Pediatric Blood Pressure and Adult Preclinical Markers of Cardiovascular Disease

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ABSTRACT: A high blood pressure level in adults is considered the single most important modifiable risk factor for global disease burden, especially those of cardiovascular (CV) origin such as stroke and ischemic heart disease. Because blood pressure levels have been shown to persist from childhood to adulthood, elevations in pediatric levels have been hypothesized to lead to increased CV burden in adulthood and, as such, might provide a window in the life course where primordial and primary prevention could be focused. In the absence of substantive data directly linking childhood blood pressure levels to overt adult CV disease, this review outlines the available literature that examines the association between pediatric blood pressure and adult preclinical markers of CV disease.

KEYWORDS: pediatric, blood pressure, hypertension, prehypertension, cardiovascular disease, carotid intima-media thickness, flow-mediated dilatation, endothelial function, arterial stiffness, review

INTRODUCTION

Despite steady declines in cardiovascular (CV) disease morbidity and mortality in advanced economies since the 1960s, CV disease accounts for the largest proportion of mortality and remains the major contributor to health-care costs worldwide.1

CV Disease Begins Early

Early-life and later life exposures combine to exert an increased risk on overt adult CV disease.2 However, some childhood exposures have been shown to have stronger associations with markers of adult CV health compared with measures of the same exposure taken in adulthood.3 With developments in novel and noninvasive imaging methods, markers of early CV (poor) health can be quantified in the young and apparently healthy populations. Markers of CV health that associate with clinical CV disease include carotid artery intima-media thickness (IMT), large artery elasticity, endothelial function, left ventricular geometry, presence of calcium in the coronary arteries, and retinal vascular architecture. These measures provide a surrogate end point that allows the effects of exposures and interventions on markers of CV health to be studied earlier in the disease life course. Although long-term clinical trials would be ideal to test the value of modifying early-life exposures on CV disease development in adulthood, observational studies with multiple follow-ups across the life course provide the chance to decipher an individual’s risk factor path toward CV disease. Using noninvasive imaging, prospective cohort studies linking early-life risk factors with CV health markers in adulthood have accumulated over the past 20 years.3

Early-life Factors Associated with Adult CV Health

Current evidence suggests that preclinical markers of CV health in adulthood associate with multiple early-life risk factors such as birth size and adiposity, blood pressure, own and parental smoking, blood lipid levels, family history, and socioeconomic factors (among others).3–5 Therefore, addressing early-life risk factors could lead to a lifelong benefit. Previously, it was shown that individuals who resolved their pediatric risk status of overweight and obesity, high low-density lipoprotein cholesterol, and the metabolic syndrome by young adulthood had a level of CV health similar to those who were not at increased risk in childhood.3 However, two risk factors have emerged from this work, which show that exposure in childhood has a sustained risk on adult CV health, irrespective of adult exposure—passive smoking and elevated blood pressure,1 of which blood pressure will be the focus of this report.
**Childhood Blood Pressure Levels Predict Adult Blood Pressure Levels**

Although hypertension is seen as a risk factor that is established and treated in adulthood, blood pressure has been shown to track (or persist) from childhood to adulthood, whereby those with elevated childhood levels have an increased risk of developing adult prehypertension and hypertension.\(^6\)\(^-\)\(^8\) Although the strength of tracking has been shown to vary between studies and depends on baseline age, length of follow-up,\(^7\) and susceptibility alleles,\(^9\) there is the expectation that early identification of children with elevated levels or prevention of children developing elevated levels would lead to improvements in primary and primordial prevention of later CV diseases. Indeed, a recent report has indicated that if elevated blood pressure in childhood could be prevented, approximately 10% of elevated blood pressure (defined as prehypertension or hypertension) in young adulthood would be avoided.\(^10\) Given the global burden of disease attributable to adult hypertension,\(^11\) these tracking data hint that even a small shift in the distribution of pediatric blood pressure levels (left or right) would have a profound impact on hypertension-related disease and health-care costs. This is particularly concerning given the documented recent trend is toward increased blood pressure levels among children,\(^12\)\(^-\)\(^14\) which seems largely, though not completely, attributable to increases in childhood obesity.\(^15\)

**Childhood Blood Pressure and Adult Preclinical CV Disease**

Following the confirmation that childhood blood pressure tracks into adulthood, several groups with longitudinal data spanning childhood to adulthood began to undertake non-invasive imaging for markers of CV health. In the absence of data directly linking childhood blood pressure levels with adult CV disease outcomes, these data provide the best indication of whether childhood blood pressure levels will have a residual or lasting long-term effect on adult CV health. Studies examining the association of pediatric blood pressure with adult markers of preclinical CV disease are overviewed in Table 1. The relative importance of childhood blood pressure levels tends to vary by adult outcome, subgroup, and the factors considered for adjustment.

Carotid IMT, a structural marker of atherosclerosis that precedes overt plaque development, tended to be thicker among those with higher levels of childhood systolic blood pressure and pulse pressure independent of other childhood risk factors and adult blood pressure.\(^4\)\(^,\)\(^16\) Pooled analysis of data from four prospective cohorts showed that carotid IMT increased as childhood systolic blood pressure increased,\(^17\)\(^,\)\(^18\) although this effect has not been observed among all cohorts,\(^19\)\(^,\)\(^20\) and the strength of the effect differed by race and sex.\(^21\) A recent study highlighted that multiple measurements of elevated blood pressure in early life improves prediction of adult hypertension but not elevated carotid IMT.\(^22\)

Only one study, the Cardiovascular Risk in Young Finns Study, has examined the association between childhood blood pressure and adult brachial flow-mediated dilatation, a marker of endothelial function,\(^23\) considered one of the first processes underlying atherosclerosis changes in arteries. These data showed that an increased level of systolic blood pressure among adolescent males aged 12–18 years was associated with reduced flow-mediated dilatation as measured in adulthood 21 years later. However, no association was observed among females, males aged 3–9 years at baseline, or childhood diastolic blood pressure. The lack of effect observed for most comparisons may have been a consequence of lower CV load among these subgroups or the well-documented natural variation in flow-mediated dilatation that may have resulted in increased measurement error. Some of the measurement limitation of flow-mediated dilatation could be overcome by examining adult circulating blood biomarkers of endothelial activation and dysfunction. However, we are not aware of any studies that have prospectively examined the association with childhood blood pressure.

The presence and degree of calcium in the coronary arteries detected from computed tomography is directly related to the amount of atherosclerotic plaque. Two studies have examined the associations between childhood blood pressure and adult coronary artery calcium. Using data from the Muscatine Study,\(^24\) Mahoney et al found that blood pressure in childhood was not associated with coronary calcium measured in adulthood. In contrast, Hartiala et al found childhood systolic blood pressure and change in systolic blood pressure between childhood and adulthood to be independent predictors of total calcium score approximately 28 years later in the Cardiovascular Risk in Young Finns Study.\(^25\) Interestingly, childhood systolic blood pressure was a stronger predictor of adult coronary calcium than low-density lipoprotein cholesterol or change in systolic blood pressure between childhood and adulthood. No effect was observed for childhood diastolic blood pressure.

Evidence for an independent effect of pediatric blood pressure on adult CV outcomes appears most consistent for large artery elasticity, with childhood blood pressure levels tending to be one of the strongest or the only childhood predictor of loss in adult elastic properties.\(^26\)\(^-\)\(^30\) An important study by Ferreira et al using data from the Amsterdam Growth and Health Longitudinal Study showed that the life-course trajectory in blood pressure (systolic, diastolic, and pulse) differs already in early adolescence between those who become adults with the most stiff versus those with the least stiff carotid arteries.\(^28\) The divergence in blood pressure levels between groups became more pronounced with age, with the difference remaining independent of adiposity, which also had a time-varying effect on adult carotid stiffness, and other risk factors and potential confounders.

A number of studies have examined the association between childhood blood pressure levels and adult left ventricular remodeling. Most suggest an independent effect of...
adolescent (12–18 years) sBP was negatively associated with adult cIMT among females (β = 0.15 and r = 0.10) than males (β = 0.10 and r = 0.06) in univariable models. Among females, SBP and DBP were not associated with adult cIMT in a multivariable model that included childhood cholesterol and BMI.

Compared to those with normal BP at both time points, individuals with childhood elevated BP had increased odds of high adult cIMT (OR = 1.00, 95% CI 0.80–1.25) in a multivariable model adjusting for childhood BMI and lipids. Associations with childhood DBP were not reported.

In univariable models, childhood SBP was associated with adult cIMT in males (β = 0.022), and females (β = 0.012, SE = 0.004) whereas childhood DBP was significant only among males (β = 0.011 mm, SE = 0.005). Adolescent (12–18 years) SBP was significantly associated with adult cIMT (β = 0.013 mm, SE = 0.003) in a multivariable model that adjusted for age, sex, and childhood LDL-cholesterol, BMI, and smoking status.

Childhood SBP was a significant multivariable predictor of adult cIMT among white females (β = 0.132 mm per 1-tUnit increase in age-, race-, and sex-specific z-score) and black males (β = 0.241 mm) but not white males (β = 0.082 mm) or black females (β = 0.115 mm) in a model that included childhood BMI and lipids. Associations with childhood DBP were not reported.

Childhood (3–9 years) pulse pressure was not associated with adult cIMT among men (β = 0.003–0.013) increase in adult cIMT independent of adolescent MAP, BMI, physical activity, adult MAP, pulse pressure, BMI, smoking and carotid diameter.

In multivariable analyses that pooled data from four child to adult cohorts and considered associations from 3-year age groups (3 y, 6 y, 9 y, 12 y, 15 y, 18 y), childhood SBP was associated with adult cIMT at age 6 y (β = 0.102 mm for a one-unit increase in z-score, SE = 0.033), 12 y (β = 0.078 mm, SE = 0.023), 15 y (β = 0.063 mm, SE = 0.022), and 18 y (β = 0.064 mm, SE = 0.027).

Compared to those with normal BP at both time points, individuals with elevated BP in childhood and adulthood had increased risk of high adult cIMT (RR = 1.82; 95% CI 1.47–2.38); those who had resolved their elevated BP status between childhood and adulthood had a marginally increased risk of high adult cIMT (RR = 1.24; 95% CI 0.92–1.67).

Compared to children with normal BP, those with elevated BP had increased odds of high adult cIMT >80th age- and sex-specific percentile (OR = 1.4; 95% CI 1.0–1.9). A 1-SD increase in childhood SBP and DBP was associated with a 0.173 mm and 0.082 mm, respectively, in adult cIMT.

Compared with a single measurement, multiple measurements of elevated blood pressure in childhood improved prediction of adult hypertension (single elevated blood pressure AUC = 0.60 vs. two elevated blood pressures in childhood AUC = 0.63, P = 0.003) but not elevated cIMT (single elevated blood pressure AUC = 0.59 vs. two elevated blood pressures in childhood AUC = 0.59, P = 0.82).

Adolescent (12–18 years) SBP was negatively associated with adult FMD among men but not women. Childhood SBP (3–9 years) was not associated with adult FMD among men or women. Childhood and adolescent DBP were not associated with adult FMD. For adolescent males, a significant effect remained (β = −0.049%; SE = 0.016 per 1 mmHg increase) with multivariable adjustment for adolescent risk factors (BMI, lipids, smoking, insulin, birth weight) and brachial diameter.

(Continued)
adolescent sBP predicted adult C aC independently of change in CITATION = sBP was the only childhood predictor of adult brachial-ankle 24–44 Compared to those with normal childhood BP, those with elevated Mean age 24–39 40–46 2.7 29–37 - elevated childhood BP predicted high adult arterial PWV when the AGE AT 30–42 Childhood SBP (per z-score increase) was the only childhood higher childhood s BP was associated with adult lV mass index Childhood SBP and DBP (per z-score increase) were not a 1-sd increase in childhood s BP was positively associated with Childhood SBP and DBP were not significantly different between Childhood DBP was a significant predictor of adult concentric LV population Childhood SBP were reported) Among children with medical record-verified family history of CVD <55 y of age, SBP and pulse pressure increased along with LV mass over a 10 year period. However, the proportion of between-subject difference in LV mass accounted by SBP and pulse pressure was small compared with a model that considered ethnicity, gender, and adiposity. Childhood DBP was a significant predictor of adult concentric LV hypertrophy vs. normal geometry (OR = 1.14 per 1-unit increase, 95% CI 1.03–1.26) independent of other childhood risk factors including adiposity. The correlation between childhood DBP and adult LV mass index was stronger among those with a family history of coronary heart disease than in those without (r = 0.65 versus r = 0.16). Higher childhood SBP was associated with adult LV mass index (β = 0.08 g/m²/1 per 1-SD increase, 95% CI: 0.01–0.14) and odds of adult LV hypertrophy (OR = 1.27, 95% CI: 1.04–1.54). Similar patterns were observed for DBP (data not reported by authors).

Table 1. (Continued)

| OUTCOME                        | CITATION | POPULATION | AGE AT BASELINE (Y) | AGE AT LAST FOLLOW-UP (Y) | MAIN FINDINGS                                                                 |
|-------------------------------|----------|------------|---------------------|---------------------------|-----------------------------------------------------------------------------|
| Coronary artery calcium       |          |            |                     |                           |                                                                             |
| Mahoney, 1996                 | N = 384  | 8–18       | 29–37               |                           | Childhood SBP and DBP were not significantly different between those who had CAC in adulthood and those who did not. |
| Hartiala, 2012                | N = 589  | 12–18      | 40–46               |                           | Adolescent SBP predicted adult CAC independently of change in SBP during the 27-year follow-up (OR = 1.38; 95% CI: 1.08–1.77), for 1-SD increase in adolescence systolic BP. Change in SBP between adolescence and adulthood was marginally associated with adult CAC (OR = 1.25; 95% CI: 0.98–1.60) for 1-SD increase. |
| Large artery elastic properties|          |            |                     |                           |                                                                             |
| Li, 2004                      | N = 835  | 4–17       | 24–44               |                           | SBP was the only childhood predictor of adult brachial-ankle PWV (β = 0.85 cm/s per age-, sex, and race-standardized z-score increase). Cumulative burden of SBP from childhood to adulthood was also a multivariable predictor of adult PWV (AUC = 0.29 m/s per z-score increase). |
| Juonala, 2005                 | N = 2255 | 3–18       | 24–39               |                           | A 1-SD increase in pulse childhood SBP was positively associated with adult YEM (β = 23.7 mmHg/mm; SE = 3.7) and negatively associated with adult CAC (β = 0.106%/10 mmHg; SE = 0.017) independent of age, sex, and childhood adiposity. |
| Ferreira, 2012                | N = 373  | 13         | 36                  |                           | Individuals in the highest third of carotid stiffness at age 36 years were defined by higher MAP, SBP, and DBP in adolescence (age 13 or 14 years) and experienced larger increases in these measures between childhood and adulthood compared with those with the least stiff arteries at age 36 years. |
| Aatola, 2013                  | N = 1241 | 6–15       | 33–42               |                           | Elevated childhood BP predicted high adult arterial PWV when the definition of high BP was age-specific (RR = 1.5, 95% CI: 1.1–2.0), age and sex specific (RR = 1.6, 95% CI: 1.2–2.2), and age, sex and height specific (RR = 1.7, 95% CI: 1.2–2.2). |
| Li, 2014                      | N = 680  | 4–17       | 24–44               |                           | Childhood SBP (per z-score increase) was the only childhood risk factor significantly associated with adult brachial-ankle PWV (β = 34.27 cm/s; SE = 9.28). Similar results were observed for DBP (data not shown by authors). There was no significant interaction between SBP and race/sex, though the effect tended to be stronger amongst females. |
| Liang, 2014                   | N = 1259 | 6–18       | 30–42               |                           | Compared to those with normal childhood BP, those with elevated childhood BP had increased odds for carotid-femoral PWV ≥80th percentile (OR = 1.8; 95% CI: 1.3–2.4). A 1-SD increase in childhood SBP and DBP was associated with a 0.105 cm/s and 0.099 m/s increase in adult carotid-femoral PWV. |
| Yun, 2015                     | N = 945  | 4–17       | 24–43               |                           | Childhood SBP and DBP (per z-score increase) were not associated with adult aorta-femoral PWV (β = 0.012 m/s and β = 0.045 m/s). Adult aorta-femoral PWV was associated with total AUC of SBP (β = 0.201 m/s), incremental AUC of SBP (β = 0.173 m/s), total AUC of DBP (β = 0.174 m/s) and incremental AUC of DBP (β = 0.158 m/s). |
| Left ventricular parameters   |          |            |                     |                           |                                                                             |
| Dekkers, 2002                 | N = 687  | Mean age (SD) = 14 (3) | Not reported (length of follow-up 10 years) | Among children with medical record-verified family history of CVD <55 y of age, SBP and pulse pressure increased along with LV mass over a 10 year period. However, the proportion of between-subject difference in LV mass accounted by SBP and pulse pressure was small compared with a model that considered ethnicity, gender, and adiposity. |
| Toprak, 2008                  | N = 824  | 5–18       | 24–44               |                           | Childhood DBP was a significant predictor of adult concentric LV hypertrophy vs. normal geometry (OR = 1.14 per 1-unit increase, 95% CI: 1.03–1.26) independent of other childhood risk factors including adiposity. |
| Magnussen, 2014               | N = 181  | 9–15       | Mean age (SD) = 31.3 (2.6) | The correlation between childhood DBP and adult LV mass index was stronger among those with a family history of coronary heart disease than in those without (r = 0.65 versus r = 0.16). |
| Lai, 2014                    | N = 1061 | 4–18       | 24–46               |                           | Higher childhood SBP was associated with adult LV mass index (β = 0.08 g/m²/1 per 1-SD increase, 95% CI: 0.01–0.14) and odds of adult LV hypertrophy (OR = 1.27, 95% CI: 1.04–1.54). Similar patterns were observed for DBP (data not reported by authors). |

Table 1. (Continued)
systolic and diastolic childhood blood pressure on adult left ventricular remodeling, although the effect seems to be reduced following adjustment for childhood adiposity or heightened among those with positive family history of premature CV disease.

A recent study from the Cardiovascular Risk in Young Finns Study is the first to examine the association between blood pressure across the life-course and retinal vascular architecture measured in adulthood. Viewed noninvasively using ophthalmology equipment, measures of retinal vascular architecture have been shown to associate with both large artery atherosclerosis and subclinical microvascular disease. Being of a similar diameter, retinal vessels are thought to provide a disease model of what is occurring in the coronary microcirculation. Tapp et al showed that higher systolic and diastolic blood pressure, both as a single measure from childhood and change between childhood and adulthood, associated with retinal arteriolar narrowing and other markers, including arteriolar length-to-diameter ratio and arteriolar tortuosity.

Summary and Future Research Directions

Given the available literature on the likely role of childhood blood pressure on CV health, several organizations including the National Heart Lung and Blood Institute (NHLBI) and the National High Blood Pressure Education Program (NHBPEP) have issued guidelines on the screening and treatment of children with elevated blood pressure levels. Though the evidence for these guidelines is mostly based on observational data and has amounted to criticism from the US Preventive Services Task Force in a recent recommendation statement, there remains considerable support from pediatric blood pressure specialists.

The data overviewed here have largely strengthened the case for attention to pediatric blood pressure levels. However, a number of facets of the data from these long-term observation studies that have used preclinical markers of CV health require further investigation.

Critical age or age window for screening. The NHLBI and NHBPEP guidelines recommend population-wide screening for blood pressure beginning from the age of three years. However, it is not known if there is a critical age or an age window in youth when blood pressure most strongly predicts those who develop adult CV. Juonala et al found that systolic blood pressure was not a significant predictor of adult carotid IMT before the age of 12 years, suggesting that screening for systolic blood pressure prior to this age might not detect those who go on to have higher CV risk in adulthood. Ferreira et al built on these findings by illustrating that differences in blood pressure were already present at the age of 13 years between those who went on to develop the most stiff carotid arteries in adulthood and those with the least stiff arteries, and the difference in blood pressure became more pronounced with age. A limitation of the current guidelines by the NHLBI and NBPBEP is that elevated blood pressure is defined on the basis of exceeding a certain cut-point at a single age point. Ferreira et al highlighted the limitation of using a single time point by showing that those who exceeded the NHBPEP blood pressure cut-points were not at an increased risk

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Table 1. (Continued)

| OUTCOME                           | CITATION                  | POPULATION                        | AGE AT BASELINE (Y) | AGE AT LAST FOLLOW-UP (Y) | MAIN FINDINGS                                                                 |
|----------------------------------|---------------------------|-----------------------------------|---------------------|---------------------------|-----------------------------------------------------------------------------|
| Cumulative burden of SBP and incremental burden (increase of SBP across the life-course) were both significantly associated with LV mass index ($\beta = 0.14 \text{ g/m}^2$, 95% CI = 0.09–0.20 and $\beta = 0.10 \text{ g/m}^2$, 95% CI = 0.05–0.16) and odds of LV hypertrophy (OR = 1.47, 95% CI = 1.20–1.90 and OR = 1.43, 95% CI = 1.19–1.72). |
| Childhood SBP and DBP were negatively associated with adult arteriolar diameter ($\beta = -0.341$ pixels and $\beta = -0.287$ pixels) and positively associated with arteriolar length-to-diameter ratio ($\beta = 0.112$ and $\beta = 0.144$) and for SBP arteriolar tortuosity ($\beta = 0.156 \times 10^{-3}$). Change in SBP and DBP from childhood to adulthood was also negatively associated with arteriolar diameter ($\beta = -0.331$ pixels and $\beta = -0.350$ pixels) and positively associated with arteriolar length-to-diameter ratio ($\beta = 0.153$ and $\beta = 0.138$). |

Retinal vascular architecture

| Tapp, 2015$^{36}$ | N = 657 (46% male) | 3–9 | 24–40 | Childhood SBP and DBP were negatively associated with adult arteriolar diameter ($\beta = -0.341$ pixels and $\beta = -0.287$ pixels) and positively associated with arteriolar length-to-diameter ratio ($\beta = 0.112$ and $\beta = 0.144$) and for SBP arteriolar tortuosity ($\beta = 0.156 \times 10^{-3}$). Change in SBP and DBP from childhood to adulthood was also negatively associated with arteriolar diameter ($\beta = -0.331$ pixels and $\beta = -0.350$ pixels) and positively associated with arteriolar length-to-diameter ratio ($\beta = 0.153$ and $\beta = 0.138$). |

Abbreviations: AUC, area under the receiver operating characteristic curve; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CI, confidence interval; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; DBP, diastolic blood pressure; FMD, flow-mediated dilatation; LDL, low-density lipoprotein; LV, left ventricular; MAP, mean arterial pressure; OR, odds ratio; PWV, pulse wave velocity; RR, relative risk; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; Y eM, Young’s elastic modulus.
of having increased arterial stiffness in adulthood compared with those below the cut-point. Assessing blood pressure over multiple ages and monitoring increases in blood pressure over time, termed the *horse-racing effect*, might improve identification of children on a trajectory toward poorer CV health in adulthood. Because blood pressure tracking data have shown that not all children with elevated levels become adults with elevated levels and that a high proportion of adults with hypertension started out as children with normal levels, the consideration of blood pressure trajectories, rate of change, or variability within an age window from life-course analyses may be important to identify those children who do not meet traditional cut-offs but nevertheless are at an increased risk.

**Pediatric blood pressure cut-points and future CV health.** Although cut-points for what constitutes prehypertension and hypertension in the pediatric setting have been issued by the NHBPEP, the reporting of associations between these cut-points and preclinical CV outcomes is scant. Publications from the Cardiovascular Risk in Young Finns Study have shown that the NHBPEP classifications predict adult hypertension and high pulse wave velocity, but more data are needed. Moreover, due to the complexity and sheer number of critical values in the NHBPEP classification, other *simpler* cut-offs have been proposed that, if shown to have similar predictive utility, might help reduce the substantial underdiagnosis of pediatric hypertension in the clinical setting.

**Utility of single and combined blood pressure measures in childhood in predicting adult CV health.** Although a number of studies reviewed here suggest that blood pressure measured at a single time point in childhood predicts preclinical markers of CV disease in adulthood, uncertainty exists as to the relative importance of various pediatric blood pressure components that lead to adult outcomes. For example, data from the Framingham Heart Study show that the predictiveness of a certain blood pressure measure, and their combinations, changes across the adult life course.

Most of the studies in Table 1 do not systematically show for comparison the predictive utility of different blood pressure measurements (eg, systolic, diastolic phase IV, diastolic phase V, mean arterial, and pulse) nor consider that the utility of these measures may differ by age or pubertal status. The role of isolated systolic and diastolic hypertension and prehypertension in childhood has also largely not been considered in these studies.

**Data reporting.** There appears stronger trends for systolic blood pressure compared with diastolic blood pressure for some of the preclinical CV markers reported in Table 1, which may be expected, given the weaker tracking of diastolic blood pressure. However, a number of studies do not report effect sizes or standard errors for nonsignificant findings, and several studies report that the effect was similar for diastolic blood pressure as for systolic, though these data are not shown. Moreover, there was a high degree of heterogeneity between the studies in the type of analysis conducted and the reporting of effect estimates. Even those that report regression coefficients differ by the unit increase in blood pressure (eg, 1 mmHg, 10 mmHg, standard deviation, or z-score). These data will be important for future systematic reviews and meta-analyses, should they be conducted, and so should be routinely reported where possible.

**Factors that predict resolution and impact of resolution on adult CV health.** The study by Juhola et al highlighted some residual, lasting, effect of elevated childhood blood pressure on adult carotid IMT that cannot be completely avoided by acquiring a normal blood pressure level in adulthood. Similar analyses should be undertaken with other adult preclinical markers of CV health to confirm these findings and the risk factors that contribute to the resolution of elevated levels. Although a study has shown that those who resolved their elevated blood pressure levels in the time between childhood and adulthood had lower gains in body mass index, alcohol consumption, and higher vegetable consumption relative to those who maintained elevated levels, other factors need to be explored. A recent study by Su et al highlighted the potential importance of adverse childhood experiences (eg, abuse, neglect, and dysfunctional household) in the development of adult blood pressure trajectories. Although these data are not from randomized controlled trials, these types of analyses help identify what factors may help in amending trajectories toward lower risk.

**Conclusion**

Literature has accumulated from prospective cohort studies over the past 20 years that have examined the association between pediatric blood pressure levels and early preclinical markers of adult CV disease. These data suggest that childhood blood pressure levels may have direct and long-lasting effects on adult CV health. While we wait for outcome data to accumulate on clinical end points in these cohorts, these studies will continue to provide data on other important questions that need to be answered to refine our understanding of the long-term contribution of childhood blood pressure to adult CV health.

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HIGHLIGHTS OF THIS REVIEW

What is already known
- Cardiovascular disease begins early in life and has a long manifest stage before clinical end-points such as myocardial infarction and stroke present.
- Evidence from prospective cohort studies show that pediatric blood pressure levels predict blood pressure status and early preclinical markers of CV disease measured decades later in adulthood.
- Because of these data, the National High Blood Pressure Education Program, and National Heart Lung and Blood Institute have issued guidelines on the screening and treatment of children with elevated blood pressure levels.

Future research directions
- Data are needed to identify the best blood pressure cut-points, combination of blood pressure measurements, and critical age or age window for blood pressure screening among children for future risk prediction of adult cardiovascular health.
- Because long-term interventions are unlikely to span childhood to adulthood, observational data on the factors that predict resolution of elevated blood pressure between childhood and adulthood and impact of resolution on adult cardiovascular health are needed.
- Data linking childhood blood pressure to clinical cardiovascular end-points are needed.

Author Contributions
Wrote the first draft of the manuscript: CGM. Contributed to the writing of the manuscript: KJS. Agreed with manuscript results and conclusions: CGM and KJS. Developed the structure and arguments for the paper: CGM. Made critical revisions: KJS. Both the authors reviewed and approved the final manuscript.

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