of risk was similar according to the simple 1, simple 2, or complex BP definition ($50\%$, $P = .007$, $60\%$, $P = .001$, and $70\%$, $P = .001$, respectively). Prediction of high adult PWV by the simplified definitions was equal with the

**TABLE 2**: Baseline (1980) and Follow-up (2007) Characteristics of Study Subjects by PWV Status in Adulthood

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low PWV</th>
<th>High PWV</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of subjects</td>
<td>994</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>37.7 ± 3.3</td>
<td>37.7 ± 3.3</td>
<td>.87</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 9</td>
<td>172 ± 9</td>
<td>.37</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118 ± 13</td>
<td>128 ± 14</td>
<td>$&lt; .0001$</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 ± 11</td>
<td>81 ± 11</td>
<td>$&lt; .0001$</td>
</tr>
<tr>
<td>Prevalence of elevated BP, $a$</td>
<td>230 (23.1)</td>
<td>120 (48.6)</td>
<td>$&lt; .0001$</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>7.7 ± 1.1</td>
<td>9.9 ± 1.4</td>
<td>$&lt; .0001$</td>
</tr>
</tbody>
</table>

Low PWV was defined as values below the age-, gender-, and heart-rate-specific 80th percentile. High PWV was defined as values at or above the age-, gender-, and heart-rate-specific 80th percentile. Values are mean ± SD or n (%). Comparison between groups were performed using age- and gender-adjusted regression analysis for continuous variables, $\chi^2$ tests for categorical variables, and $t$ test to examine differences in age.

*a* Classified as systolic BP $\geq 130$ mm Hg and/or diastolic blood pressure $\geq 85$ mm Hg.
prediction provided by the complex definition (Table 4). Neither AUC nor NRI were significantly different between the simple 1 and complex definition ($P = .25$ and $P = .13$, respectively) or between the simple 2 and complex definition ($P = .68$ and $P = .35$, respectively). The simple 1 and simple 2 definitions had higher sensitivity than complex definition (61.5, 66.8, and 53.0, respectively) but lower specificity (48.0, 44.5, and 59.3, respectively). All definitions had high NPV (83.4, 84.4, and 83.5, respectively).

**Sensitivity Analyses**

To test the robustness of our findings, we performed analyses using other standardized cut-points corresponding to the 70th, 75th, 85th, and 90th percentiles of PWV with essentially similar results (Supplemental Tables 5 and 6). We made also 2 additional subgroup analyses. First, we studied age and gender differences in 2 age groups and used 9 years of age as a cut-point. This cut-point was chosen because Juonala et al reported that risk factor measurements obtained at or after 9 years of age were predictive of subclinical atherosclerosis in adulthood in this cohort. All 3 definitions made equal predictions for high PWV for older girls and boys, except the simple 1 definition for boys (Supplemental Table 7). Predictions for younger subjects were not statistically significant which at least partly can be explained by small group sizes (170 girls and 114 boys). Second, we used age- and gender-specific 85th percentile for BMI in 1980 as a cut-point to define subjects as normal weight or overweight. All 3 definitions made equal predictions for high PWV (1.8–2.1) for overweight subjects (Supplemental Table 8). These predictions were not statistically significant, possibly because of small group size ($N = 185$).

**DISCUSSION**

This study shows that elevated pediatric BP predicts increased PWV in adulthood. We also observed that 2 simplified definitions$^{12,13}$ for elevated pediatric BP predict high adult PWV equivalent to the more complex definition currently endorsed by the NHBPEP.$^{10}$ This finding is clinically meaningful because both these simplified tables could be more easily implemented as a screening tool in pediatric health care settings and outside of a physician’s office when the height percentile required for the complex definition may not be obtainable. We found also that subjects having high PWV in adulthood had higher BP values in childhood. Moreover, they have higher prevalence of elevated BP in childhood regardless the BP definition. In adulthood, differences between these groups were markedly greater (eg, the prevalence of elevated BP was more than twofold in the high-PWV group). Overall, all these observations suggest that early exposure to elevated BP plays an important role in the development of arterial stiffness and CVD.

Previous studies have reported clear tracking of BP, and especially elevated BP, from childhood to adulthood.$^{7–9}$ Additionally, systolic BP in childhood predicts hypertension,$^{9,30,31}$ arterial stiffness,$^{17–19,32}$ and coronary artery calcium$^4$ in adulthood. Our findings are in agreement with these reports showing that subjects having elevated BP in childhood are at higher risk of having increased PWV in adulthood. The risk is increased if elevated BP in childhood is defined according to either the NHBPEP table or 1 of the 2 simplified tables. To the best of our knowledge, this is the first study to demonstrate that all these definitions are able to differentiate youth at increased risk of high PWV in adulthood.

The stiffening process of large arteries is complex.$^{33,34}$ It is suggested that elevated blood BP causes mechanical load that leads to overproduction of collagen and degradation and remodeling of normal elastin.$^{33,34}$ As mentioned earlier, elevated BP tracks from childhood to adulthood$^{7–9}$ thus having long-term influence on the stiffening process. To slow down this process, it is necessary to identify subjects whose

### TABLE 3

**RR and 95% CI of High PWV in Adulthood According to the 3 Definitions for Elevated Pediatric BP**

<table>
<thead>
<tr>
<th>Simple 1 Definition (Age)</th>
<th>Simple 2 Definition (Age and Gender)</th>
<th>Complex Definition (Age, Gender, and Height Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>1.1–2.0</td>
<td>1.2–2.2</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.007</td>
<td>.001</td>
</tr>
</tbody>
</table>

High PWV was defined as values at or above the age-, gender-, and heart rate-specific 80th percentile. All estimates adjusted for age and gender. CI, confidence interval; RR, relative risk.

### TABLE 4

**Sensitivity, Specificity, PPV, NPV, AUC With 95% CIs, and NRI Values of the 3 Definitions for Elevated Pediatric BP to Predict High PWV in Adulthood**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>AUC</th>
<th>95% CI</th>
<th>$P$ value</th>
<th>NRI, %</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple 1 definition (age)</td>
<td>61.5</td>
<td>48.0</td>
<td>22.7</td>
<td>83.4</td>
<td>0.548</td>
<td>0.508–0.587</td>
<td>.25*</td>
<td>2.8</td>
<td>0.13*</td>
</tr>
<tr>
<td>Simple 2 definition (age and gender)</td>
<td>66.8</td>
<td>44.5</td>
<td>23.0</td>
<td>84.4</td>
<td>0.556</td>
<td>0.517–0.596</td>
<td>0.68*</td>
<td>2.8</td>
<td>0.13*</td>
</tr>
<tr>
<td>Complex definition (age, gender, and height percentile)</td>
<td>53.0</td>
<td>59.3</td>
<td>24.4</td>
<td>83.5</td>
<td>0.561</td>
<td>0.521–0.602</td>
<td>.35*</td>
<td>1.0</td>
<td>0.35*</td>
</tr>
</tbody>
</table>

High PWV was defined as values at or above the age-, gender- and heart rate-specific 80th percentile. CI, confidence interval.

* Simple 1 vs complex.

b Simple 2 vs complex.
high BP needs adequate intervention and treatment. It is especially important to make early diagnosis of hypertension in childhood because hypertension is a major modifiable risk factor. However, hypertension and prehypertension in children and adolescents are mostly undiagnosed.11,12 This is a major clinical problem, and every effort should be made to help physicians in the screening process. Before it is possible to make correct diagnosis of hypertension, it is first necessary to identify elevated BP measurements. Because of that, Kaelber and Pickett15 and Mitchell et al12 proposed the new BP tables to aid in decision-making between normal and abnormal pediatric BP. Mitchell et al reported sixfold improvement, from 15% to 77%, in recognition of hypertensive pressures when using their simplified table than NHBPEP table.12 This user-friendly screening tool could lead to wider screenings and diagnosis of prehypertension and hypertension in children and adolescents such that effective lifestyle interventions and medication could be optimized for health outcomes. Because the clinical screening of elevated BP is more efficient with the simplified tables, it is important to know how well the simplified tables identified subjects at increased CVD risk. In this study, we found that the simplified definitions made almost identical predictions for high PWV as the complex definition. In addition, AUC and NRI analyses showed no difference between the simplified and complex definitions. The complex definition had lower sensitivity (53.0%) for high PWV than simple 1 and simple 2 (61.5%–66.8%, respectively) definitions, and all definitions had satisfactory (83.4%–84.4%) NPV. These findings further support the usability of both simplified tables to identify children and adolescents needing additional evaluation of BP. It is also worth mentioning that relative risks of high PWV for overweight subjects were equal (1.8–2.1) according to all 3 definitions. These predictions were not statistically significant, but this may be due to small group size. The strength of this study is the large randomly selected cohort of young adults followed for 27 years since childhood. However, our study has some limitations that need to be considered in the interpretation of our findings. First, the CircMon-based PWV measurement method is not yet widely used in epidemiologic settings, apparently limiting comparability of our findings with observations from other cohorts. However, PWV values measured by CircMon are highly comparable to those measured by Doppler ultrasound method.25 Also reference values for PWV measured with CircMon method24 are similar to those observed in other studies in which varying methods of measurement have been used, indicating the generalizability of our findings. Second, bias due to non-participation in the follow-up study needs to be considered. Baseline characteristics in 1980 were mainly similar among participants and non-participants, with the exception of age. This statistically significant difference can be explained by the large number of participants because the absolute difference was small and not clinically meaningful. Therefore, the current study cohort appears to be fairly representative of the original study population. Third, as shown in Supplemental Tables 7 and 8, these results should be interpreted with caution for children aged <9 years and overweight subjects. Finally, the ethnic homogeneity of our study cohort limits the generalizability of our results to white European subjects.

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