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Screening for High Blood Pressure in Children and Adolescents: Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review the evidence about screening for high blood pressure in children and adolescents to delay the onset of or reduce adverse health outcomes related to high blood pressure.

Data Sources: MEDLINE, Embase, International Pharmaceutical Abstracts, the Cochrane Library, and trial registries through September 3, 2019; bibliographies from retrieved articles, outside experts, and surveillance of the literature through February 25, 2020.

Study Selection: Two investigators independently selected studies using a priori defined inclusion and exclusion criteria. For this update, we included studies of screening for primary and secondary hypertension in asymptomatic children and adolescents. For benefits and harms of treatments or the association between hypertension in children and adolescents and intermediate outcomes in adults, we included participants with primary or secondary hypertension or elevated blood pressure. We selected studies that evaluated the diagnostic accuracy of blood pressure measurements in children and adolescents within primary care settings. We also included epidemiological studies that assessed the association between high blood pressure in children and adolescents and hypertension and other intermediate outcomes in adults. We included intermediate outcomes only if they were closely related to hypertension (e.g., left ventricular hypertrophy, urinary albumin excretion, retinal vascular changes, and intima media thickness). For treatment of hypertension, we selected controlled trials of pharmacological agents, lifestyle interventions, or combination treatments. We excluded studies with poor methodological quality and studies conducted in developing countries.

Data Extraction and Analysis: One investigator extracted data and a second checked accuracy. Two reviewers independently rated methodological quality for all included studies using predefined criteria. Because data were insufficient for meta-analyses, we qualitatively synthesized findings for each key question.

Data Synthesis: We included 42 studies (43 publications). We did not identify any studies directly evaluating health benefits or harms of screening. We also did not find studies assessing whether effective treatment of abnormal blood pressure during childhood has an impact on hypertension and other intermediate outcomes during adulthood. Furthermore, we did not find any studies that addressed screening for secondary hypertension in asymptomatic children.

One fair study (n=247) assessed the diagnostic test accuracy of six office-based blood pressure measurements, 1 to 2 weeks apart, compared with ambulatory blood pressure monitoring as the reference standard. Office-based blood pressure measurements used recommendations of the Fourth Report as thresholds. Using systolic blood pressure (SBP) at the 90th percentile as a cutoff for abnormal blood pressure, the sensitivity of office-based measurements was 81.6 percent (confidence interval [CI] not reported) with a specificity of 70.3 percent (CI not reported).

Twenty studies on data from nine national and international cohorts evaluated the association between high blood pressure in childhood and hypertension or other intermediate outcomes

during adulthood. Despite substantial heterogeneity, studies consistently reported associations between abnormal blood pressure in childhood and abnormal blood pressure in adulthood. The strength of associations varied across studies (odds ratios [ORs] ranged from 1.1 to 4.5, relative risk [RR] ranged from 1.45 to 3.60, hazard ratios [HRs] ranged from 2.8 to 3.2; duration of followup ranged from 10 to 33 years). Studies also reported associations between abnormal blood pressure during childhood and carotid intima-media thickness (OR: 1.24, 95% CI, 1.13 to 1.37 [mean duration of followup was 25 years]; HRs ranged from 2.03 to 3.07 [duration of followup ranged from 10 to 21 years]; correlation coefficients ranged from 0.04 to 0.16 [duration of followup ranged from 21 to 31 years]), left ventricular hypertrophy (ORs ranged from 1.30 to 1.59, mean duration of followup was 25 years; HRs ranged from 1.92 to 3.41; duration of followup ranged from 10 to 21 years), and microalbuminuria (regression coefficients ranged from 0.016 to 0.315; mean duration of followup was 16.1 years).

Twenty randomized, controlled trials (RCTs) and a meta-analysis assessing treatments for hypertension in children and adolescents met inclusion criteria. The majority of studies excluded children with known secondary hypertension. Thirteen fair-quality placebo-controlled RCTs and one meta-analysis evaluated the efficacy of various pharmacological treatments. All studies reported greater reductions of SBP and diastolic blood pressure (DBP) measurements in participants who received pharmacological treatments compared with those treated with placebo. The magnitude of reductions, however, varied, and not all differences reached statistical significance. Pooled reductions of SBP were -4.38 mmHg (95% CI, -2.16 to -7.27) for angiotensin-converting enzyme (ACE) inhibitors, -3.07 mmHg (95% CI, -1.44 to -4.99) for angiotensin receptor blockers (ARBs), -3.20 mmHg (95% CI, +2.23 to -8.69) for beta blockers, -3.10 mmHg (95% CI, +0.45 to -6.52) for calcium channel blockers, and -0.12 mmHg (95% CI, +3.46 to -3.69) for mineralocorticoid receptor antagonists. Followup of studies was limited to 2 to 4 weeks.

One fair-quality trial, conducted from 1979 to 1981 in the United States and using a combination of a pharmacological treatment (low-dose propranolol/chlorthalidone) and lifestyle interventions (dietary and exercise modifications for children and parents), reported a statistically significant reduction of SBP (-7.6 mmHg) and DBP (-6.9 mmHg) after 6 months.

A DASH (Dietary Approaches to Stop Hypertension) −type diet (high in fruits, vegetables, and low-fat dairy foods) achieved statistically significant reductions in SBP (-2.2 mmHg) and DBP (-2.8 mmHg) in a completers-only analysis of one fair-quality RCT. The effect did not last beyond the intervention period.

Two fair-quality RCTs assessing physical exercise reported statistically significant decreases in SBP after 3 and 8 months (-8.3 and -4.9 mmHg, respectively) compared with lifestyle as usual. Only the study lasting 8 months reported a significant decrease in DBP (-3.8 mmHg vs. not reported).

Based on evidence from three fair-quality trials, a low-sodium diet and progressive muscle relaxation did not achieve any significant or clinically relevant changes in SBP or DBP.

Regarding harms of treatments, six fair-quality RCTs reported similar risks of adverse events between various pharmacological treatments (beta blocker, calcium channel blockers, angiotensin-converting enzyme, inhibitors or angiotensin receptor blockers) and placebo. The duration of trials, however, was limited to 2 to 4 weeks. One fair-quality RCT reported similar risks for adverse events between a combination of pharmacotherapy and lifestyle interventions and a control group without treatment over 6 months.

Limitations: Only English-language studies were included. No direct evidence for the benefits or harms of screening was identified. In addition, the indirect evidence pathway from screening to improvement of health outcomes is scarce, of limited applicability, or entirely missing for some steps of the pathway. The evidence on diagnostic accuracy was limited to one poor quality study. Epidemiological studies determining associations between high blood pressure in childhood and adulthood used various definitions and thresholds; the results were generally consistent in demonstrating an association, although the strength of association varied. Pharmacological treatment studies were limited to durations of 2 to 4 weeks of followup and excluded children with secondary hypertension; no evidence was available for long-term effectiveness. The mean age of children in these studies ranged between 12 and 14 years; the generalizability of results to younger children or children with secondary hypertension is unknown. Studies of treatment were generally too short and underpowered for harm outcomes. We did not assess the comparative effectiveness or harms of treatments.

Conclusions: We identified no direct evidence that compared screening with no screening in asymptomatic children and adolescents. Epidemiological studies indicate an association between hypertension in childhood and adolescence and hypertension in adulthood. Large longitudinal cohort studies also provide evidence that hypertension in adolescents and young adults is associated with end-stage renal disease and mortality from cerebrovascular events during adulthood. The proportion of spontaneous resolution of hypertension in children and the long-term benefits and harms of treatment, however, remain unclear. The evidence is also inconclusive whether the diagnostic accuracy of blood pressure measurements is adequate for screening asymptomatic children and adolescents in primary care. Short-term pharmacological treatments appear effective and safe, but no evidence with a followup of more than 4 weeks is available.

No evidence exists to determine whether screening for hypertension is effective in identifying children with secondary hypertension who are asymptomatic. Most treatment studies excluded children with secondary hypertension.

Table of Contents

Tables

Figures

Appendixes

Abbreviations

AAP	American Academy of Pediatrics	EPC	Evidence-based Practice Center
ABPM	ambulatory blood pressure monitoring	ER	extended release
ACE	angiotensin converting enzyme	FDA	Food and Drug Administration
ADAPT	Dietary/Exercise Alteration Program Trial	HR	hazard ratio
AE	adverse event	IMT	intima media thickness
AHA	American Heart Association	ITT	intent to treat
AHRQ	Agency for Health Research & Quality	KQ	key question
ARBs	angiotensin II receptor blockers	LFT	liver function test
AUC	area under curve	mmHg	millimeters of mercury
B/HT	bisoprolol fumarate/hydrochlorothiazide	NA	not applicable
BAM	breathing awareness meditation	NR	not reported
BMI	body mass index	PMR	progressive muscle relaxation
BP	blood pressure	PPV	positive predictive value
BPM	beats per minute	PWV	pulse wave velocity
CIMT	carotid intima-media thickness	RCT	randomized, controlled trial
CINCH	Candesartan in Children with Hypertension	REF	reference
CKD	chronic kidney disease	RR	relative risk
CQ	contextual question	SBP	systolic blood pressure
DASH	Dietary Approaches to Stop Hypertension	SD	standard deviation
DBP	diastolic blood pressure	US	United States
DM	diabetes mellitus	USPSTF	United States Preventive Services Task Force
ECG	electrocardiograph	vs.	versus

Chapter 1. Introduction

Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2013 recommendation on screening for primary hypertension in children and adolescents.[1] The 2013 recommendation was an update of the 2003 recommendation on this topic and is summarized as follows:

- The USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease (CVD) in childhood and adulthood (I statement).

The USPSTF made the 2013 recommendation based on an updated systematic review (search through July 2012) conducted by the Oregon Health & Science University Evidence-based Practice Center (EPC).[1] The USPSTF issued an I statement because there was no direct evidence available demonstrating that screening for hypertension in children and adolescents reduced adverse health outcomes, and limited evidence existed for assessing the harms of systematic screening. Therefore, the USPSTF could not determine the balance of benefits and harms of screening for hypertension in children and adolescents.

Condition Definition and Etiology

The newest definitions for abnormal blood pressure for children and adolescents were established by the American Academy of Pediatrics (AAP) in 2017.[2] For children 1 to 13 years of age, hypertension is defined as three auscultatory blood pressure measurements at three different visits that are above the 95th percentile based on age, height, and sex or above 130/90 mmHg (millimeters of mercury), whichever is lower. AAP defines Stage 1 hypertension as blood pressure between the limits listed above and the limits for Stage 2 hypertension. Stage 2 hypertension for children 1 to 13 years of age is defined as the 95th percentile for children of a given age, height, and sex plus 12 mmHg or 140/90 mmHg, whichever value is lower. AAP defines elevated blood pressure (previously termed "prehypertension") for children 1 to 13 years as between 90th and 94th percentile for a given age, height, and sex, or 120-129/<80 mmHg, whichever value is lower.[2]

Thresholds for adolescents 13 years of age and older now mirror those guidelines of the 2017 American Heart Association (AHA) and American College of Cardiology for adults regardless of height and sex.[3] Stage 1 hypertension for children age 13 years or older is 130-139/80-89 mmHg. Stage 2 hypertension for children age 13 years or older is >140/>90 mmHg. Elevated blood pressure for children age 13 years or older is defined as 120 to 129/<80 mmHg. For all age groups, blood pressure should be taken in the right arm with an appropriately sized cuff. The AAP recommends that the diagnosis should be confirmed by ambulatory blood pressure monitoring (ABPM), although it is not required to make a diagnosis. Confirmatory ABPM uses a

portable measuring device in the home setting to take blood pressure measurements every 20 to 30 minutes over a designated period of time, often 24 hours. It can be used to rule out white coat hypertension and confirm a diagnosis of hypertension in those that have either had 1 year of elevated blood pressures or three different occasions of elevated blood pressures in the clinical setting.[2]

Table 1 summarizes current blood pressure thresholds for diagnosing abnormal blood pressure in children.

Prior to the publication of the 2017 AAP guideline, clinicians followed the 2004 "Fourth Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" ("Fourth Report")[4]; the 2011 National Heart, Lung, and Blood Institute's guidelines used the same diagnostic thresholds and percentile as the Fourth Report.[5] In contrast to the Fourth Report, the 2017 guideline (1) uses the term "elevated blood pressure" rather than "prehypertension"; (2) uses new normative values for blood pressure by age, height, and sex from only normal-weight individuals rather than including overweight and obese individuals as well; (3) uses absolute blood pressure thresholds rather than percentiles for teenagers; and (4) calls for a greater role for ABPM in diagnosis.[6] One 2018 study found that in the same adolescent study population, 27 percent would be diagnosed with systolic hypertension by the 2017 guidelines compared with 16 percent based on the Fourth Report.[6] Another study using data from the Bogalusa Heart Study found that compared with thresholds from the Fourth Report the new reference standard (2017 guidelines) resulted in a reclassification of 8 percent of children to higher blood pressure categories and a reclassification of 1 percent to lower blood pressure categories.[7] The newly reclassified children with abnormal blood pressure were more likely than their propensity score–matched normotensive counterparts to develop hypertension in adulthood, whereas the children reclassified to lower blood pressure categories had similar adult hypertension outcomes to their propensity score–matched normotensive counterparts.

Etiology and Natural History

Primary hypertension, by definition, does not have an identifiable cause. Secondary hypertension in children is most commonly caused by renal or renovascular disease; it can also be caused by congenital cardiac abnormalities such as aortic coarctation, endocrine disorders, environmental exposures, medications, neurofibromatosis, and other genetic disorders.[8]

Children with primary hypertension are more likely than normotensive children to develop hypertension in adulthood.[9-12] They are also more likely to develop intermediate cardiovascular outcomes, such as as increased left ventricular mass, carotid intima-media thickness (CIMT), and increased pulse wave velocity.[9] The association between intermediate outcomes in childhood and health outcomes in adulthood, however, is unclear. These risks are discussed in greater detail below in Key Question (KQ) 4 and Contextual Question (CQ) 3 (**Appendix A**).

Untreated secondary hypertension can lead to similar sequelae as those of primary hypertension. In addition, untreated underlying secondary causes of hypertension can lead to serious sequelae

related to their etiologies. For example, untreated renal artery stenosis, a leading cause of secondary hypertension, can lead to renal failure.

Prevalence and Burden of Disease/Illness

The overall reported prevalence of hypertension (both primary and secondary) in children and adolescents ranges in studies from 0.54 percent to 29 percent, with most studies reporting between 3 percent to 4 percent of children having hypertension.[13-17] These data come from observational studies from a variety of settings, including a primary care network, insurance program, health care system, and schools.

Prevalence is higher in children and adolescents who are overweight and obese. Prevalence is also higher in African American and Hispanic children compared with non-Hispanic white children. One small study suggests that approximately half of children with hypertension have primary hypertension; children age 13 years or older are more likely to have primary hypertension (60%), while those under age 6 years are less likely to have primary hypertension (17%).[18] Greater detail is provided in **Appendix A**.

The prevalence cited above may underestimate the actual prevalence for children age 13 years or older because it is based on studies conducted before the adoption of uniform definitions in 2017. The thresholds for high blood pressure with the new uniform definitions are lower than the previous thresholds, which were placed at the 95th percentile for children of a given age, height, and sex. However, the new 2017 uniform definitions result in thresholds that are slightly higher than measurements at the 95th percentile for younger adolescents of a given age and sex at lower heights.

Risk Factors

Children with family histories of hypertension are 2 to 3 times as likely to develop primary hypertension.[19, 20] Children with specific chronic conditions are also at higher risk of developing hypertension. Obesity is a common comorbid condition with hypertension in children, with prevalence rates estimated between 3.8 percent and 20.2 percent in children with obesity (body mass index greater [BMI] greater than 95th percentile for age and sex).[21-24] Children with a BMI at the 95th to 98th percentile are 2 times as likely to develop hypertension as their normal-weight peers.[25] Rates of hypertension increase in relationship to increasing BMI.[21-24, 26] Children with sleep-disordered breathing (including snoring, sleep fragmentation, and obstructive sleep apnea) are approximately 3 times as likely to develop hypertension, and a higher severity correlates with higher risk.[9, 27, 28] Children born prematurely or with low birth weight also have a higher prevalence of hypertension (7.3%) than their term and normal birth weight peers.[29-33]

Chronic kidney disease is the most common cause of secondary hypertension, and it increases the risk of hypertension considerably. Approximately half of children and adolescents with chronic kidney disease are hypertensive, and the proportion is higher for those with end-stage kidney disease. Between 34 percent and 79 percent of patients with secondary hypertension have

a structural renal abnormality, while 12 percent to 13 percent have renovascular disease.[31, 34, 35] Nearly 20 percent of pediatric hypertension may be attributable to chronic kidney disease.[36] Infants and young children with hypertension are more likely to have an underlying renal etiology, while adolescents with hypertension are more likely to have primary hypertension.

Rationale for Screening

Some studies have found that children with hypertension have early signs of intermediate cardiac outcomes that have been shown to predict cardiovascular events in adults, such as increased left ventricular mass, CIMT, and pulse wave velocity.[37-39] Screening for hypertension in childhood may lead to earlier treatment, therefore reducing the risk of adult hypertension as well as cardiovascular complications resulting from hypertension. In addition, given higher rates of secondary hypertension in children than in adults, screening for hypertension in childhood may lead to diagnosis of underlying etiologies that are amenable to treatment, thus preventing nonhypertensive sequelae related to those etiologies.

For the purposes of this report, screening for hypertension involves measuring blood pressure using an oscillometric (automated) or auscultatory (manual) method and is conducted by a qualified health care professional. Diagnosis of hypertension requires confirmation of elevated blood pressure above diagnostic thresholds on three separate occasions by qualified health care professionals because blood pressure can be temporarily elevated at any given time by inappropriate cuff size, patient nervousness ("white coat hypertension"), recent physical activity, recent medications, or pain. To establish a diagnosis, blood pressure should be measured using auscultation because blood pressure norms are based on auscultatory measurement, and oscillometric devices overestimate both SBP and diastolic blood pressure (DBP).[8, 40]

Treatments/Interventions

Treatments for hypertension in children and adolescents vary depending on severity, associated symptomatology, and comorbidities. It is unknown whether treatment efficacy or harms vary by age. Lifestyle changes, including dietary and physical activity changes, may be effective for patients with asymptomatic, less severe hypertension without evidence of comorbidities (such as diabetes or chronic kidney disease). Studies have supported the effectiveness of the Dietary Approaches to Stop Hypertension (DASH), which emphasizes high intake of fruits, vegetables, whole grains, and lean meats, in addition to low sodium and low sugar intake. Moderate to vigorous physical activity 3 to 5 times each week has been shown to help lower blood pressure. Stress reduction activities can also be effective in decreasing blood pressure.[2]

Children and adolescents with hypertension refractory to lifestyle changes, symptomatic hypertension, or comorbidities may require pharmacologic interventions. Classes of antihypertensives include angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, central alpha-agonists, diuretics, and vasodilators. Treatment choices are generally guided by response to medications or a patient's comorbidities.[2]

Current Clinical Practice

Current screening practices vary. Bright Futures, the AAP's preventative care guide, has recommended routine blood pressure screening for children 3 years of age or older since its first edition was published in 1994.[41] This may have led to routine screening as commonplace in many pediatrics offices. Currently, many pediatricians follow the most recent AAP 2017 clinical practice guideline to begin screening all patients for hypertension at least annually and high-risk patients at each visit beginning at 3 years of age.[2] This guideline recommends ABPM (citing USPSTF's most recent adult blood pressure recommendations) for the confirmation of hypertension in children and adolescents; however, it is unknown how frequently this is being implemented. The AHA,[42] National Heart, Lung, and Blood Institute,[5] National High Blood Pressure Education Program,[4] Hypertension Canada,[43] and European Society of Hypertension[44] recommend routine screening starting at age 3 years. The American Academy of Family Physicians[45] and UK National Screening Committee[46] guidelines cite insufficient evidence for or against routine screening.

Chapter 2. Methods

Key Questions and Analytic Framework

The EPC investigators, USPSTF members, and AHRQ Medical Officers developed the scope and KQs for this review.

The analytic framework illustrates the KQs that guided the review (**Figure 1**).

1. Does screening for high blood pressure (i.e., persistently elevated blood pressure or hypertension) in children and adolescents delay the onset of or reduce adverse health outcomes related to high blood pressure?
2. What is the diagnostic accuracy of screening tests for high blood pressure in children and adolescents?
3. What are the adverse effects, such as labeling and anxiety, of screening for high blood pressure in children and adolescents?
4. What is the association between high blood pressure in children and adolescents and high blood pressure and other intermediate outcomes in adults?
5. What is the effectiveness of drug, nondrug, and combination interventions for treating high blood pressure in children and adolescents?
6. What is the effectiveness of drug, nondrug, and combination interventions initiated for the treatment of high blood pressure in children and adolescents for reducing blood pressure and improving other intermediate outcomes in adults?
7. What is the effectiveness of drug, nondrug, and combination interventions initiated for the treatment of high blood pressure in children and adolescents for reducing adverse health outcomes related to high blood pressure in adults?
8. What are the adverse effects of drug, nondrug, and combination interventions for treating high blood pressure in children and adolescents?

In addition to our KQs, we also looked for evidence related to four CQs.

1. What is the prevalence of primary and secondary hypertension in asymptomatic children and adolescents in primary care settings?
2. What are the optimal ages at which to start screening for high blood pressure and the optimal time intervals at which to repeat screening in children and adolescents?
3. What are the associations between intermediate outcomes related to high blood pressure in children and adolescents and health outcomes related to high blood pressure in children, adolescents, and adults?
4. What are the effectiveness and adverse effects of drug, nondrug, and combination interventions for treating the underlying conditions of secondary hypertension in children and adolescents?

We do not show these questions in the analytic framework because they were not analyzed using the same systematic review process as the KQs. Findings related to the CQs are summarized in **Appendix A**.

Data Sources and Searches

We searched MEDLINE® (via PubMed) for English-language articles published between June 1, 2012, and September 3, 2019, and the Cochrane Library, Embase, and International Pharmaceutical Abstracts for English language articles. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant population, interventions, comparisons, outcomes, timing, and setting elements. **Appendix B** describes the search strategies in detail. We conducted surveillance of the literature through February 25, 2020.

We conducted targeted searches for unpublished literature by searching Cochrane Reviews, Cochrane Trials, Embase, ClinicalTrials.gov, Health Services Research Projects in Process (HSRProj), and the World Health Organization's International Clinical Trials Registry Platform. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and screened all previously unidentified relevant articles. We also manually reviewed all literature suggested by peer reviewers or Federal partners and, if appropriate, incorporate studies into the final review.

Because we extended the population of interest for this update to children and adolescents with secondary hypertension (see below under Study Selection), we rescreened studies that the previous report excluded for "ineligible population" and rescreened articles that a search for "secondary hypertension" in the bibliographic database of the previous report yielded.

Study Selection

We developed inclusion and exclusion criteria for selecting studies based on populations, interventions, comparators, outcomes, timing, settings, and study designs; these are described in detail in **Appendix B Table 1**. Based on comments on the 2013 report and discussions with the USPSTF during the scoping phase of this update, we adapted inclusion and exclusion criteria for this update in the following ways:

- We extended the population of interest to children and adolescents with secondary hypertension.
- We excluded pharmacological dose-ranging studies without a placebo control group from the assessment of benefits and harms of treatments (KQ 5 and KQ 8) because assay sensitivity cannot be established without a placebo-controlled design.
- We excluded information from placebo-controlled withdrawal phases of dose-ranging studies for the assessment of harms because participants with serious or intolerable adverse events would have likely dropped out during the prior dose-ranging phase.

Briefly, for this update we included studies of screening for hypertension in asymptomatic children and adolescents. For benefits and harms of treatments or the association between hypertension in children and adolescents and intermediate outcomes in adults we included participants with primary or secondary hypertension or elevated blood pressure. For studies of diagnostic test accuracy, we required a relevant reference standard comparison. For example, we

excluded studies that compared single blood pressure measurements with followup measurements after a specific time period. We also excluded studies of interventions for the treatment or prevention of overweight and obesity and interventions for the primary prevention of hypertension. We included intermediate outcomes only if they were closely related to hypertension (e.g., left ventricular hypertrophy, urinary albumin excretion, retinal vascular changes, and CIMT).

We imported all citations identified through searches and other sources into EndNote Version X8 (Clarivate Analytics, Philadelphia).

Two investigators independently reviewed titles and abstracts. We then dually and independently reviewed the full text of all articles that either reviewer marked for potential inclusion at the title/abstract level. We resolved disagreements by discussion and consensus; if necessary, we sought adjudication of conflicts from other experienced members of the review team. **Appendix C** lists citations and reasons for exclusion for studies that we excluded at the full-text review stage.

In addition to citations from the update literature search, we incorporated citations from studies included in the previous report, which covered the publication period through June 2012.[1]Using predefined criteria developed by the USPSTF, two investigators independently assessed the quality of each study as good, fair, or poor.[47] The USPSTF criteria are listed in **Appendix D**. Disagreements were resolved by discussion and consensus. We rated trials with fatal flaws as poor quality (i.e., high risk of bias).

One team member abstracted pertinent information from each included study including details on study design and the population, interventions, comparisons, outcomes, timing, and setting elements. A second investigator checked all data abstractions for completeness and accuracy. We resolved differences by consensus or adjudication by a third senior investigator. We did not rate the risk of bias of association studies (KQ 4) because risk-of-bias tools are designed to identify potential biases in causal inference.

Data Synthesis and Analysis

We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in tabular or narrative format. To determine whether meta-analyses were appropriate, we assessed both the number of trials available and their clinical and methodological heterogeneity following established guidance.[48] Because of the dearth of data, we were unable to conduct meta-analyses, in addition to the ones that we included from a published systematic review for KQ 5. We assessed the strength of evidence (SOE) based on AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, which specifies the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major outcome of interest.[49] A senior reviewer initially developed SOE assessments for each relevant outcome. A second senior reviewer checked the SOE ratings; discrepancies were resolved through discussion or the independent assessment of a third senior reviewer. In addition, we assessed the applicability of the evidence for each relevant outcome to

a U.S. primary care setting. Although we did not rate the risk of bias of association studies, we used study design criteria to rate the overall body of evidence for these studies.

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF Web site for public comment from June 28, 2018, to July 25, 2018. In response, we revised the inclusion criteria to be more explicit regarding intermediate outcomes, removed a limitation on the sample size of observational studies, and adjusted screening ages to 3 to 18 years to match the AAP's recommendation. The final version of the research plan was posted on the USPSTF Web site on November 1, 2018.[50] A draft report was reviewed by three content experts, three representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments received. In response to these comments, we included new studies published since the first literature search, included studies with a randomized withdrawal design for assessing the effectiveness of pharmaceutical interventions, and clarified future research needs.

USPSTF Involvement

This review was funded by AHRQ. Staff of AHRQ and members of the USPSTF participated in developing the scope of work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

In the following sections, we summarize the evidence by KQ. **Appendix D** presents quality rating criteria and quality ratings for each eligible study; **Appendix E** provides detailled evidence tables for each included study. **Table 2** summarizes SOE ratings for relevant outcomes and presents a summary of findings.

We screened 4,588 titles/abstracts and 304 full-text articles and identified 42 studies (43 publications) that met inclusion criteria (**Figure 2**). We excluded four studies that were in the previous report that did not meet inclusion criteria for this update.[51-54] **Appendix F Table 1** summarizes the reasons why these studies were excluded.

Benefits of Screening (Key Question 1)

We identified no studies that examined the direct effect of screening for hypertension in children or adolescents in delaying the onset of or reducing adverse health outcomes related to hypertension.

Diagnostic Test Accuracy (Key Question 2)

Key Points

- One fair diagnostic test accuracy study (n=247) reported that the sensitivity of six office-based blood pressure measurements, 1 to 2 weeks apart, was 81.6 percent (confidence interval [CI] not reported) with a specificity of 70.3 percent (CI not reported). The reference standard was ABPM.

Summary of the Evidence

For the diagnostic test accuracy of blood pressure screening (KQ 2), we identified one fair-quality study.[6] The U.S.-based SHIP AHOY (Study of Hypertension in Pediatric, Adults Hypertension Onset in Youth) study is an ongoing cross-sectional cohort study to determine blood pressure levels and phenotypes that predict blood pressure–related target organ damage in adolescents. In a sample of the first 247 participants of this study, investigators assessed the diagnostic test accuracy of six blood pressure measurements obtained by auscultation over two visits 1 to 2 weeks apart. The study enrolled healthy volunteers or patients referred for abnormal blood pressure ages 11 to 19 years. Exclusion criteria, among others, were stage 2 hypertension, use of antihypertensive medications, and secondary hypertension. The prevalence of hypertension in this population was 29 percent.

Abnormal blood pressure for office-based measurements was defined according to the Fourth Report.[4] The reference standard was 26-hour ambulatory monitoring at 20-minute intervals. Abnormal blood pressure for the reference standard was defined based on the AHA

recommendations for pediatric ABPM.[42] Using systolic blood pressure (SBP) at the 90th percentile as a threshold, the sensitivity of two office-based blood pressure measurements was 81.6 percent (CI not reported) with a specificity of 70.3 percent (CI not reported) compared with ABPM.

Harms of Screening (Key Question 3)

We identified no studies that compared harms of screening in a screened versus an unscreened population.

Association Between High Blood Pressure in Children and Intermediate Outcomes in Adults (Key Question 4)

Key Points

- Twenty publications,[7, 10-12, 55-70] drawing from nine data sources, reported on the association between abnormal blood pressure in childhood and abnormal blood pressure or other intermediate outcomes in adulthood.
- Studies presented measures of association such as odds ratios (ORs), relative risks (RRs), and hazard ratios (HRs) and measures of predictive accuracy such as sensitivity and positive predictive value (PPV). Studies focusing on the association between abnormal blood pressure in childhood and abnormal blood pressure in adulthood generally reported ORs (ranging from 1.1 to 4.5), RRs (ranging from 1.45 to 3.60), and HRs (ranging from 2.8 to 3.2, mean duration of followup ranged from 10 to 33 years), suggesting an association between abnormal blood pressure in childhood and abnormal blood pressure in adults. Results for predictive accuracy measures such as sensitivity and PPVs varied significantly, with sensitivity ranging from 0.0 to 0.89 (with most values below 0.6) and PPVs ranging from 0.05 to 0.97 (again with most values below 0.6).
- Studies reported associations between abnormal blood pressure in childhood and CIMT in adulthood (OR, 1.24 [95% CI, 1.13 to 1.37], mean duration of followup was 25 years; HRs ranged from 2.03 to 3.07, duration of followup ranged from 10 to 21 years; correlation coefficients ranged from 0.04 to 0.16, duration of followup ranged from 21 to 31 years).
- Studies also reported associations between abnormal blood pressure during childhood and left ventricular hypertrophy (ORs ranged from 1.30 to 1.59, mean duration of followup was 25 years; HRs ranged from 1.92 to 3.41; duration of followup ranged from 10 to 21 years).
- Limited evidence found increased risk of subclinical CVD in adulthood (HRs ranged from 2.20 to 3.21) for those with a history of childhood prehypertension or hypertension.
- Limited evidence also found increased risk of microalbuminuria in adults for those with a history of elevated blood pressure in childhood. This effect was observed among African American participants (regression coefficients range from 0.016 to 0.315, mean duration of followup was 16.1 years) but not white participants.

Summary of the Evidence

We identified 20 relevant publications. One publication pooled data from four databases (Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, and the Childhood Determinants of Adult Health study).[69] A second publication from the i3C Consortium pooled data from six databases (Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health study, the Insulin Study, and the Kaunas Study).[70] All others were analyses of cohorts drawn from single databases. Specifically, 18 drew from six data sources (4 based in the United States [1 unnamed cohort of school children in Boston, MA,[55] the Fels Longitudinal Study,[10, 56] Bogalusa,[7, 57-61] and Muscatine[62, 63]] 1 based in Finland [Young Finns[11, 12, 64-67]], and 1 based in New Zealand [the Dunedin Multidisciplinary Health and Development Study[68]]).

Ten publications[7, 11, 61, 62, 65-70] and three (the Childhood Determinants of Adult Health study, the Insulin study, and the Kaunas study) databases are new to this update (**Appendix E Tables 1 to 3**). The evidence base is marked by substantial heterogeneity across and within data sources; publications even within the same data source do not use consistent criteria for determining hypertension in childhood or adulthood. Participants' ages vary from 2 to 18 years of age. The duration of followup ranges from 12[55] to 31 years.[66] The timing, methods, and thresholds for recording blood pressure and characterizing hypertension also vary in childhood and adulthood. The number of measurements in childhood vary from a single measure (selecting the second of 2 measurements) to a mean of 6; the measurement interval varies from a single time point to a span of 6 months. Most studies used a standard mercury sphygmomanometer; one also used Hawksley random-zero sphygmomanometers.[55]

Although most studies reported on systolic, diastolic, or blood pressures above a prespecified threshold, the definition of hypertension in childhood varied, as did the reference standard. Threshold values for hypertension in childhood ranged from >75th percentile to >99th percentile. The reference standards for the threshold also varied: some were cohort specific, some were based on standardized data, and some were not specified. The timing, methods, and thresholds of outcome measures in adults similarly varied within and across data sources. Measures of association between childhood hypertension measures and adult outcomes varied and included PPV, sensitivity, specificity, or areas under the receiver operating characteristics curve, risk ratios, HRs, regression coefficients, and correlation coefficients. Finally, publications reported on both cohort-wide associations and associations within subgroups defined by age, sex, and race.

As in the previous review, we did not rate the quality of these studies but note that the heterogeneity in the evidence base extends to quality as well. All the sources of heterogeneity described above create challenges in interpreting the results and reduce the certainty that can be attached to any conclusions.

As with the previous review, we present results for the association between (1) abnormal blood pressure (elevated blood pressure or hypertension) in children and adults and (2) abnormal blood pressure in children and intermediate outcomes in adults. Given the significant and recent changes in thresholds for defining abnormal blood pressure in children and adults, the synthesis

below focuses attention on the definitions most applicable to current clinical practice. Current definitions rely on data from normal-weight children only.[71] As a result, studies relying on previous definitions that included overweight and obese children may have been likely to identify more severe cases of hypertension than current standards.

In each category of results, we first present findings from publications that use current criteria or previously established criteria for abnormal blood pressure in children and then summarize results that do not use standard criteria. When possible or relevant, we also structure the results to focus on current or recent standards for abnormal blood pressure in adults first, followed by nonstandard definitions. **Table 3** maps the evidence against childhood and adult standards.

Association Between Abnormal Blood Pressure in Children and Abnormal Blood Pressure in Adults

Association Between Abnormal Blood Pressure in Children and Abnormal Blood Pressure in Adults Using Current Definitions of Childhood Hypertension

One publication, drawing from the Bogalusa Heart Study,[7] followed 3,940 children over 25 years, on average. The publication used the 2017 AAP guidelines[2] to categorize study participants as having elevated blood pressure, being hypertensive, or being normotensive and assessed the RR of adult hypertension, as defined by the current AHA standards.[3] The publication reported that children with elevated blood pressure had an adjusted RR of 1.45 (95% CI, 1.30 to 1.61) for developing hypertension as adults. For children with hypertension, the adjusted RR was 1.66 (95% CI, 1.47 to 1.87). The study reported similar results when adult hypertension was defined using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria.[72] Specifically, children with elevated blood pressure had an adjusted RR of 1.62 (95% C1, 1.35 to 1.95) for developing hypertension as adults. For children with hypertension, the adjusted RR was 1.98 (95% CI, 1.45 to 2.39).

Association Between Abnormal Blood Pressure in Children and Abnormal Blood Pressure in Adults Using Prior Standardized Definitions of Childhood Hypertension

Nine publications from five data sources (Cardiovascular Risk in Young Finns,[11, 12, 65-67] Bogalusa Heart Study,[7, 61] the Dunedin Multidisciplinary Health and Development Study,[68] and one pooled analysis of the Bogalusa Heart Study, Muscatine Study, Young Finns Study, and the Childhood Determinants of Adult Health study)[69] relied on prior standards (the Fourth Report)[4] in reporting on the association between childhood hypertension or prehypertension and adult hypertension.

Among the publications relying on prior standards (the Fourth Report definitions for abnormal childhood blood pressure), publications varied in their definitions of adult hypertension, even when drawing from the same data source.[4] Adult hypertension was defined using current AHA standards,[3, 7] prior standards,[73] and nonstandard definitions.

Overall, we found consistent results for associations between abnormal blood pressure in childhood and abnormal blood pressure in adulthood, regardless of the definition of hypertension and method of measurement. Results from other databases also support a consistent association between abnormal blood pressure in childhood and abnormal blood pressure in adulthood. We present results for current adult hypertension standards, prior standards, and nonstandard definitions below.

Current adult hypertension standards. Three publications used prior childhood standards and current adult standards. One publication of 1,540 adults from the Young Finns Study, followed over 27 years, provided data on blood pressure in children (abnormal blood pressure defined as >90th percentile based the Fourth Report[74] standards) or adolescents and abnormal blood pressure in adults (abnormal blood pressure defined as SBP>120 mmHg and DBP>80 mmHg or self-reporting of antihypertensive medication use).[67] This definition of abnormal adult blood pressure corresponds with current adult AHA standards.[3] Measures of predictive accuracy, specifically, calculated sensitivity (0.55 and 0.56 [i.e., 55 and 56% of adults with abnormal blood pressure had abnormal blood pressure in childhood]) and specificity (0.63 and 0.64 [i.e., 63 to 64% of normotensive adults had normal blood pressure in childhood]) were similar among normal-weight and overweight/obese children, respectively, although the calculated PPV was higher among overweight or obese children (0.73 [i.e., 73% of those with abnormal blood pressure in childhood had abnormal blood pressure in adulthood]) than normal-weight children (0.53 [i.e., 53% of those with abnormal blood pressure in childhood had abnormal blood pressure in adulthood]).

One publication, drawing from the Bogalusa Heart Study,[7] followed 3,940 children over 25 years, on average. As noted above, this publication presented results using the 2017 standards, but the authors also used the Fourth Report[4, 74] standards to categorize study participants as prehypertensive, hypertensive, or normotensive and assessed the RR of adult hypertension, as defined by the current AHA standards.[3] The results are presented here for completeness. The publication reported that children with prehypertension had an adjusted RR of 1.49 (95% C1, 1.34 to 1.65) for developing hypertension as adults. For children with hypertension, the adjusted RR was 1.71 (95% CI, 1.48 to 1.98).

One analysis pooled results from four databases (Bogalusa Heart Study, Muscatine Study, Young Finns Study, and the Childhood Determinants of Adult Health study, and used the Fourth Report to define childhood abnormal blood pressure and standards consistent with current AHA standards for adult abnormal blood pressure.[4, 69] The PPV was 0.60; in other words, 60 percent of children with abnormal blood pressure had abnormal blood pressure in adulthood.

Prior adult hypertension standards. One publication, drawing from the Bogalusa Heart Study,[7] followed 3,940 children over 25 years, on average, and as described above, presented results using current adult standards. The publication also used the Fourth Report[4, 74] standards to categorize study participants as prehypertensive, hypertensive, or normotensive and assessed the RR of adult hypertension, as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria.[72] The publication reported that children with prehypertension had an adjusted RR of 1.53 (95% C1,

1.28 to 1.82) for developing hypertension as adults. For children with hypertension, the adjusted RR was 1.95 (95% CI, 1.55 to 2.46).

One study comprising two publications,[12, 65] also drawing from the Young Finns Study, enrolled 3,596 children in Finland age 3 to 18 years and provided followup for 2, 204 participants 27 years later. Adult hypertension was defined as SBP≥140 mmHg or DBP ≥90 mmHg or self-reported antihypertensive medication use. This definition is consistent with prior hypertension standards for adults.[73] The study reported that being prehypertensive or hypertensive (as defined by the Fourth Report[74] thresholds) as adolescents or children is associated with an OR of adult hypertension ranging from 2.1 to 2.8 (the specific odds vary by age and sex). In other words, the odds of being hypertensive as an adult are more than twice as high for hypertensive than normotensive children. The PPV for age 6 to 18 years is 0.44, with a sensitivity of 0.1 and a specificity of 0.97.[12, 65] In general, PPVs and sensitivities increase with the age of the child. PPV ranges from a low of 0.11 at age 6 to a peak of 0.58 at age 12.

Another publication from the Young Finns data source[66] tracking 1,927 participants over an average of 29 years used the Fourth Report[74] standards for prehypertension or hypertension and prior standards for adult hypertension.[73] This publication reported similar AUCs (area under curve) regardless of number of observations of abnormal blood pressure in childhood (AUCs range from 0.60 to 0.63).

The results for overall predictive accuracy from the Young Finns Study are consistent with the findings from the Dunedin Multidisciplinary Health and Development Study[68] and the Bogalusa Heart Study.[61] The Dunedin sample of 975 participants relied on the Fourth Report[74] standards for prehypertension (now referred to as "elevated blood pressure") or hypertension at age 7 and 11 years and prior standards for adults for prehypertension (≥120 mmHg) and hypertension (≥140 mmHg) at age 38. AUCs range from 0.68 to 0.70. Underlying the similarity in AUCs between the two data sources (Young Finns and Dunedin), however, are differences in sensitivity (lower in the Dunedin study, ranging from 0.05 to 0.37) and specificity (higher in the Dunedin study, ranging 0.87 to 0.99) than in the Young Finns Study.

One publication drawing from the Bogalusa Heart Study (n=1, 225 adults, followed over a mean of 27 years) used prior adult standards for hypertension and compared simple and complex definitions of childhood hypertension and prehypertension and their association with adult hypertension (defined as ≥140/90 mmHg or taking antihypertensive medicine).[61] The authors noted the multiplicity of cutoffs arising from the use of reference standards in the complex definition and the resultant difficulty in interpreting the results. The complex definition of prehypertension used thresholds from ≥90th percentile (or ≥120/80 mmHg) to <95th percentile based on age-, height-, and sex-based blood pressure reference standards of the Fourth Report. The simple definition, by contrast, used a fixed cutoff, modified by age.[a] The authors reported increased HRs for the presence of adult hypertension (ranging from 2.8 to 3.2, all statistically

[a] For children (6–11 years), prehypertension was defined as SBP≥110 and/or DBP≥70 mmHg; SBP<120 and DBP<80 mmHg also indicated prehypertension. For adolescents (12–17 years), prehypertension was defined as SBP≥120 and/or DBP≥80 mmHg); SBP<130 and DBP<85 mmHg also indicated prehypertension. Hypertension was defined as SBP≥120 and/or DBP≥80 mmHg for children, and SBP≥130 and/or DBP≥85 mmHg for adolescents.

significant [participants with childhood hypertension were 2.8 times to 3.2 times more likely to develop adult hypertension over the course of the observation period than participants without hypertension]), regardless of how childhood hypertension was defined.

Nonstandard adult hypertension definitions. The odds for adult hypertension when using a nonstandard definition of adult hypertension are similar to the odds for the same outcome when using prior standards. A publication from the Young Finns data source, tracking 2,625 participants over 21 to 27 years for the Fourth Report definition of childhood hypertension and a different threshold for adult hypertension (SBP ≥130 mmHg or DBP ≥85 mmHg or self-reported use of antihypertensive medication), reported an OR of 2.12 (95% confidence interval [CI], 1.82 to 2.61).[11]

Association Between Abnormal Blood Pressure in Children and Abnormal Blood Pressure in Adults Using Nonstandardized Definitions of Childhood Hypertension

Despite variations in definitions, all studies were generally consistent in demonstrating an association between abnormal blood pressure in childhood and abnormal blood pressure in adulthood. Seven publications from four data sources reported on the association between childhood hypertension and adult hypertension and used nonstandardized definitions of hypertension, generally relying on a percentile cutoff within their own data source. The data sources included an unnamed cohort of school children in Boston, MA[55]; the Fels longitudinal cohort[10, 56]; the Bogalusa Heart Study[57, 60]; and the Muscatine Study.[62, 63] One publication using a within-cohort 80th percentile threshold[57] offered results for multiple thresholds.(75th, 80th, 90th, 95th, or 99th).[55, 60, 62, 63] Other publications defined abnormal blood pressure as 90th percentile and above in the cohort. Most publications used a within-cohort threshold of 90th percentile to define abnormal blood pressure in adults, with the exception of the two publications from the Fels Study. One Fels publication used a threshold of DBP >90 mmHg,[56] and the second used a threshold SBP >130 mmHg or DBP >85 mmHg.[10] Publications reporting associations (ORs and RRs[10, 56, 57, 62, 63]) offered estimates by age of the child, age of the adult, sex, race, and threshold, ranging from 1.1 to 9.0. Although studies did not always report CIs, when reported the intervals generally excluded a null effect. In the case of exceptions (e.g., for boys age 14 to 18 years, OR for hypertension in adulthood; 1.1 [95% CI, 0.5 to 2.4]), it was unclear whether the lack of statistical significance could have been the result of chance or small sample size.[10]

Publications reporting predictive accuracy[55, 60] reported low sensitivity (0 to 0.66) and relatively high specificity (0.77 to 1.00) by age, sex, and blood pressure threshold value.

Association Between Abnormal Blood Pressure in Children and Other Intermediate Outcomes in Adults

Seven publications (6 reported on 2 individual databases [Bogalusa Heart Study[7, 58, 59, 61] and Cardiovascular Risk in Young Finns Study[64, 66]]; 1 pooled analysis from the iC3 Consortium of 6 databases [Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health study, the Insulin Study, and the Kaunas Study[70]]) examined the relationship between abnormal childhood blood pressure and intermediate outcomes in adults. One publication used current definitions of hypertension in children.[7] Three

publications used the Fourth Report definitions[4, 74] of hypertension, and the others used other thresholds or did not define the threshold.

Association Between Abnormal Blood Pressure in Children and Carotid Intima-Media Thickness in Adults

Six publications assessed CIMT. Two publications, one each from the Bogalusa[61] and Young Finns databases,[66] reported on the association between childhood hypertension and adult CIMT using the Fourth Report[4] thresholds. Additionally, one study presented data pooled across multiple databases[69] using the Fourth Report[4] thresholds. Three other publications used other thresholds.[59, 64, 70] The evidence presentation below first focuses on results using the Fourth Report thresholds, followed by results using other thresholds.

Results using the Fourth Report[74] thresholds suggest an association between abnormal blood pressure in children and CIMT in adults, although the magnitude is unclear. Specifically, a recent publication from the Bogalusa database (n=1, 225 adults, followed over a mean of 27 years) compared simple and complex definitions (described above) of children with hypertension and prehypertension and their association with adult CIMT.[61] Both simple and complex definitions suggest a statistically significant association between childhood prehypertension or hypertension and high CIMT in adulthood, with HRs ranging from 2.03 to 3.07.[61]

An exploration of 1,927 participants from the Young Finns Study examined whether the frequency of blood pressure measurement was associated with improved prediction. The authors defined thresholds for abnormal blood pressure (hypertension or prehypertension) based on the Fourth Report.[74] The authors found weak correlations for the association between childhood SBP and adult CIMT (correlation coefficients ranging from 0.12 to 0.16) for a frequency of one to three measurements of blood pressure; these correlations were statistically significant for all frequencies of blood pressure measurement. Correlation coefficients for childhood DBP and adult CIMT were smaller and ranged from 0.04 to 0.06 for one to three measures; two of the three measures were statistically significant, despite the weak correlation.[66]

One analysis pooled results from four databases (Bogalusa Heart Study, Muscatine Study Young Finns Study, and the Childhood Determinants of Adult Health study) and used the Fourth Report to define childhood abnormal blood pressure and standards consistent with current AHA standards for adult abnormal blood pressure.[69] The study found that individuals who had elevated blood pressure in both childhood and adulthood had a higher RR of CIMT (RR, 1.76 [95% CI, 1.21 to 2.56]).

Results from publications using thresholds other than the Fourth Report[74] are inconsistent. One publication pooled results across six databases (n=5,925, mean followup=25.8 years) and used age-, sex-, and study-specific thresholds of 90th percentile to define abnormal blood pressure in children and high CIMT in adults.[70] For high SBP, the publication reported an OR of 1.24 (95% CI, 1.13 to 1.37). One publication from the Young Finns Study (n=2, 229) found that SBP >80th percentile in adolescence (ages 12 to 18 years) had a small association with the presence of CIMT 21 years later in adulthood (regression coefficient 0.013; $p<0.001$).[64] One publication from the Bogalusa database (n=486) found no association between an undefined childhood SBP

risk and incidence of CIMT an average of 22 years later in adulthood (highest quartile vs. lower three quartiles, OR, 1 [95% CI, 0.80 to 1.25]).[59]

Association Between Abnormal Blood Pressure in Children and Intermediate Outcomes Other Than CIMT in Adults

Three publications from the Bogalusa database[7, 58, 61] reported on the association between abnormal blood pressure in children and intermediate outcomes other than CIMT in adults. The Bogalusa publications varied in the use of reference standards, size of the sample, and specific outcomes.

One publication, drawing from the Bogalusa database (n=3940),[7] assessed the association between childhood prehypertension/elevated blood pressure or hypertension and adult hypertension, using the 2017[2] and the Fourth Report[4] standards. The publication also reported adjusted RRs for adult left ventricular hypertrophy; these RRs ranged from 1.30 to 1.59, and all results were statistically significant.

One publication drawing from the Bogalusa database (n=1, 225) found significantly higher HRs among children and adolescents with prehypertension or hypertension (using either simple or complex [Fourth Report] definitions) for any subclinical CVD (HRs range from 2.20 to 3.21), left ventricular hypertrophy (HRs range from 1.92 to 3.41), and higher aorta-femoral pulse wave velocity in adulthood (HRs range from 2.22 to 3.51).[61] Subclinical atherosclerosis was defined as values equal to or greater than the age-, sex-, and race-specific 80th percentile of CIMT.[61]

One publication of 2, 122 children from the Bogalusa Heart Study examined the association of childhood blood pressure (≥90th percentile by age, ethnicity, and sex [assumed to be cohort specific]) with microalbuminuria in adulthood (mean age 26 years).[58] Among black participants, SBP, DBP, and the annual change in SBP and DBP from childhood to adulthood were independent predictors of development of microalbuminuria (based on regression analysis, regression coefficients range from 0.016 to 0.315). Among white participants, SBP and DBP were not significantly associated with microalbuminuria (regression coefficients range from 0.002 to 0.063).[58]

Effectiveness of Interventions for Treating High Blood Pressure in Children and Adolescents (Key Question 5)

Key Points

- Thirteen fair-quality, placebo-controlled, randomized, controlled trials (RCTs) and a meta-analysis[75] assessing the efficacy of various pharmacological treatments reported greater reductions of SBP and DBP measurements in participants who received pharmacological treatments compared with those treated with placebo.[76-88] The magnitude of reductions, however, varied, and not all differences reached statistical significance. Pooled reductions in SBP were -4.38 mmHg for angiotensin-converting enzyme (ACE) inhibitors, -3.07 mmHg for angiotensin receptor blockers (ARBs), -3.20

mmHg for beta blockers, -3.10 mmHg for calcium channel blockers, and -0.12 mmHg for mineralocorticoid receptor antagonists. Followup of placebo-controlled periods in these studies was limited to 2 to 4 weeks.

- One fair-quality trial using a combination of a pharmacological treatment with lifestyle interventions reported a statistically significant reduction of SBP (-7.6 mmHg) and DBP (-6.9 mmHg) after 6 months.[89]
- A fair-quality DASH (Dietary Approaches to Stop Hypertension)−type diet (high in fruits, vegetables, and low-fat dairy foods) achieved statistically significant reductions in SBP (-2.2 mmHg) and DBP (-2.8 mmHg) in a completers-only analysis.[90] The effect, however, did not last beyond the intervention period.
- Two fair-quality RCTs assessing physical exercise reported statistically significant decreases in SBP after 3[91] and 8 months (-8.3 and -4.9 mmHg, respectively).[92] Only the study lasting 8 months[92] reported a significant decrease in DBP (-3.8 mmHg vs. not reported).
- Two fair-quality low-sodium diet[93, 94] and one fair-quality progressive muscle relaxation[95] RCTs did not achieve any significant or clinically relevant changes in SBP or DBP.

Summary of the Evidence

Twenty RCTs (21 publications) and one meta-analysis assessing treatments for hypertension in children and adolescents met inclusion criteria (**Appendix E Tables 4 to 6**). Two trials and the meta-analysis are new to this update.[75, 87, 91] Thirteen trials and the meta-analysis assessed pharmacological treatments,[75-88] six trials evaluated lifestyle interventions,[90-95] and one trial assessed a combination of drug treatment and lifestyle intervention.[89, 96] We did not identify any observational studies that met our inclusion criteria. All trials were of fair methodological quality (**Appendix F Table 2**).

The majority of studies excluded children with known secondary hypertension. Three pharmacological trials[81, 83, 84] and four trials that assessed different lifestyle interventions[92-95] included children with hypertension regardless of etiology.[92-95] **Table 4** provides a summary of results for each intervention.

Pharmacological Treatments

Study Characteristics

Thirteen RCTs with data on more than 2,300 participants assessed the efficacy of pharmacological interventions, including ACE inhibitors (enalapril,[82] fosinopril,[81] lisinopril[83]), ARBs (candesartan,[77] losartan,[84] olmisartan,[85] telmisartan,[79]) beta-blockers (metoprolol succinate ER,[76] combination of bisoprolol fumarate and hydrochlorothiazide,[80]) calcium channel blockers (amlodipine,[88]felodipine ER[78])and mineralocorticoid receptor antagonists (eplerenone[86]). (**Appendix E Table 4**). Eight RCTs used randomized withdrawal designs;[81-88] five RCTs employed a concurrent placebo-controlled design.[76-80] None of the studies provided efficacy outcomes beyond 4 weeks. The number of participants in the studies ranged from 73 to 304; all studies included at least one site in the United States. The majority of participants were male and

white. Most studies excluded children or adolescents with severe hypertension (mostly defined as SBP ≥20 mmHg or DBP ≥10 mmHg above the 99th percentile). Only three studies permitted the inclusion of participants with secondary hypertension.[81, 83, 84] The proportion of children with secondary hypertension in these studies, however, was not reported. Some trials included treatments that are not approved by the Food and Drug Administration (FDA) for the treatment of hypertension in children or used doses that were outside FDA-approved dosing ranges.

Results

The meta-analysis included 12 of the 13 RCTs that have been included for this update.[75] It combined treatment arms of individual drugs regardless of the dose. The study was designed as a network meta-analysis; however, for the purpose of this report we summarize comparisons with placebo only. Because of the star-shaped network, none of these estimates are based on indirect comparisons. Pooled reductions of SBP were -4.38 mmHg (95% CI, -2.16 to -7.27) for ACE inhibitors, -3.07 mmHg (95% CI, -1.44 to -4.99) for ARBs, -3.2 mmHg (95% CI, +2.23 to -8.69) for beta blockers, -3.1 mmHg (95% CI, +0.45 to -6.52) for calcium channel blockers, and -0.12 mmHg (95% CI, +3.46 to -3.69) for mineralocorticoid receptor antagonists. Followup of placebo-controlled periods of all studies was limited to 2 to 4 weeks.

The study that was not included in this meta-analysis assessed candesartan in 240 children and adolescents ages 6 to 17 years.[77] The followup was 4 weeks. Participants treated with candesartan achieved greater reductions in SBP (-6.56 mmHG [95% CI, not reported]; p<0.001) and DBP (-4.76 mmHG [95% CI, not reported]; p=0.003) than those in the placebo group. More children and adolescents on active treatments achieved blood pressures below the 95th percentile than those on placebo (65% vs. 31%; p=NR).

Pharmacological Treatments Combined With Lifestyle Interventions

Study Characteristics

One open-label trial (2 publications) with 6 and 30 months followup determined the effectiveness of a combination of a pharmacological treatment with lifestyle interventions compared with no intervention.[89, 96] The trial (Franklinton Blood Pressure Intervention Study) was conducted from 1979 to 1981 in the United States. It enrolled children and adolescents age 8 to 18 years with blood pressure measurements above the 90th percentile (n=95) who were detected during school-based screening. The intervention consisted of low-dose propranolol/chlorthalidone therapy with an educational program directed toward dietary and exercise modifications for children and parents (i.e., educational materials, cooking classes for parents, individual dietary consultations, pledges, t-shirt rewards).[89] In addition, the program expanded community availability of low-sodium foods in grocery stores, restaurants, and school lunches and a school-based exercise component.

Results

At the 6-month followup, SBP and DBP had decreased significantly (SBP, -7.6 mmHg; p<0.0001; DBP, -6.9 mmHg; p<0.01) compared with the control group. After 30 months of

followup, SBP (-3.59 mmHg; p<0.01) and DBP (-1.73 mmHg; p<0.05) were significantly lower in the intervention group compared with the control group. We rated the quality for the 30-month followup as poor because loss to followup was high (40%), and authors conducted an intention-to-treat analysis with last observation carried forward (assuming lasting adherence), which could bias results toward a greater difference between groups.[96]

Lifestyle Interventions

Study Characteristics

Six RCTs assessed the effectiveness of lifestyle interventions in children and adolescents with elevated blood pressure or hypertension (**Appendix E Table 4**).[90-95] Lifestyle interventions included dietary interventions,[90, 93, 94] progressive muscle relaxation,[95] and physical exercise.[91, 92] Studies were conducted in Australia, Denmark, Korea, and the United States and lasted between 8 weeks and 3 years. Four studies were conducted in the 1980s and 1990s.[92-95] Sample sizes ranged from 40 to 210 participants who were recruited mostly through screening programs at public schools. Blood pressure thresholds to be eligible for enrollment varied between the 80th and 95th percentile adjusted for age, sex, and height.

Results

A DASH-type diet (high in fruits, vegetables, and low-fat dairy foods) for mostly overweight adolescents with elevated blood pressure or stage 1 hypertension (n=57) led to a decrease in SBP and DBP measurements compared with a regular hospital-based diet in a completers-only analysis (SBP, -2.2 mmHg; p<0.01; DBP, -2.8 mmHg; p<0.05).[90] Three months after the intervention, however, average SBP and DBP measurements were similar again between the groups (SBP, 120.1 vs. 120.0; DBP, 75.2 vs. 76.4). Intention-to-treat analyses did not substantially alter results.

Two RCTs that assessed the impact of physical exercise, one from Denmark[92] and one from Korea,[91] reported mostly statistically significant decreases in SBP and DBP. The Danish study enrolled children age 9 to 11 years with blood pressure measurements above the 95th percentile (n=69).[92] The intervention group received three extra lessons a week of the regular school physical education program. Compared with the control group, SBP (-4.9 mmHg p<0.05) and DBP (-3.8 mmHg; p<0.05) decreased significantly after 8 months of the intervention.

The Korean study randomized obese, adolescent girls (n=40) with elevated blood pressure to combined resistance and aerobic exercise for 12 weeks or no exercise.[91] SBP decreased significantly in the intervention group (-8.3 mmHg; p<0.05), but DBP did not change significantly (data not reported by study).

Low-sodium diet[93, 94] and progressive muscle relaxation[95] did not achieve any significant or clinically relevant changes in SBP or DBP.

Effectiveness of Interventions for Treating High Blood Pressure in Children and Adolescents on High Blood Pressure and Intermediate Outcomes in Adulthood (Key Question 6)

We identified no studies that reported on the effectiveness of treatments for primary childhood hypertension and subsequent reduction of blood pressure or other intermediate outcomes in adulthood.

Effectiveness of Interventions for Treating High Blood Pressure in Children and Adolsescents on Health Outcomes in Adulthood (Key Question 7)

We identified no studies that reported on the effectiveness of treatments for primary childhood hypertension and subsequent reduction of adverse health outcomes in adulthood.

Harms of Interventions for Treating High Blood Pressure in Children and Adolescents (Key Question 8)

Key Points

- Six fair-quality RCTs[76-81] reported similar risks of adverse events between various pharmacological treatments (beta blocker, calcium channel blockers, ACE, inhibitors or angiotensin receptor blockers [ARBs]) and placebo. The duration of trials, however, was limited to 2 to 4 weeks.
- One fair-quality RCT reported similar risks for adverse events between a combination of pharmacotherapy (low-dose propranolol/chlorthalidone) with lifestyle interventions (dietary and exercise modifications for children and parents) and a control group without treatment over 6 months.[89]

Summary of the Evidence

Seven RCTs[76-81, 89] provide results on harms of interventions used to treat children and adolescents with elevated blood pressure or hypertension (**Appendix E Table 8**). All studies were of fair methodological quality (**Appendix F Table 2**) and assessed pharmacological treatments, except one study that assessed pharmacological treatment in combination with lifestyle interventions.[89] Table 5 provides a summary of results on risk of harms for each intervention.

Pharmacological Treatments

The included RCTs assessed the risk of harms of ER metoprolol succinate,[76] candesartan,[77] felodipine ER,[78] fosinopril,[81] telmisartan,[79] and a combination of bisoprolol fumarate and hydrochlorothiazide[80] based on data for 909 participants. We describe characteristics of these studies in more detail in KQ 5, except for the study by Li et al,[81] which did not meet eligibility criteria for KQ 5. This dose-ranging RCT allocated 255 children age 6 to 16 years to different doses of lisinopril. Because the treatment phase did not include a placebo arm, the study was not eligible for KQ 5. After 4 weeks of treatment, 221 participants entered a placebo-controlled withdrawal phase that provided data on harms.

Telmisartan and a combination of bisoprolol with hydrochlorthiazide are currently not FDA approved for the treatment of children and adolescents. Some trials included doses that were outside FDA-approved dosing ranges; adverse events, however, were generally reported only for the combined active treatment arms.

Overall, risks of experiencing any adverse event and risks of specific adverse events were similar between active treatments and placebo over 2 to 4 weeks. The only study that reported statistically significant differences in risks of adverse events assessed a combination of bisoprolol with hydrochlorthiazide.[80] In this study, children in the placebo group had significantly higher risks for adverse events (75% vs. 53%; p=0.047) and serious adverse events (16% vs. 2%; p=0.016) than children on active treatment. This finding is most likely attributable to chance effects because of the small sample size (n=94).

Pharmacological Treatments Combined With Lifestyle Interventions

One trial with a 6-month followup of low-dose propranolol/chlorthalidone in combination with an educational program (see more details in KQ 5) compared with no intervention did not report specific data on adverse events.[89] Authors state that the incidence of adverse events was low in both groups. One participant withdrew from propranolol/chlorthalidone treatment because of nightmares.

Lifestyle Interventions

None of the included studies for KQ 5 reported data on adverse events.

Chapter 4. Discussion

This chapter begins with a summary of review findings for each KQ. Following those sections, we present limitations of the evidence and the review and end with conclusions.

Summary of Evidence

Table 2 details the summary of the evidence for this update review. Our review did not identify any studies that addressed the overarching question (KQ 1) of whether screening for hypertension in children and adolescents compared with no screening reduces the risk of adverse health outcomes related to hypertension during childhood or adulthood. In addition, we did not find any studies that addressed screening for secondary hypertension in asymptomatic children.

For diagnostic test accuracy of blood pressure screening (KQ 2), one fair study (n=247) reported a sensitivity of office-based measurements of 81.6 percent (CI not reported) with a specificity of 70.3 percent (CI not reported) compared with ABPM as a reference standard.

For adverse events of screening (KQ 3), we did not identify any eligible studies.

For the association between abnormal blood pressure in childhood and abnormal blood pressure or intermediate outcomes in adulthood (KQ 4), 20 studies, all observational, provided results from nine databases. The studies were characterized by substantial heterogeneity in the selection of thresholds for childhood and adult hypertension. Despite the heterogeneity, studies generally reported ORs (ranging from 1.1 to 4.5), RRs (ranging from 1.45 to 3.60), and HRs (ranging from 2.8 to 3.2), suggesting an association between childhood hypertension and abnormal blood pressure or intermediate cardiovascular outcomes in adulthood. However, the results were much less consistent and favorable using a different measure of the predictive accuracy such as sensitivity or PPV.[97] The results suggested sensitivity ranging from 0.0 to 0.89 (with most values below 0.6) and PPVs ranging from 0.05 to 0.97 (again with most values below 0.6). These results suggest low SOE of association between abnormal blood pressure in childhood and abnormal blood pressure in adulthood.

Results for the association between abnormal blood pressure in childhood and intermediate cardiovascular outcomes in adulthood, specifically CIMT, were consistent with an OR of 1.24 (95% CI, 1.13 to 1.37) and HRs ranging from 2.03 to 3.07.

For the effectiveness of treatment of hypertension in children and adolescents (KQ 5), 13 fair-quality placebo-controlled RCTs and one meta-analysis evaluated the efficacy of various pharmacological treatments. All studies reported greater reductions in SBP and DBP measurements in participants who received pharmacological treatments compared with those treated with placebo. The magnitude of reductions, however, varied, and not all differences reached statistical significance. Pooled reductions of SBP were -4.38 mmHg (95% CI, -2.16 to -7.27) for ACE inhibitors, -3.07 mmHg (95% CI, -1.44 to -4.99) for ARBs, -3.20 mmHg (95% CI, +2.23 to -8.69) for beta blockers, -3.10 mmHg (95% CI, +0.45 to -6.52) for calcium channel

blockers, and -0.12 mmHg (95% CI, +3.46 to -3.69) for mineralocorticoid receptor antagonists. The SOE for reduction was moderate; studies, however, were limited to 2 to 4 weeks of followup.[76-80] A combination of drug treatment and several lifestyle components provided low strength evidence of reduction of blood pressure after 6 months (SBP, -7.6 mmHg; DBP,-6.9 mmHg).[89] Likewise, two RCTs provided low strength evidence that physical exercise reduces SBP during 3 (-8.3 mmHg) and 8 (-4.9 mmHg) months.[91, 92] Only a study lasting 8 months reported a significant decrease in DBP (-3.8 mmHg vs. not reported).[92] Low strength evidence showed that a DASH diet did not provide a lasting reduction of blood pressure.[90] Two RCTs provided moderate strength evidence that a low-sodium diet did not achieve a reduction of blood pressure in children.[93, 94] Likewise, low strength evidence indicated that progressive muscle relaxation did not achieve any significant changes in SBP or DBP.[95]

No eligible studies addressed the effectiveness of treating childhood hypertension to reduce blood pressure or other intermediate outcomes (KQ 6) or adverse health outcomes (KQ 7) in adulthood.

For harms of treatment (KQ 8), six fair-quality RCTs[76-81, 89, 96] reported similar risks of adverse events between various pharmacological treatments (beta blocker, calcium channel blockers, ACE inhibitors, or ARBs) and placebo during 2 to 4 weeks of treatment. We assessed the SOE as low for these outcomes. No long-term studies on risk of harms were available.

A pooled analysis of FDA data did not meet our inclusion criteria because it was not based on a systematic search of the literature but provides an otherwise comprehensive assessment of the risks of harms of pharmacological treatments in children and adolescents.[98] This study was an individual patient data meta-analysis of 10 RCTs that were submitted to FDA between 1998 and 2005.[98] Overall, the pooled analysis included data on 1,707 children (6 to 17 years of age; 55% white; 62% male) treated with amlodipine, benazepril, enalapril, felodipine, fosinopril, irbesartan, lisinopril, losartan, quinapril, ramipril, or placebo. All trials excluded children with severe hypertension or renal disease. The placebo-controlled phases of these 10 trials ranged from 2 weeks to 4 weeks. Quinapril and ramipril are currently not FDA approved for use in children.

Authors pooled event rates for all active treatments as a class compared with placebo. Overall, proportions of children with adverse events were similar between active treatments and placebo (39.3% vs. 38.4%; p=0.72). In addition, risks for specific adverse events were similar between active treatments and placebo, including gastrointestinal events (6.9% vs. 6.40%), infections (5.2% vs. 6.0%), respiratory disorders (13.0% vs. 11.1%), or general disorders (11.7% vs. 11.8%).

A subgroup analysis of this study focused on cough in children treated with ACE inhibitors or ARBs.[99] Based on data of 1, 299 subjects and a followup of 2 to 4 weeks, the risk of cough was similar between children treated with ACE inhibitors (3.2%), ARBs (1.8%), or placebo (2.5%; p=0.86 for active drugs vs. placebo).

Limitations

The main limitation of the evidence base is the lack of research directly assessing the effectiveness of screening for hypertension to reduce adverse outcomes of hypertension in childhood and adulthood. In addition, the indirect evidence pathway from screening to improvement of health outcomes is scarce, of limited applicability, or entirely missing for some steps of the pathway. In the context of this limited evidence base on the direct and indirect pathway, the evidence on the association between abnormal blood pressure in childhood and outcomes in adulthood takes on greater weight.

We found only one study on the diagnostic test accuracy of blood pressure measurements to detect hypertension, which has some limitations regarding applicability.

Studies reporting on the association between abnormal blood pressure in childhood and abnormal blood pressure or other intermediate outcomes in adulthood were very heterogeneous (although the results were consistent in demonstrating an association with abnormal blood pressure in adulthood). Other limitations included the variations in underlying prevalence and the use of indirect measures of predictive accuracy.

Overall, treatment studies indicate efficacy and good tolerability of pharmacological interventions, but these studies were small, of very short duration (2 to 4 weeks), and mostly limited to participants with primary hypertension. Moreover, none of the drugs were evaluated in more than one study. The magnitude of the antihypertensive effects varied across agents and was not always significantly different from placebo. The mean age of children in these studies ranged from age 12 to 14 years; the generalizability of results to younger children or children with secondary hypertension is unknown.

Because of small sample sizes and short study durations, the available pharmacological treatment studies cannot adequately determine the risks of rare but serious adverse events that are known from adult trials such as angioedema, hyperkalemia, or adverse pregnancy outcomes with ACE inhibitors, interactions with drugs or foods that change cytochrome P 450 metabolism of calcium channel blockers, or bronchoconstriction with beta blockers. We identified no studies reporting on harms associated with lifestyle interventions.

The main limitation of our methodological approach is that we limited literature searches to English-language studies. This strategy might have missed studies in Hispanic children who have a higher risk for obesity and primary hypertension than non-Hispanic White children.

In addition to the dearth of evidence to answer the KQs, this topic poses several other challenges that relate to diagnostic imprecision and the long lead time of adverse health outcomes of hypertension. First, thresholds and classifications of hypertension in children are based on normative values and not on health outcomes like in adults. Although the recent update of the AAP clinical practice guideline revised normative blood pressure values to reflect data of healthy, normal-weight children,[2] it is still unclear whether such distribution-based thresholds can adequately distinguish between children with and without hypertension. This guideline also modified the classification of hypertension in adolescents to make the recommendations

consistent with those of the American College of Cardiology/AHA guidelines for adults.[3] Recommendations for adults, however, were influenced by the SPRINT (Systolic Blood Pressure Intervention Trial) study, which enrolled participants older than 50 years of age with an increased risk of CVD.[100] It is unclear how applicable findings of this trial are to adolescents at a much lower cardiovascular risk.

Second, the exact diagnostic workup in children who screen positive is not well established. In adults, ABPM and home monitoring of blood pressure are well-established methods of detecting white-coat hypertension and masked hypertension. These methods of measuring blood pressure have stronger associations with target organ damage and cardiovascular events than office-based measurements.[101, 102] In children, ABPM is recommended by the AAP to confirm office-based measurements. Normative values and thresholds for hypertension for ABPM, however, are not well established in children and adolescents. Currently, reference values by the German Working Group on Pediatric Hypertension,[103, 104] which were established on 1,141 children in the late 1990s, are still considered the best available standard. The applicability to a U.S. setting, however, might be limited because the cohort included only Central European white children.

The evidence on the accuracy and reliability of home blood pressure monitoring as an alternative to ABPM in children and adolescents is scarce.[105] Overall, the varying standards of diagnostic workup to confirm or dismiss hypertension in children who screen positive might lead to additional unnecessary diagnostic procedures such as renal ultrasound, urinalysis, blood lab tests, and others to eventually rule out secondary hypertensions.

Third, although target organ damage because of elevated blood pressure in children is quite common, a causal association with cardiovascular events later in life is difficult to establish.[106, 107] In adults, target organ damage such as such left ventricular hypertrophy, CIMT, or arterial stiffness has been associated with an increased risk of cardiovascular events.[108] In children, studies also reported higher risks of left ventricular hypertrophy,[109-111] CIMT,[112] arterial wall stiffness,[113] or urine albumin excretion.[112] In addition, treatment studies showed the potential of reducing left ventricular mass in hypertensive children.[114, 115] Nevertheless, the association between these intermediate outcomes and cardiovascular outcomes is not established in children and has to be inferred from indirect evidence in adult populations. Because studies assessing health outcomes in children or adults are challenging because of the long followup periods that are required to reliably assess cardiovascular outcomes, indices of preclinical organ damage are currently still the best available evidence.

The ongoing International Childhood Cardiovascular Cohort Consortium (i3C) Outcomes study might be able to provide more solid and more direct evidence regarding the association between childhood hypertensions and adult cardiovascular events.[116] This study uses data on risk factors for heart disease from long-term observational studies in school children in the United States (Bogalusa, Muscatine, Cincinnati, Minneapolis), Finland, and Australia. Researchers will contact individuals (n=41,006 in total) who participated in the childhood studies to ask them to complete a heart health survey. The study will then assess whether there is link between certain risk factors for heart disease (overweight and obesity, high blood pressure, high cholesterol, smoking) measured during childhood and adolescence and cardiovascular events (coronary artery disease,

myocardial infarction, angina pectoris, heart failure, stroke, transient ischemic attack, and aneurysm) in middle-aged adults.

Large retrospective studies (presented in CQ 3) reported an association between hypertension during adolescence and cerebrovascular mortality[116-119] and between hypertension during adolescence and end-stage renal disease.[117]

Future Research Needs

Given the ethical considerations about withholding a screening intervention that is commonly used in clinical practice, an adequately powered RCT or other controlled prospective study that compares long-term health outcomes of screened and unscreened children is unlikely. Future research, therefore, needs to establish a stronger evidence base for intermediate links between screening for hypertension and relevant outcomes during childhood and adulthood. Specifically, it should determine the diagnostic test accuracy of blood pressure measurements with aneroid sphygmomanometers or oscillometric automated devices and establish clear thresholds for hypertension for 24-hour ambulatory monitoring. There is also a pressing need for long-term treatment studies that assess benefits and harms of pharmacological treatments for hypertension in children and adolescents. Such studies should have long-term followup for different ages because benefits and harms of treatments may be age dependent and hypertension in children may be self-limiting. Epidemiological research needs to address the long-term natural history of hypertension in children, specifically focused on spontaneous resolution of hypertension. The use of a new threshold for determining abnormal blood pressure in childhood has created some uncertainty related to diagnosis and prognosis. Epidemiological studies could substantially add to the evidence base with relatively low effort by applying new thresholds to existing datasets and testing the validity of these thresholds.

Conclusions

We identified no direct evidence that compared screening with no screening in asymptomatic children and adolescents. Epidemiological studies indicate an association between hypertension in childhood and adolescence and hypertension in adulthood. Large longitudinal cohort studies also provide evidence that hypertension in adolescents and young adults is associated with end-stage renal disease (ESRD) and mortality from cerebrovascular events during adulthood. Despite the evidence indicating associations between childhood or adolescent hypertension and adult hypertension, intermediate cardiovascular outcomes, or health outcomes, the evidence on other parts of the evidence chain supporting screening in unselected populations is weak. The proportion of spontaneous resolution of hypertension in children and the long-term benefits and harms of treatment, however, remain unclear. The evidence is also inconclusive whether the diagnostic accuracy of blood pressure measurements is adequate for screening asymptomatic children and adolescents in primary care. Short-term pharmacological treatments appear effective and safe but no evidence with a followup of more than 4 weeks is available.

No evidence exists to determine whether screening for hypertension is effective in identifying children with secondary hypertension who are asymptomatic. Most treatment studies excluded children with secondary hypertension.

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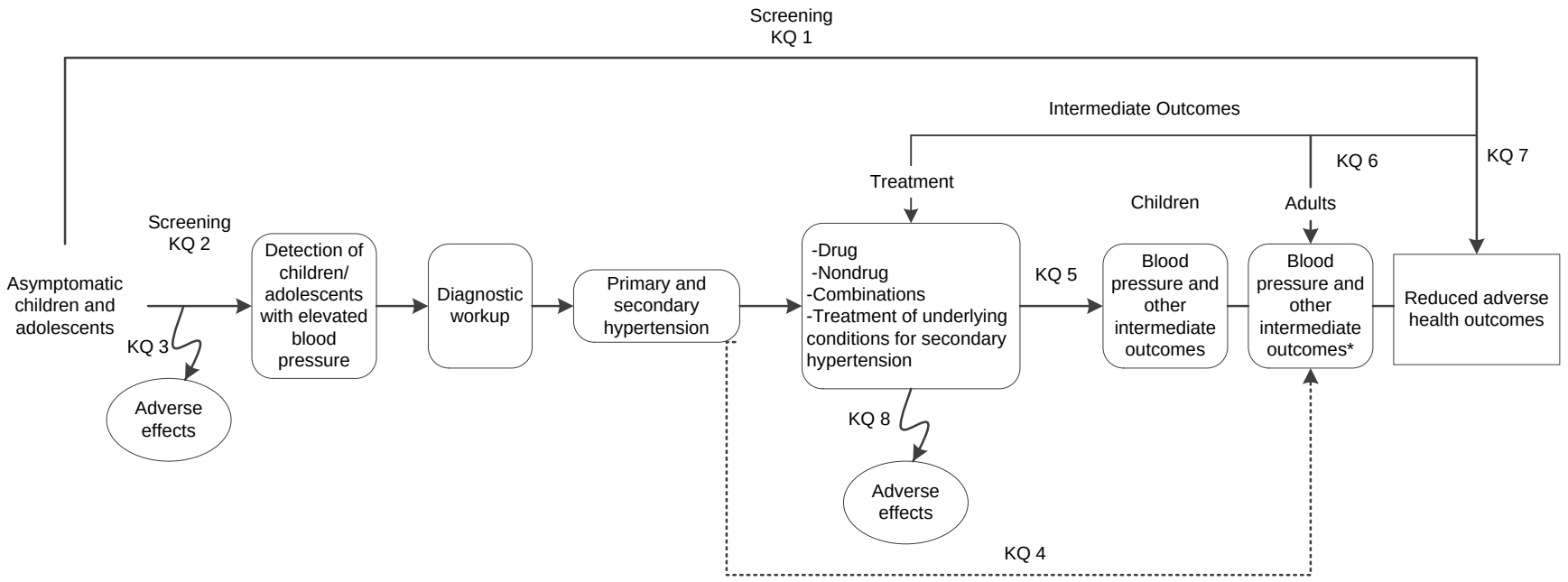
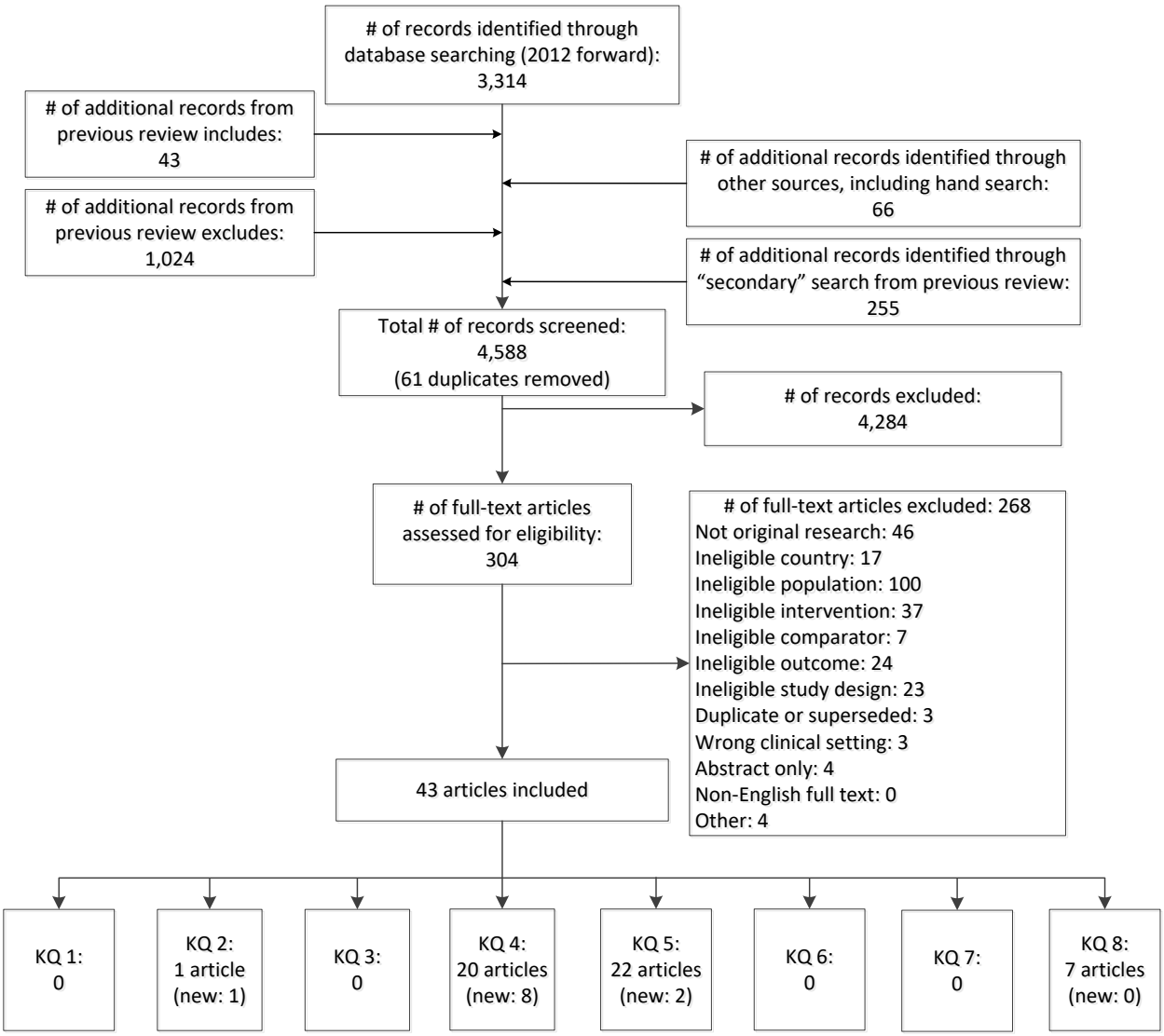
Figure 1. Analytic Framework



*Includes left ventricular hypertrophy, urinary albumin excretion (microalbuminuria), intima media thickness (measured at cartoid and/or femoral arteries), and retinal vascular changes.

Abbreviation: KQ=key question.

Figure 2. Literature Flow Diagram for Systematic Review of Screening for Hypertension in Children and Adolescents



Abbreviation: KQ=key question.

Table 1. Blood Pressure Thresholds* for Diagnosing Hypertension in Children Based on the American Academy of Pediatrics[2]

Age	Elevated BP	Stage 1 Hypertension	Stage 2 Hypertension
1-<13 years	90-94 percentiles or Systolic: 120-129 mmHg Diastolic: <80mmHg (whichever is lower)	95 percentiles to 95 percentiles +11 mmHg or Systolic: 130-139 mmHg Diastolic: 80-89 mmHg (whichever is lower)	≥95 percentiles +12 mmHg or Systolic: ≥140 mmHg Diastolic: ≥90 mmHg (whichever is lower)
≥13 years	Systolic: 120-129 mmHg Diastolic: <80mmHg	Systolic: 130-139 mmHg Diastolic: 80-89 mmHg	Systolic: ≥140 mmHg Diastolic: ≥90 mmHg

*All thresholds are defined as at least three independent auscultatory blood pressure readings.
Abbreviation: BP=blood pressure.

Table 2. Summary of Evidence for Screening for Hypertension in Children and Adolescents

Key Question	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1 Direct benefits of screening	k=0					
KQ 2 Diagnostic test accuracy	k=1 cross-sectional study[6] N=247	Sensitivity of office-based BP measurements: 81.6% Specificity: 70.3%	Consistency unknown (single study body of evidence)/ imprecise	Body of evidence limitations: Moderate Reporting bias: Not detected	LOW for diagnostic test accuracy measures	Limited applicability; only two office-based measurements: population included children with known abnormal blood pressure
KQ 3 Harms of screening	k=0					
KQ 4 Association between high BP in children and high BP or intermediate outcomes in adults	k=20 publications[10-12, 55-69] describing 9 databases, all observational, N>9,687	Low to moderate sensitivity and PPV for relationship between childhood and adult abnormal BP; results are consistent despite variable definitions	Consistent/ imprecise	Body of evidence limitations: High Reporting bias: NA	LOW for association between abnormal BP in childhood and abnormal BP in adulthood	Applicability varies because prevalence of HTN is widely variable
	k=7 publications[7, 58, 59, 61, 64, 66, 70], N>5,925	ORs for CIMT: 1.24; HRs range from 2.03 to 3.07 Weak correlations between abnormal BP in childhood and CIMT in adulthood (ranging from 0.04 to 0.16)	Consistent/ imprecise	Body of evidence limitations: High Reporting bias: NA	LOW for CIMT	Applicability varies because prevalence of HTN is widely variable
KQ 5 Effectiveness of interventions	k=13 RCTs[76-79, 81-88] N>2,300	*Pharmacological interventions* Reductions of SBP for ACE inhibitors: -4.38 mmHg ARBs: -3.07 mmHg Beta blockers: -3.20 mmHg Calcium channel blockers: -3.10 mmHg Mineralocorticoid receptor antagonists: -0.12 mmHg All comparisons with placebo after 2-4 weeks	Consistent/ Imprecise	Body of evidence limitations: Moderate Reporting bias: Not detected	MODERATE for benefit	Applies to children and adolescents age 6 to 18 years with BP above the 95th percentile; severe hypertension and secondary hypertension were excluded from most studies; study durations up to 4 weeks; no long-term studies

Table 2. Summary of Evidence for Screening for Hypertension in Children and Adolescents

Key Question	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 5 Effectiveness of interventions (continued)	k=1 RCT[89, 96] N=141	*Pharmacological + lifestyle intervention* Statistically significant reductions of SBP (-7.6 mmHg) and DBP (-6.9 mmHg) compared with control after 6 months	Consistency unknown (single study body of evidence)/ Precise	Body of evidence limitations: High Reporting bias: Not Detected	LOW for benefit	Applies to children and adolescents age 8 to 18 years with BP above the 90th percentile
	k=2 RCTs[93, 94] N=313	*Low sodium diet* No clinically relevant differences in DBP or SBP compared with control	Consistent/ Imprecise	Body of evidence limitations: Moderate Reporting bias: Not detected	MODERATE for no benefit	Applies to children and adolescents age 11 to 18 years with BP above the 85th percentile
	k=1 RCT[90] N=57	*DASH diet* Statistically significant reduction of SBP (-2.2 mmHg; p<0.01) and DBP (-2.8 mmHg; p<0.05) at the end of intervention (3 months) compared with control At 6-month followup, similar BP measurements between treatment and control group (SBP, 120.1 vs. 120.0; DBP, 75.2 vs. 76.4)	Consistency unknown (single study body of evidence)/ Imprecise	Body of evidence limitations: Moderate Reporting bias: Not detected	LOW for benefit	Applies to children and adolescents age 11 to 18 years with BP above the 90th percentile

Table 2. Summary of Evidence for Screening for Hypertension in Children and Adolescents

Key Question	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 5 Effectiveness of interventions (continued)	k=2 RCT[91, 92] N=109	*Physical exercise* Statistically significant reductions in SBP (-4.9 mmHg; p<0.05) and DBP (-3.8 mmHg; p<0.05) in children age 9 to 11 years after 8 months. Statistically significant reduction in SBP (-8.3 mmHg; p<0.05) but not DBP (data not reported) in obese adolescent girls after 3 months.	Consistent/ Imprecise	Body of evidence limitations: Moderate Reporting bias: Not detected	LOW for benefit	Applies to children age 9 to 11 years with BP above the 95th percentile and obese adolescent girls with elevated BP
	k=1 RCT[95] N=159	*Progressive muscle relaxation* No clinically relevant differences in SBP or DBP compared with control	Consistency unknown (single study body of evidence)/ Imprecise	Body of evidence limitations: Moderate Reporting bias: Not detected	LOW for no benefit	Applies to children and adolescents age 13 to 17 years with BP above the 85th percentile
KQ 6 Effectiveness of interventions on intermediate outcomes in adulthood	k=0					
KQ 7 Effectiveness of interventions on health outcomes in adulthood	k=0					

Table 2. Summary of Evidence for Screening for Hypertension in Children and Adolescents

Key Question	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 8 Harms of interventions	6 RCTs[76-79, 81] N=909	*Pharmacological interventions* Similar risks of overall adverse events between pharmacological treatments (beta blocker, calcium channel blockers, ACE inhibitors, or ARBs) and placebo over 2 to 4 weeks.	Consistent/ Very imprecise	Body of evidence limitations: Moderate	LOW for similar harms	Applies to children and adolescents age 6 to 18 years with BP above the 95th percentile; severe hypertension and secondary hypertension were excluded; study durations up to 4 weeks; no long-term studies
	1 RCT[89] N=150	*Pharmacological treatments combined with lifestyle Interventions* Similar risks of overall adverse events between pharmacological treatment (propranolol + chlorothalidone) plus lifestyle interventions and no intervention.	NA/Very imprecise	Body of evidence limitations: Moderate Indirectness: Propranolol not recommended anymore as first-line treatment	VERY LOW for similar harms	Applies to children and adolescents age 6 to 18 years with BP above the 90th percentile

Abbreviations: ACE=angiotension converting enzyme; ARB=angiotensin receptor blocker; BP=blood pressure; CIMT=carotid intima-media thickness; DASH=Dietary Approaches to Stop Hypertension; DBP=diastolic blood pressure; HR=hazard ratio; HTN=hypertension; k=number of studies; KQ=key question; N=number of participants; NA=not applicable; PPV=; RCT=randomized, controlled trial; SBP=systolic blood pressure; vs.=versus.

Table 3. Evidence Map of Studies Examining the Association Between Childhood and Adult Hypertension

Standard	Current Adult Hypertension Standards[a]	Prior Adult Hypertension Standards[b]	Nonstandard Adult Hypertension Definitions
Current childhood hypertension standards[2]	1 publication,[7] n=3,940 RRs range from 1.45 to 1.66 (all statistically significant)	1 publication,[7] n=3,940 RRs range from 1.62 to 1.98 (all statistically significant)	0 publications
Prior childhood hypertension standards[4]	2 publications;[7, 67, 69] n>5,480 RRs range from 1.49 to 1.65 (all statistically significant) Sensitivity range: 0.55 to 0.56 Specificity range: 0.63-0.64 PPV range: 0.53- 0.73	6 publications;[7, 12, 61, 65, 66, 68] n>4,127 RRs range from 1.53 to 1.95 (all statistically significant) HRs: 2.8 to 3.2 (all statistically significant) PPV range: 0.11 to 0.58 AUC range: 0.60 to 0.63 Sensitivity range: 0.05 to 0.37 Specificity range: 0.87 to 0.99	1 publication;[11] n=2,625 OR: 2.12 (95% CI, 1.82 to 2.61)
Nonstandard childhood hypertension definitions	0 publications	0 publications	7 publications;[10, 55-57, 60, 62, 63] n=4,790 ORs and RRs range: 1.1 to 9.0, generally excluding the null Sensitivity: 0 to 0.66 Specificity range: 0.77 to 1.00

[a] Abnormal BP defined as SBP>120mmHg and DPB>80 mmHg or self-reporting of antihypertensive medication use.[3]
[b] Hypertension defined as SBP≥140 mmHg or DBP ≥90 mmHg or self-reported antihypertensive medication use.[73]
Abbreviations: AUC=area under the receiver operating characteristic curve; CI=confidence interval; DBP=diastolic blood pressure; HR=hazard ratio; n=number; OR=odds ratio; PPV=positive predictive value; RR=relative risk; SBP=systolic blood pressure.

Table 4. Summary of Evidence About Effectiveness of Interventions for Treating High Blood Pressure in Children (KQ 5)

Intervention	No. of Studies and Design (k); No. of Participants (N)	Duration of Followup	Reductions in Blood Pressure
Pharmacological	k=13 RCTs[76-88] N>2300	2 to 4 weeks	Reductions of SBP were -4.38 mmHg (95% CI, -2.16 to -7.27) for ACE inhibitors, -3.07 mmHg (95% CI, -1.44 to -4.99) for ARBs, -3.2 mmHg (95% CI, +2.23 to -8.69) for beta blockers, -3.1 mmHg (95% CI, +0.45 to -6.52) for calcium channel blockers, and -0.12 mmHg (95% CI, +3.46 to -3.69) for mineralocorticoid receptor antagonists.
Pharmacological + Lifestyle	k=1 RCT.[89] N=95	6 months	Significant reduction of SBP (-7.6 mmHg) and DBP (-6.9 mmHg)
Low-sodium diet	k=2 RCTs[93, 94] N=313	8 weeks and 3 years	No clinically relevant or statistically significant reductions in SBP or DBP
DASH diet	k=1 RCT[90] N=57	3 months	Significant reduction of SBP (-2.2 mmHg) and DBP (-2.8 mmHg) at the end of intervention No lasting effect 3 months after intervention
Physical exercise	k=2 RCTs[91, 92] N=109	8 months 3 months	Significant reductions in SBP (-4.9 mmHg) and DBP (-3.8 mmHg) Significant reduction in SBP (-8.3 mmHg) but not DBP (data not reported) in obese adolescent girls
Progressive muscle relaxation	k=1 RCT[95] N=159	9 months	No clinically relevant or statistically significant reductions in SBP or DBP

Abbreviations: ACE=angiotension converting enzyme; ARB=angiotensin receptor blocker; CI=confidence interval; DASH=Dietary Approaches to Stop Hypertension; DBP=diastolic blood pressure; k=number of studies; KQ=key question; N=number of participants; RCT=randomized, controlled trial; SBP=systolic blood pressure.

Table 5. Summary of Evidence About Risk of Harms of Interventions for Treating High Blood Pressure in Children (KQ 8)

Intervention	No. of Studies and Design (k); No. of Participants (N)	Duration of Followup	Risk of Harms
Pharmacological	k=6 RCTs[76-81] N=909	2 to 4 weeks	Similar risks of overall adverse events between pharmacological treatments (beta blocker, calcium channel blockers, ACE, inhibitors, or ARBs) and placebo over 2 to 4 weeks
Pharmacological + Lifestyle	k=1 RCT[89] N=95	6 months	Similar risks compared with no intervention (no data reported)

Abbreviations: ACE=angiotension converting enzyme; ARB=angiotensin receptor blocker; k=number of included studies; KQ=key question; N=number of participants; RCT=randomized, controlled trial.

Contextual Question 1. What Is the Prevalence of Primary and Secondary Hypertension in Asymptomatic Children and Adolescents in Primary Care Settings?

Summary

Four large, retrospective observational studies addressed the prevalence of hypertension in children and adolescents in primary care in the United States in various settings. The observational studies recruited children from a large primary care network,[13] a Defense Health Insurance Program,[14] a single health care system[16] and a school.[15] Together, these studies provide data on more than 1.7 million participants. The prevalence of hypertension (both primary and secondary) estimates in these studies ranged from 0.54 percent[14] to 3.7 percent.[16] These estimates are consistent with those from a systematic review that assessed global hypertension trends in children and adolescents. In the following sections, we describe these studies in more detail.[13-17]

Detailed Findings

A 2016 retrospective cohort study by Kaelber et al[13] included data from electronic health records of 196 primary care clinics and 398,079 children across the United States. Clinic encounters occurred between 1999 and 2014. The study enrolled children and adolescents age 3 to 18 years of age who had three separate visits. The study recorded blood pressure, height, weight, visit diagnosis (ICD-9), prescriptions, race, sex, ethnicity, and insurance status. Stage I hypertension was defined by three or more blood pressure readings at or above the 95th percentile and below the 99th percentile for age, height, and sex. Stage II hypertension was defined by blood pressure readings greater than or equal to the 99th percentile for age, height, and sex. The prevalence of hypertension in this cohort was 3.3 percent. Hypertension was more common in females than males (52.6% vs. 47.4%). More children who were overweight/obese had hypertension than children classified as normal weight (54.5% vs. 45.5%, respectively).

The second observational study from 2015 published by Dobson et al[14] described the prevalence of pediatric hypertension among children in the United States enrolled in the Department of Defense's health insurance program (TRICARE). The study design was a retrospective cohort study using data from a military health database from 2006 through 2011. Hypertension was defined by two separate clinic encounters with a diagnosis code of "hypertension" of a single visit with a cardiologist or nephrologist who assigned the diagnosis code. Prevalence was calculated for the overall cohort and for pre-pubertal (age 2 to 11 years) and post-pubertal subjects (age 1 to 18 years). Overall, 1,363,626 subjects between age 2 and18 years were enrolled in TRICARE annually during the course of the study. Of those, 16,322 were diagnosed with hypertension; males represented 61 percent of those diagnosed. The prevalence of hypertension in 2011 was 1.6 percent. When stratified by age, the prevalence in children age 2 to 11 years was 0.54 percent. Among children age 12 to 18 years, the prevalence was 3.3 percent.

A retrospective cohort study by Hansen et al[16] of children and adolescent (age 3 to 18 years) from a single U.S.-based health system found a similar prevalence of hypertension of 3.6 percent.[16]

Appendix A. Contextual Questions

A prospective cohort study conducted by McNiece et al[15] from 2003 to 2005 described the prevalence of hypertension among adolescents recruited from secondary schools in Houston, Texas. Demographic information was collected as well as weight, height, and arm circumference. BMI was calculated and defined per Centers for Disease Control and Prevention standard percentile per age and sex. Each subject had blood pressure measured on three occasions with oscillometric blood pressure readings. The average of the three blood pressure measurements was used to determine blood pressure status according to the Fourth Report.[1] A total of 6,790 students participated in the study. The overall prevalence of hypertension was 3.2 percent. In adjusted analysis, "overweight" was associated with increased odds of hypertension 4.26 (OR, 95% CI, 3.12 to 5.83). No difference in associations was noted in hypertension with males 1.18 (OR, 95% CI, 0.89 to 1.57) compared with females or black and Hispanic subjects compared with white subjects, 1.07 (OR, 95% CI, 0.76 to 1.50) and 0.96 (OR, 95% CI, 0.76 to 1.36), respectively).

An international study by Flynn et al[18] reported the prevalence of primary and secondary hypertension among children with hypertension who participated in two pharmaceutical studies.[87, 120] One trial enrolled children <6 years of age with systolic blood pressure ≥95 percent.[120] Subjects were excluded if the SBP was greater than ≥25 percent of 95th SBP percentile for age, height, and sex. A second trial recruited children between 6-16 years of age with a SBP ≥95% percentile for age, sex, and weight and less than 5 percent above 99 percent percentile for height, weight, and sex.[87] The inclusion and exclusion criteria were similar between the two studies and included children with a history of aortic coarctation with a gradient of ≥30mmHg, bilateral renal artery stenosis, nonheart or renal transplantation, and use of investigational drug within 30 days or known sensitivity to angiotensin II receptor blockers. Descriptive and bivariate analyses were used to describe differences between subjects with primary hypertension and subjects with secondary hypertension. A total of 351 subjects were enrolled in the studies. Overall, approximately half of the sample had primary hypertension. Prevalence of primary hypertension increased with increasing age, 17 percent in children <6 year of age, 62 percent in children 6 to <12 years of age, and 60 percent among adolescents. The difference was statistically significant ($p<0.0001$).

A systematic review published in 2016 by Roulet et al[17] addressed global blood pressure trends in children and adolescents. Studies were included if they reported on mean blood pressure at two time points, involved children 0 to 19 years of age, were conducted in a defined region, and used a cross-sectional design and population or school-based sampling. The review included 18 studies published between 1963 and 2012. The majority of studies were conducted in "high income" countries, and three were from the United States (Appendix A Table 1). Thirteen studies were school based, and the remaining were population analyses. The total number of subjects was 2,042,470 with an age range of 4 to 19 years. Of the studies conducted in the United States, the reported overall prevalence of hypertension ranged between 1.6 percent and 3.7 percent. Two studies stratified prevalence of hypertension by sex and found the prevalence of hypertension among females to range between 1.9 percent and 5.8 percent and among males between 1.8 percent and 4.4 percent. Appendix A Table 1 summarizes prevalence estimates of the four U.S.-based observational studies and individual studies classified as "high-income,[17] as well as the other studies previously discussed.[13]

Contextual Question 2. What Are the Optimal Ages at Which to Start Screening for High Blood Pressure and the Optimal Time Intervals at Which to Repeat Screening in Children and Adolescents?

We did not find any studies that directly identified optimal ages to start blood pressure screening or optimal time intervals to repeat such screening.

Some small studies suggest that screening may be less reliable in younger ages.[127] Conversely, treatment of secondary causes of hypertension at younger ages may be associated with reduced risk of hypertension at followup (see CQ 4 for more on treatment outcomes of causes of secondary hypertension).

Screening in younger age groups is complicated by patient size and level of cooperation. Measurements are more accurate with an appropriately sized cuff and when the patient is calm and still. From a practical standpoint, these conditions that are more difficult to consistently obtain for smaller and younger children and may vary by screeners' skill level and experience. Unpublished data from Kulaga and Litwin found that 41 percent of blood pressure readings for infants age 1 to 12 months were unreliable,[127] 20 percent of those readings in children under age 3 years were unreliable, and 9 percent of those readings in children age 3 to 6 years were unreliable. Similarly, 24-hour ABPM is not reliable in children under age 5 years.[127]

Contextual Question 3. What Are the Associations Between Intermediate Outcomes Related to High Blood Pressure in Children and Adolescents and Health Outcomes Related to High Blood Pressure in Children, Adolescents, and Adults?

Summary

Hypertension can damage key organs and lead to increased morbidity and mortality. Specifically, we found evidence from large longitudinal cohort studies indicating that hypertension in adolescents and young adults is associated with ESRD and mortality from cerebrovascular events during adulthood.[116-119] The relevant studies are described in more detail below.

Detailed Findings

A 2019 retrospective study by Leiba et al[117] explored the association between hypertension in adolescence and risk of ESRD. Data for the study came from the Israel Defense Forces regional recruitment centers between January 1, 1967, and December 31, 2013. The cohort included males and females between the ages of 16 and 19 years. The Israel Defense Forces data was linked with the ESRD registry. The median followup was 19.6 years. Unadjusted and adjusted Cox proportional hazards models were conducted to estimate the risk of ERSD. A total of 2,658, 238 subjects were included in the analysis, of whom 7,997 had a diagnosis of hypertension. Ninety percent of those with hypertension were male, and approximately half were diagnosed with overweight or obesity. In adjusted analyses, hypertension was associated with an almost

twofold (HR, 1.98 [95% CI, 1.42 to 2.77]) risk of ESRD compared with nonhypertensive individuals.

A 2016 retrospective cohort study by Leiba et al[118] explored the risk of hypertension diagnosed in adolescence and cardiovascular mortality in adulthood. The cohort consisted of 2, 298, 130 subjects. The cohort included males and females between age 16 and 19 years who presented for mandatory Israeli military service. Examinations occurring between January 1, 1967, and December 2010 were included in the cohort. Individuals with a diagnosis code of "essential hypertension" were classified as having hypertension. The outcomes of interest were death secondary to cerebrovascular disease, coronary heart disease, death of unclear etiology, and total cerebrovascular death (i.e., the sum of deaths from cerebral vascular disease, coronary artery disease, and sudden death). The mean followup time was 19.9 years. Information on the outcomes of interest was obtained through the Israel Ministry of Health and linked to an individual's record. Cox proportional hazard models were used to estimate risk and were adjusted for BMI. Males and subjects with higher BMI were more likely to be hypertensive. Individuals with hypertension had a HR of 3.12 (95% CI, 1.76 to 5.54, $p<0.001$) of cerebrovascular death. Individuals with hypertension, however, did not have an increase in risk of death from coronary artery disease or sudden death. In the adjusted model, hypertension was not associated with mortality from CVD mortality.

A retrospective cohort study by Gray et al[119] from 2011 explored the risk of mortality from CVD among men with a diagnosis of hypertension. Males enrolling in Harvard University undergraduate programs between 1916 and 1950 and who completed a health survey in 1962 or 1966 were included in the study. Mean age of enrollment was 18.3 (1.7) years. Median followup time was 60 years. The cohort was approximately 80 percent complete. Information on blood pressure was obtained during routine medical examination. Blood pressure was classified according to the 7th Report on the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[72] The outcome of interest was overall mortality, mortality from CVD, coronary artery disease, and stroke. Information on outcome measures was obtained from the Harvard Alumni Office, which collects copies of death certificates of its alumni. A total of 18,881 men were included in the study. Men with prehypertension had an increased risk of death from cardiovascular mortality (HR, 1.13 [95% CI, 1.04 to 1.24]) and coronary heart disease (HR, 1.21 [95% CI, 1.07 to 1.36]) compared with men with normal blood pressure. No association was seen between overall mortality or mortality secondary to stroke in men with a diagnosis of prehypertension compared with men with normal blood pressure. Men with Stage 1 or 2 hypertension at the time of university entry had increased risk for all-cause mortality (Stage 1 hypertension HR, 1.14 [95% CI, 1.06 to 1.18]; Stage 2 hypertension HR, 1.28 [95% CI, 1.11 to 1.48]), mortality from CVD (Stage 1 hypertension HR, 1.28 [95% CI, 1.14 to 1.44]; Stage 2 hypertension HR, 1.51 [95% CI, 1.23 to 1.86]), and mortality from coronary heart disease (Stage 1 hypertension HR, 1.46 [95% CI, 1.25 to 1.70]); Stage 2 hypertension 1.89 (95% CI, 1.46 to 2.45) compared with men with normal blood pressure. No association was seen between hypertension at the time of university entry and risk for stroke.

To clarify the association between CVD in childhood and adult outcomes, the i3C was developed.[116] The consortium includes seven international and U.S.-based longitudinal

studies.[128] Two of the specific aims for the study are to evaluate the relationship between childhood cardiovascular risk factors and adult cardiovascular endpoints and determine the association of cardiovascular risk score trajectories on adult cardiovascular endpoints.[116] The Consortium is an ongoing study and is funded through November 2019.

Contextual Question 4. What Are the Effectiveness and Adverse Effects of Drug, Nondrug, and Combination Interventions for Treating the Underlying Conditions of Secondary Hypertension in Children and Adolescents?

Summary

Treatment of underlying etiologies is largely successful in reducing blood pressure in a large proportion of children and adolescents with secondary hypertension. Treatment success varies somewhat by etiology of secondary hypertension and sometimes by patient age at the time of treatment. For most causes of secondary hypertension, evidence is limited by relatively small case series and retrospective cohort studies.

Detailed Findings

Renal Disease

The most frequent causes of pediatric secondary hypertension are renal parenchymal and renovascular disease. A prospective longitudinal cohort study followed 20 children with proteinuria from chronic nephropathy that were treated with an ACE inhibitor with or without an ARB from 2002 to 2014 and found that nine (45%) had achieved remission at the 48-month followup. Eight children (40%) required decreases in doses due to hypotension (n=6) or hyperkalemia (n=2); no children had severe refractory hyperkalemia, anemia, or other serious adverse events related to treatment.[129]

A number of recent retrospective chart reviews have found that treatment of renovascular disease with percutaneous transluminal angioplasty (PTA), surgery, and/or medications generally improves or resolves hypertension.[130-133] One chart review found that of 46 children having been treated with PTA, surgery, and/or medication, most (86%) had normal or improved blood pressure at median 6.5 years followup.[130] Another case series of 28 patients undergoing a total of 42 PTAs found that 10 patients (36%) were deemed cured with sustained normal blood pressures and an additional eight (32%) had improved blood pressures. Three patients (11%) had major complications as a result of PTA (renal loss, false aneurysm requiring additional surgery, seizure and burst balloon with fragmentation of guidewire). Eighteen PTAs (43%) in an unclear number of patients resulted in minor complications.[131] Another looked at outcomes of 78 children who underwent PTA for renovascular hypertension. Thirty-six (46%) were asymptomatic at baseline and diagnosed with renovascular hypertension only after investigation of underlying cause of incidentally found hypertension. This study found that blood pressure improved in 49 patients (63%) after PTA, of whom 18 (23%) had complete resolution of their hypertension. Complications occurred in 13 (11%) of 114 procedures, including one patient death from

hemorrhage.[132] In another study of 24 patients with renovascular hypertension treated with medication, PTA, and/or surgery, nine were well controlled at followup, while five developed chronic kidney disease.[133]

Aortic Disease

Aortic coarctation is a less frequent but serious etiology of secondary hypertension that can lead to cardiac failure and death if left untreated. A 2012 Cochrane review aimed at assessing the effectiveness and safety of PTA compared with surgery in aortic coarctation examined the full text of only five potential studies, all of which were excluded for lack of an eligible comparator.[134] One retrospective review of 87 patients undergoing surgical correction for aortic coarctation found that most did not need long-term antihypertensive medications and that the proportion of patients needing them was higher if surgical correction occurred after 12 months of age (40%) compared with between 1 and 12 months of age (29%) or less than 1 month of age (7%).[135] A prospective, 19-site study of children with hypertension from aortic coarctation in the Coarctation of the Aorta Stent Trial also found that younger age at time of treatment correlated with better long-term outcomes. At the 24-month followup, 53 percent (n=21) of those who had been on antihypertensive medications at baseline no longer required them, while 10 percent (n=4) were using a decreased number of antihypertensives and 3 percent (n=1) were on a higher number of antihypertensive medications. Continued use of antihypertensive medications was associated with older age at the time of stent implantation. Of the total 105 patients with aortic coarctation that were included, 104 had successful stent placement, of which all had immediate reduction in blood pressure and sustained improvement at followup. There were no reported procedural deaths or adverse events and a total of 11 stent fractures over the 2-year followup.[136] Another study examined 31 patients who had undergone stent management for aortic coarctation a mean of 5.3 years after correction. Investigators asked participants to engage in exercise while being monitored with 24-hour ABPM and found that 45 percent of participants had hypertension. This study excluded younger children that investigators felt were unable to engage in the exercise component; given other studies' associations between better outcomes with younger age of repair, this may overestimate the proportion of children with hypertension at followup.[137]

Two studies examined treatments of midaortic syndrome or narrowing of the abdominal aorta. One systematic review of patients with midaortic syndrome looked at 184 articles about 630 individual cases.[138] Most were hypertensive at the time of presentation (87%), and most cases were idiopathic (64%). They were treated with medications, surgery, and/or PTA with or without stenting. Of the 68 percent of cases that reported followup data, 119 cases (19%) were normotensive without antihypertensive medications, 167 (26.5%) were normotensive on antihypertensive medications, 48 (8%) were uncontrolled, and 121 (19%) were normotensive without mention of whether on medications. Of those cases reporting mortality data, 2.3 percent of PTA cases and 2.9 percent of surgical cases led to death related to intervention with higher rates of complications in those with associated arteritis.[138] One retrospective chart review of 53 children with midaortic syndrome treated with PTA, surgery, and/or medications found that 69 percent were normotensive at most recent followup. Thirteen of the 22 patients who had left ventricular hypertrophy at presentation (59%) had resolution at followup. All five patients who had left ventricular dysfunction at presentation recovered function completely at followup. There

were 16 complications in 59 catheterization procedures, including one death, and five complications in 22 surgical procedures.[139]

Other Causes of Secondary Hypertension

A retrospective chart review of 10 pediatric patients with pheochromocytoma treated with alpha blockade and beta blockade medications before surgery found that all patients were able to discontinue all blood pressure medications.[140]

A meta-analysis of treatments for polycystic ovarian syndrome reviewed four randomized, controlled trials comparing metformin to oral contraceptive pill treatment.[141] The meta-analysis did not comment on blood pressure outcomes. It did find that treatment with metformin better reduced BMI and dysglycemia, oral contraceptive pills better improved menstrual cycle frequency and acne, and the two medication types improved hirsuitism similarly. Adverse events included gastrointestinal upset, headache, mastalgia, and mood changes.[141]

Appendix A Table 1. Study Characteristics and Prevalence of Hypertension

Author, Year of Publication	Setting	Study Period	Number of Participants	Age (years)	Prevalence of HTN (SD)
Din-Dzietham et al, 2007[a121]	United States	1963-2002	26,405	8-17	3.7% (0.4)
Dobson et al, 2015[14]	United States/military health system	2006-2011	Average of 1,363,626 enrolled each year	2-18	Overall: 1.6% (NR) Age 2-11: 0.54% (NR) Age 12-18: 3.3% (NR)
Freedman et al, 2012[a122]	United States	1974-1993	11,478	5-17	Boys: 4.1% (NR) Girls: 5.8% (NR)
Hansen et al, 2007[16]	United States/single health care system	1999-2006	14, 187	3-18	3.6% (NR)
Kaelber et al, 2016[13]	United States/ CER consortium	1999-2014	>1.2 million	3-18	3.3% (NR)
Khang et al, 2011[a123]	South Korea	1998-2008	5,905	10-19	Boys: 4.4% (NR) Girls: 1.9% (NR)
Lin, et al, 2012[a124]	Taiwan	1996-2006	2,557	12-14	Boys: 29.7 (NR) Girls: 20.7 (NR)
McCrindle et al, 2010[a125]	Canada	2002-2008	20,719	14-15	9% (NR)
McNiece et al, 2007[15]	United States/school based	2003-2005	6,790	11-17	3.2% (NR)
Xi et al, 2016[a126]	United States	1999-2012	14, 270	6-17	1.6% (0.3) Boys: 1.8% (0.5) Girls: 1.4% (0.2)

[a] Study was reported in systematic review by Roulet et al.

Abbreviations: HTN=hypertension; NR=not reported; SD=standard deviation.

Detailed PubMed Search Strategy

Combined KQs PubMed (September 3, 2019)

	Terms	Results
#1	Search ((((“Hypertension “[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match	459266
#5	Search ((((“Hypertension”[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match Filters: Publication date from 2012/06/01; Humans; English; Child: birth-18 years	8522 8
#6	Search ”Mass Screening”[Mesh] Sort by: Best Match	122515
#7	Search (#5 AND #6) Sort by: Best Match	121
#8	Search ”Blood Pressure Determination”[Mesh] Sort by: Best Match	36787
#9	Search (#5 OR #8) Sort by: Best Match	82693
#13	Search (#5 OR #8) Sort by: Best Match Filters: Publication date from 2012/06/01; Humans; English; Child: birth-18 years	8665
#14	Search ”Sensitivity and Specificity”[Mesh] OR sensitivity [tw] OR specificity [tw] Sort by: Best Match	1806029
#15	Search (#13 AND #14) Sort by: Best Match	826
#1	Search ((((“Hypertension”[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match	459266
#6	Search ((((“Hypertension”[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match Filters: Publication date from 2012/06/01; Humans; English; Child: birth-18 years	8526
#7	Search ”Longitudinal Studies”[Mesh] Sort by: Best Match	126104
#8	Search (#6 AND #7) Sort by: Best Match	336
#9	Search (((((“Atherosclerosis”[Mesh]) OR “Vascular Diseases”[Mesh]) OR “Albuminuria”[Mesh]) OR “Cerebrovascular Disorders”[Mesh]) OR “Hypertrophy, Left Ventricular”[Mesh]) OR “Hypertension”[Mesh] Sort by: Best Match	1625304
#10	Search (#8 AND #9) Sort by: Best Match	196
#11	Search (“pregnancy”) OR “infant” Sort by: Best Match	1899814
#12	Search (#10 NOT #11) Sort by: Best Match	146
#2	Search (“Hypertension/diet therapy”[Mesh] OR “Hypertension/drug effects”[Mesh] OR “Hypertension/drug therapy”[Mesh] OR “Hypertension/prevention and control”[Mesh] OR “Hypertension/radiotherapy”[Mesh] OR “Hypertension/rehabilitation”[Mesh] OR “Hypertension/surgery”[Mesh] OR “Hypertension/therapy”[Mesh]) Sort by: Best Match	95121
#3	Search ((((“Weight Loss”[Mesh]) OR “Exercise”[Mesh]) OR “Feeding Behavior”[Mesh]) OR “dietary modification” [tw] OR “Diet, Sodium-Restricted”[Mesh]) Sort by: Best Match	379923
#4	Search ((((((((“Angiotensin II Type 2 Receptor Blockers”[Mesh]) OR “Angiotensin-Converting Enzyme Inhibitors”[Mesh]) OR “Labetalol”[Mesh]) OR “Adrenergic beta-Antagonists”[Mesh]) OR “Atenolol”[Mesh]) OR “Bisoprolol”[Mesh]) OR “Metoprolol”[Mesh]) OR “Propranolol”[Mesh]) OR “Calcium Channel Blockers”[Mesh]) OR “Amlodipine”[Mesh]) OR “Felodipine”[Mesh] Sort by: Best Match	133073
#5	Search ((((((((“Isradipine”[Mesh]) OR “Nifedipine”[Mesh]) OR ““[Mesh]) OR “Diuretics”[Mesh]) OR “Hydrochlorothiazide”[Mesh]) OR “Chlorthalidone”[Mesh]) OR “Furosemide”[Mesh]) OR “Spironolactone”[Mesh]) OR “Triamterene”[Mesh]) OR “Amiloride”[Mesh] Sort by: Best Match	112507
#6	Search ”Vasodilator Agents”[Mesh]) OR ““[Mesh]) OR ““[Mesh]) OR ““[Mesh]) OR “Captopril”[Mesh]) OR “Enalapril”[Mesh]) OR “Fosinopril”[Mesh]) OR “Lisinopril”[Mesh]) OR “Losartan”[Mesh]) OR “benazepril” [Supplementary Concept]) OR “quinapril” [Supplementary Concept]) OR “irbesartan” [Supplementary Concept]) Sort by: Best Match	106836
#7	Search (#4 OR #5 OR #6) Sort by: Best Match	278715
#8	Search (((“administration and dosage” [Subheading]) OR “adverse effects” [Subheading]) OR “therapeutic use” [Subheading]) OR “toxicity” [Subheading] Sort by: Best Match	4583527
#9	Search (#7 AND #8) Sort by: Best Match	142368
#10	Search (#3 OR #9) Sort by: Best Match	519578
#11	Search ((((“Hypertension”[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match	459266
#12	Search (#10 AND #11) Sort by: Best Match	58883
#13	Search (#2 OR #12) Sort by: Best Match	119758

	Terms	Results
#17	Search (#2 OR #12) Sort by: Best Match Filters: Publication date from 2012/06/01; Humans; English; Child: birth-18 years	1925
#1	Search ((((“Hypertension “[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match	450839
#2	Search ((((“Hypertension “[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match Filters: Systematic Reviews	5902
#6	Search ((((“Hypertension “[Mesh]) OR “Prehypertension”[Mesh]) OR “Blood Pressure”[Mesh])) OR “persistently elevated blood pressure” Sort by: Best Match Filters: Systematic Reviews; Publication date from 2012/06/01; Humans; English; Child: birth-18 years	230
#1	Search ”secondary hypertension” Sort by: Best Match	1793
#2	Search (“Hypertension”[Mesh]) AND “secondary”[Title/Abstract] Sort by: Best Match	7800
#3	Search (((((((“Aortic Coarctation”[Mesh]) OR “Cushing Syndrome”[Mesh]) OR “Hyperthyroidism”[Mesh]) OR “Mineralocorticoid Excess Syndrome, Apparent”[Mesh]) OR “Sleep Apnea, Obstructive”[Mesh]) OR “Pheochromocytoma”[Mesh]) OR “Renal Artery Obstruction”[Mesh]) OR “Collagen Diseases”[Mesh] Sort by: Best Match	128680
#4	Search ”Hypertension”[Mesh] Sort by: Best Match	247097
#5	Search (#3 AND #4) Sort by: Best Match	10950
#6	Search (((((((“Hypertension, Renovascular”[Mesh]) OR “Williams Syndrome”[Mesh]) OR “Turner Syndrome”[Mesh]) OR “Endocrine System Diseases”[Mesh]) OR “Neurodegenerative Diseases”[Mesh]) OR “Aldosterone”[Mesh]) OR “Pheochromocytoma”[Mesh]) OR “Tuberous Sclerosis”[Mesh] Sort by: Best Match	1246427
#7	Search (#4 AND #6) Sort by: Best Match	45321
#8	Search (#1 OR #2) Sort by: Best Match	8302
#9	Search (#8 OR #5 OR #7) Sort by: Best Match	55650
#12	Search (#8 OR #5 OR #7) Sort by: Best Match Filters: Humans; English; Child: birth-18 years	5850
#13	Search ”Pregnancy”[Mesh] Sort by: Best Match	868479
#14	Search (#12 NOT #13) Sort by: Best Match	5226
#15	Search (#12 NOT #13) Sort by: Best Match Filters: Systematic Reviews	64

PubMed Unduplicated Total=2,984; unique in database=2,941

Other Data Sources

Cochrane Total=158
Cochrane Reviews=54
Cochrane Trials=104
Embase=325
ClinicalTrials.gov=19
Health Services Research Projects in Process (HSRProj)=8
World Health Organization International Clinical Trials Registry Platform=26
Total Unduplicated Database=3, 290

Appendix B. Additional Methods Information

Secondary Hypertension Gap Search PubMed (Inception through September 3, 2019)

	Terms	Results
#15	Search ((((“Aortic Coarctation”[Mesh]) OR “Hyperthyroidism”[Mesh]) OR “Pheochromocytoma”[Mesh]) OR “Renal Artery Obstruction”[Mesh]) OR “Polycystic Ovary Syndrome”[Mesh] Sort by: Best Match	90495
#16	Search ”Renal parenchymal disease”[tw] OR “Renovascular disease”[tw] Sort by: Best Match	1204
#17	Search (#15 OR #16) Sort by: Best Match	91198
#18	Search ”Pregnancy”[Mesh] Sort by: Best Match	868479
#19	Search (#17 NOT #18) Sort by: Best Match	85135
#23	Search (#17 NOT #18) Sort by: Best Match Filters: Publication date from 2010/01/01; Humans; English; Child: birth-18 years	3088
#24	Search (#17 NOT #18) Sort by: Best Match Filters: Systematic Reviews; Publication date from 2010/01/01; Humans; English; Child: birth-18 years	56
#15	Search ((((“Aortic Coarctation”[Mesh]) OR “Hyperthyroidism”[Mesh]) OR “Pheochromocytoma”[Mesh]) OR “Renal Artery Obstruction”[Mesh]) OR “Polycystic Ovary Syndrome”[Mesh] Sort by: Best Match	88886
#16	Search ”Renal parenchymal disease”[tw] OR “Renovascular disease”[tw] Sort by: Best Match	14
#17	Search (#15 OR #16) Sort by: Best Match	88895
#18	Search ”Pregnancy”[Mesh] Sort by: Best Match	844812
#19	Search (#17 NOT #18) Sort by: Best Match	83015
#23	Search (#17 NOT #18) Sort by: Best Match Filters: Publication date from 2010/01/01; Humans; English; Child: birth-18 years	2912
#24	Search (#17 NOT #18) Sort by: Best Match Filters: Systematic Reviews; Publication date from 2010/01/01; Humans; English; Child: birth-18 years	58

PubMed Secondary Hypertension=58; unique in database=55

Appendix B Table 1. Study Selection Criteria Based on Population, Interventions, Comparators, Outcomes, Timing, and Study Design

Criteria	Include	Exclude
Populations	**KQs 1-3:** Asymptomatic children and adolescents age 3 t o18 years with no known diagnosis of elevated blood pressure or hypertension KQs 4-8: Studies in which all participants have elevated blood pressure or hypertension	Pregnant adolescents; populations in which the majority of children or adolescents have high risk for developing high blood pressure and are being treated in a specialty clinic for the underlying condition (e.g., children and adolescents with obesity, neurofibromatosis, chronic kidney disease, cardiac abnormalities, specific genetic disorders)
Interventions	**KQs 1, 3:** Screening for high blood pressure with three separate measurements, using auscultatory or oscillometric devices (based on established normative thresholds) **KQ 2:** Index test consisting of at least one blood pressure measurement, using auscultatory or oscillometric devices (based on established normative thresholds) **KQs 5-8:** Antihypertension medications that are currently approved by the U.S. Food and Drug Administration for use in children, adolescents, or both Lifestyle modifications, including diet and exercise Combinations of drug and lifestyle interventions	**KQs 1, 3:** Screening that cannot be implemented in primary care settings Screening with fewer than three separate blood pressure measurements **KQ 2:** Diagnostic tests not used for screening in primary care settings **KQs 5-8:** Interventions that treat underlying causes of secondary hypertension (these interventions will be addressed in CQ 3) Interventions for which treatment of high blood pressure is not the primary objective of the study (i.e., diet and physical activity interventions for weight loss or prevention of weight gain); interventions for the primary prevention of high blood pressure
Comparator	**KQs 1, 3:** No screening **KQ 2:** Diagnosis of elevated blood pressure or hypertension after additional diagnostic workup (e.g., 24-hour or ambulatory blood pressure measurement) **KQs 5-8**: Placebo, delayed intervention, or other inactive interventions	**KQ 2:** Any reference test not specified in the inclusion criteria; studies with no reference test **KQs 5-8:** Active interventions or usual care

Appendix B Table 1. Study Selection Criteria Based on Population, Interventions, Comparators, Outcomes, Timing, and Study Design

Criteria	Include	Exclude
Outcomes	Left ventricular hypertrophy (defined using left ventricular mass index, measures of left ventricular geometry, or both) Urinary albumin excretion (microalbuminuria) IMT (measured at carotid, femoral, or both arteries) Retinal vascular changes **KQ 2:** Measures of test accuracy (e.g., positive and negative predictive value, likelihood ratios, sensitivity, specificity, receiver operating characteristic curves) **KQ 3:** Labeling, anxiety, and school absenteeism **KQ 4:** Predictive and prognostic validity (e.g., positive and negative predictive value, likelihood ratios, sensitivity, specificity); measures of association (e.g., odds ratio, risk ratio, correlation or regression coefficient) **KQ 8:** Harms of drug and nondrug interventions for high blood pressure	**KQ 2:** Correlation Studies that do not provide enough data to recreate 2x2 tables to calculate sensitivity and specificity **KQs 5, 6:** Measures of cognitive function Blood pressure variability, such as diurnal variation, or nocturnal blood pressure dipping Arterial wall dysfunction, including measures of arterial stiffness, pulse wave velocity, and augmentation index Metabolic measures, namely glucose tolerance or other measures of impaired glucose tolerance, insulin level, lipid profile, and homocysteine level Uric acid level Inflammatory markers, including C-reactive protein Changes in weight or BMI
Settings	**KQs 1, 3**: Primary care clinics, well-child/adolescent visits, or ambulatory settings; school- or community-based screening **KQ 4:** All settings **KQs 5-8:** Pediatric and family practices, pediatric specialty/subspecialty clinics, inpatient or long-term care settings, emergency or urgent care facilities, or ambulatory settings; school- or community-based treatment	**KQs 1-3:** Pediatric specialty/subspecialty clinics, emergency or urgent care facilities **KQs 5-8:** Settings that are not comparable to or referable from primary care
Study Designs	**KQ 1:** Randomized, controlled trials, controlled clinical trials, observational studies with a comparison group (e.g., comparative cohort and case-control studies), and systematic reviews **KQ 2:** Studies of diagnostic test accuracy **KQs 3, 8:** Randomized, controlled trials, controlled clinical trials, observational studies with a comparison group (e.g., cohort and case-control studies), and systematic reviews; if none identified, will accept uncontrolled before-after studies **KQ 4:** Longitudinal cohort studies **KQs 5-7:** Randomized, controlled trials, controlled clinical trials, observational studies with a comparison group (e.g., large [sample size >1,000] cohort and case-control studies), and systematic reviews	

Abbreviations: BMI=body mass index; CQ=contextual questions; CVD=cardiovascular disease; ESRD=end-stage renal disease; IMT=intima-media thickness; KQ=key question.

List of Exclusion Codes:

X1: Wrong language
X2: Not original research
X3: Wrong population
X4: Wrong study design
X5: Wrong geographic setting
X6: Wrong clinical setting
X7: Wrong or no intervention
X8: Wrong or no comparator
X9: Wrong or no outcome
X10: Abstract only
X11: Duplicate or superseded
X12: Other

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2. Adeniran SA, Toriola AL. Effects of different running programmes on body fat and blood pressure in schoolboys aged 13-17 years. Journal of sports medicine and physical fitness. 1988;28(3):267-73. Exclusion Code: X3.
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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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186. Podoll A, Grenier M, Croix B, et al. Inaccuracy in pediatric outpatient blood pressure measurement. Pediatrics. 2007;119(3):e538-43. Exclusion Code: X8.
187. Polonia J, Santos AR, Gama GM, et al. Accuracy of twenty-four-hour ambulatory blood pressure monitoring (night-day values) for the diagnosis of secondary hypertension. J Hypertens. 1738 Intial Search 02.10.11;13(12 Pt 2):1738-41. PMID: 8903643. Exclusion Code: X3.
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197. Roulet C, Bovet P, Brauchli T, et al. Secular trends in blood pressure in children: a systematic review. J Clin Hypertens (Greenwich). 2017 May;19(5):488-97. doi: 10.1111/jch.12955. PMID: 28097834. Exclusion Code: X4.
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201. Sadiq M, Ur Rehman A, Qureshi AU, et al. Covered stents in the management of native coarctation of the aorta--intermediate and long-term follow-up. Catheter Cardiovasc Interv. 2013 Oct 1;82(4):511-8. doi: 10.1002/ccd.24945. PMID: 23821694. Exclusion Code: X5.
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203. Sakalli H, Baskin E, Bayrakci US, et al. Acidosis and hyperkalemia caused by losartan and enalapril in pediatric kidney transplant recipients. Exp Clin Transplant. 2014 Aug;12(4):310-3. doi: 10.6002/ect.2013.0172. PMID: 27129124. Exclusion Code: X4.
204. Samuel JP, Samuels JA, Brooks LE, et al. Comparative effectiveness of antihypertensive treatment for older children with primary hypertension: study protocol for a series of n-of-1 randomized trials. Trials. 2016 Jan 8;17:16. doi: 10.1186/s13063-015-1142-y. PMID: 26259808. Exclusion Code: X2.
205. Santi M, Simonetti BG, Leoni-Foglia CF, et al. Arterial hypertension in children. Curr Opin Cardiol. 2015 Jul;30(4):403-10. doi: 10.1097/hco.0000000000000191. PMID: 24603455. Exclusion Code: X2.
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207. Schaefer F, van de Walle J, Zurowska A, et al. Efficacy, safety and pharmacokinetics of candesartan cilexetil in hypertensive children from 1 to less than 6 years of age. J Hypertens. 2010;28(5):1083-90. Exclusion Code: X4.
208. Seeman T, Dostálek L, Gilík J. Control of hypertension in treated children and its association with target organ damage. Am J Hypertens. 2012;25(3):389-95. Exclusion Code: X4.
209. Seeman T, Gilik J. Long-term control of ambulatory hypertension in children: improving with time but still not achieving new blood pressure goals. Am J Hypertens. 2013 Jul;26(7):939-45. doi: 10.1093/ajh/hpt048. PMID: 23610239. Exclusion Code: X3.
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212. Shen W, Zhang T, Li S, et al. Race and sex differences of long-term blood pressure profiles from childhood and adult hypertension: The Bogalusa Heart Study. Hypertension (Dallas, Tex. : 1979). 2017;70(1):66-74. Exclusion Code: X3.
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214. Singh S, Kaur J, Thumburu KK, et al. Predictors of childhood obesity and adulthood blood pressure levels. Cardiology (Switzerland). 2016;134:63. doi: 10.1159/000447505. Exclusion Code: X10.
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217. Slark J, Khan MS, Bentley P, et al. Knowledge of blood pressure in a U.K. general public population. J Hum Hypertens. 2014 Aug;28(8):500-3. doi: 10.1038/jhh.2013.136. PMID: 24430705. Exclusion Code: X2.
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221. Stabouli S, Kotsis V, Rizos Z, et al. Left ventricular mass in normotensive, prehypertensive and hypertensive children and adolescents. Pediatr Nephrol. 2009 Aug;24(8):1545-51. doi: 10.1007/s00467-009-1165-2. PMID: 19444486. Exclusion Code: X9.
222. Stabouli S, Kotsis V, Toumanidis S, et al. White-coat and masked hypertension in children: association with target-organ damage. Pediatr Nephrol. 2005 Aug;20(8):1151-5. doi: 10.1007/s00467-005-1979-5. PMID: 15947982. Exclusion Code: X9.
223. Stabouli S, Sideras L, Vareta G, et al. Hypertension screening during healthcare pediatric visits. J Hypertens. 2015 May;33(5):1064-8. doi: 10.1097/hjh.0000000000000505. PMID: 25955627. Exclusion Code: X4.
224. Steinberger J, Moran A, Hong CP, et al. Adiposity in childhood predicts obesity and insulin resistance in young adulthood. J Pediatr. 2001;138(4):469-73. Exclusion Code: X3.
225. Stenn PG, Noce A, Buck C. A study of the labelling phenomenon in school children with elevated blood pressure. Clin Invest Med. 1981;4(3-4):179-81. PMID: 7337989. Exclusion Code: X3.
226. Stergiou G, Stambolliu E, Bountzona I, et al. Home Blood Pressure Monitoring in Children and Adolescents: Systematic Review of Evidence on Clinical Utility. Curr Hypertens Rep. 2019;21(8)doi: 10.1007/s11906-019-0967-2. Exclusion Code: X7.
227. Stergiou GS, Boubouchairopoulou N, Kollias A. Accuracy of automated blood pressure measurement in children: evidence, issues, and perspectives. Hypertension. 2017 Jun;69(6):1000-6. doi: 10.1161/hypertensionaha.116.08553. PMID: 27050239. Exclusion Code: X2.
228. Stergiou GS, Nasothimiou E, Giovas P, et al. Diagnosis of hypertension in children and adolescents based on home versus ambulatory blood pressure monitoring. J Hypertens. 2008 2008/08;26(8):1556-62. doi: 10.1097/hjh.0b013e328301c411. Exclusion Code: X12.
229. Stern B, Heyden S, Miller D, et al. Intervention study in high school students with elevated blood pressures. Dietary experiment with polyunsaturated fatty acids. Nutr Metab. 1980;24(3):137-47. Exclusion Code: X7.
230. Stone ML, Kelly J, Mistry M, et al. Use of nicardipine after cardiac operations is safe in children regardless of age. Ann Thorac Surg. 2018 Jan;105(1):181-5. doi: 10.1016/j.athoracsur.2017.05.035. PMID: 29621144. Exclusion Code: X3.
231. Subasinghe AK, Wark JD, Gorelik A, et al. The association between inflammation, obesity and elevated blood pressure in 16-25-year-old females. J Hum Hypertens. 2017 Sep;31(9):580-4. doi: 10.1038/jhh.2017.33. PMID: 28662937. Exclusion Code: X3.
232. Suh I, Nam CM, Jee SH, et al. Twelve-year tracking of blood pressure in Korean school children: the Kangwha Study. Yonsei Med J. 1999;40(4):383-7. Exclusion Code: X9.
233. Sullivan JE, Keefe D, Zhou Y, et al. Pharmacokinetics, safety profile, and efficacy of aliskiren in pediatric patients with hypertension. Clin Pediatr (Phila). 2013 Jul;52(7):599-607. doi: 10.1177/0009922813483875. PMID: 24246011. Exclusion Code: X7.

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234. Sun D, Wang T, Heianza Y, et al. A history of asthma from childhood and left ventricular mass in asymptomatic young adults: The Bogalusa Heart Study. JACC Heart Fail. 2017 Jul;5(7):497-504. doi: 10.1016/j.jchf.2017.03.009. PMID: 28902162. Exclusion Code: X3.
235. Sun J, Steffen LM, Ma C, et al. Definition of pediatric hypertension: are blood pressure measurements on three separate occasions necessary? Hypertens Res. 2017 May;40(5):496-503. doi: 10.1038/hr.2016.179. PMID: 28284520. Exclusion Code: X4.
236. Tabatabaie M, Hooman N, Arjmandi-Rafsanjani K, et al. Ambulatory blood pressure monitoring for children with beta-thalassemia major: a preliminary report. Iran J Kidney Dis. 2013 Jul;7(4):299-303. PMID: 23428013. Exclusion Code: X3.
237. Tabbutt S, Nicolson SC, Adamson PC, et al. The safety, efficacy, and pharmacokinetics of esmolol for blood pressure control immediately after repair of coarctation of the aorta in infants and children: a multicenter, double-blind, randomized trial. J Thorac Cardiovasc Surg. 2008;136(2):321-8. Exclusion Code: X8.
238. Thompson M, Dana T, Bougatsos C, et al. Screening for hypertension in children and adolescents to prevent cardiovascular disease. Pediatrics. 2013 Mar;131(3):490-525. doi: 10.1542/peds.2012-3523. PMID: 27531686. Exclusion Code: X12.
239. Tkaczyk M, Stanczyk M, Miklaszewska M, et al. What has changed in the prevalence of hypertension in dialyzed children during the last decade? Ren Fail. 2017 Nov;39(1):283-9. doi: 10.1080/0886022x.2016.1260033. PMID: 28240622. Exclusion Code: X3.
240. Toprak A, Wang H, Chen W, et al. Relation of childhood risk factors to left ventricular hypertrophy (eccentric or concentric) in relatively young adulthood (from the Bogalusa Heart Study). Am J Cardiol. 2008;101(11):1621-5. Exclusion Code: X3.
241. Trachtman H, Frymoyer A, Lewandowski A, et al. Pharmacokinetics, pharmacodynamics, and safety of lisinopril in pediatric kidney transplant patients: implications for starting dose selection. Clin Pharmacol Ther. 2015 Jul;98(1):25-33. doi: 10.1002/cpt.127. PMID: 25631221. Exclusion Code: X3.
242. Trevisan M, Cooper R, Ostrow D, et al. Dietary sodium, erythrocyte sodium concentration, sodium-stimulated lithium efflux and blood pressure. Clinical science (London, England : 1979). 1981;61 Suppl 7:29s-32s. Exclusion Code: X3.
243. Trudeau F, Shephard RJ, Arsenault F, et al. Tracking of physical fitness from childhood to adulthood. Canadian journal of applied physiology = Revue canadienne de physiologie appliquee. 2003;28(2):257-71. Exclusion Code: X3.
244. Tucker DT, Smothers M, Lewis C, et al. Effects of decreased dietary salt intake on blood pressure in preschool children. J Natl Med Assoc. 1989;81(3):299-302. Exclusion Code: X3.
245. Tullus K. Safety concerns of angiotensin II receptor blockers in preschool children. Arch Dis Child. 2011;96(9):881-2. Exclusion Code: X2.
246. Urbina EM, de Ferranti S, Steinberger J. Observational studies may be more important than randomized clinical trials: weaknesses in US Preventive Services Task Force recommendation on blood pressure screening in youth. Hypertension. 2014 Apr;63(4):638-40. doi: 10.1161/hypertensionaha.113.02662. PMID: 28827377. Exclusion Code: X2.
247. Urbina EM, Khoury PR, McCoy CE, et al. Comparison of mercury sphygmomanometry blood pressure readings with oscillometric and central blood pressure in predicting target organ damage in youth. Blood Press Monit. 2015;20(3):150-6. Exclusion Code: X3.
248. Valvo E, Bedogna V, Casagrande P. Ambulatory blood pressure measurement in assessing the antihypertensive effect of benazepril plus hydrochlorothiazide in a fixed combination. Clin Ther. 1993;15(4):650-6. Exclusion Code: X3.
249. Van Horn L, Vincent E. The CHILD 1 and DASH diets: rationale and translational applications. Pediatr Ann. 2013 Sep;42(9):372-4. doi: 10.3928/00904481-20130823-11. PMID: 24205227. Exclusion Code: X2.
250. Vandongen R, Jenner DA, Thompson C, et al. A controlled evaluation of a fitness and nutrition intervention program on cardiovascular health in 10- to 12-year-old children. Prev Med. 1995;24(1):9-22. Exclusion Code: X3.

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251. Vieira da Silva MA, Mendes da Silva AP, Artigas Giorgi DM, et al. Successive blood pressure measurements to evaluate suspected and treated hypertension. Blood Press Monit. 2016 Apr;21(2):69-74. doi: 10.1097/mbp.0000000000000161. PMID: 26859736. Exclusion Code: X3.
252. Voiculescu A, Heusch A, Duppers P, et al. Duplex ultrasound findings before and after surgery in children and adolescents with renovascular hypertension. Ultrasound Med Biol. 2014 Dec;40(12):2786-93. doi: 10.1016/j.ultrasmedbio.2014.07.011. PMID: 24125483. Exclusion Code: X3.
253. Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2010 May;95(5):2023-37. doi: 10.1210/jc.2009-2830. PMID: 20230240. Exclusion Code: X2.
254. Walczak-Galezewska M, Szulinska M, Miller-Kasprzak E, et al. The effect of nebivolol and ramipril on selected biochemical parameters, arterial stiffness, and circadian profile of blood pressure in young men with primary hypertension: A 12-week prospective randomized, open-label study trial. Medicine (Baltimore). 2018 Jul;97(30):e11717. doi: 10.1097/md.0000000000011717. PMID: 27384018. Exclusion Code: X3.
255. Wang J, Qiu B, Du JL, et al. The effects of a low-salt diet on the efficacy of different antihypertensive drug regimens. J Clin Pharmacol. 2015 Dec;55(12):1362-8. doi: 10.1002/jcph.559. PMID: 25991503. Exclusion Code: X3.
256. Webb NJ, Lam C, Shahinfar S, et al. Efficacy and safety of losartan in children with Alport syndrome--results from a subgroup analysis of a prospective, randomized, placebo- or amlodipine-controlled trial. Nephrol Dial Transplant. 2011 Aug;26(8):2521-6. PMID: CN-00812687 NEW. Exclusion Code: X3.
257. Webb NJ, Wells T, Tsai M, et al. Single-dose pharmacokinetics and safety of azilsartan medoxomil in children and adolescents with hypertension as compared to healthy adults. Eur J Clin Pharmacol. 2016 Apr;72(4):447-57. doi: 10.1007/s00228-015-1987-8. PMID: 26997629. Exclusion Code: X7.
258. Webb NJ, Wells TG, Shahinfar S, et al. A randomized, open-label, dose-response study of losartan in hypertensive children. Clin J Am Soc Nephrol. 2014 Aug 7;9(8):1441-8. doi: 10.2215/cjn.11111113. PMID: 25336550. Exclusion Code: X3.
259. Wells TG, Blowey DL, Sullivan JE, et al. Pharmacokinetics of olmesartan medoxomil in pediatric patients with hypertension. Paediatr Drugs. 2012 Dec 1;14(6):401-9. doi: 10.2165/11631450-000000000-00000. PMID: 22949530. Exclusion Code: X7.
260. Williams KM, Shah AN, Morrison D, et al. Hypertensive retinopathy in severely hypertensive children: demographic, clinical, and ophthalmoscopic findings from a 30-year British cohort. J Pediatr Ophthalmol Strabismus. 2013;50(4):222-8. Exclusion Code: X9.
261. Wingen AM, Fabian-Bach C, Schaefer F, et al. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. Lancet (London, England). 1997;349(9059):1117-23. Exclusion Code: X3.
262. Wu B, Xu T, Li Y, et al. Interventions for reducing inflammation in familial Mediterranean fever. Cochrane Database Syst Rev. 2018(10)doi: 10.1002/14651858.CD010893.pub3. PMID: CD010893. Exclusion Code: X3.
263. Yin X, Liu Q, Bovet P, et al. Performance of blood pressure-to-height ratio as a screening tool for elevated blood pressure in pediatric population: a systematic meta-analysis. J Hum Hypertens. 2016 Nov;30(11):697-702. doi: 10.1038/jhh.2016.12. PMID: 27432869. Exclusion Code: X7.
264. Yip GW-K, So H-K, Li AM, et al. Validation of A&D TM-2430 upper-arm blood pressure monitor for ambulatory blood pressure monitoring in children and adolescents, according to the British Hypertension Society protocol. Blood Press Monit. 2012;17(2):76-9. doi: 10.1097/MBP.0b013e328351d4a4. Exclusion Code: X5.
265. Yong LC, Kuller LH. Tracking of blood pressure from adolescence to middle age: the Dormont High School Study. Prev Med. 1994;23(4):418-26. Exclusion Code: X3.

266. Yong LC, Kuller LH, Rutan G, et al. Longitudinal study of blood pressure: changes and determinants from adolescence to middle age. The Dormont High School follow-up study, 1957-1963 to 1989-1990. Am J Epidemiol. 1993;138(11):973-83. Exclusion Code: X3.

267. Yoon EY, Kopec K, McCool B, et al. Differences in blood pressure monitoring for children and adolescents with hypertension among pediatric cardiologists and pediatric nephrologists. Clin Pediatr (Phila). 2014 Sep;53(10):1008-12. doi: 10.1177/0009922813512176. PMID: 25280976. Exclusion Code: X6.

268. Zocalo Y, Curcio S, Garcia-Espinosa V, et al. Comparative analysis of arterial parameters variations associated with inter-individual variations in peripheral and aortic blood pressure: cross-sectional study in healthy subjects aged 2-84 years. High Blood Press Cardiovasc Prev. 2017 Dec;24(4):437-51. doi: 10.1007/s40292-017-0231-2. PMID: 27619066. Exclusion Code: X3.

Randomized, Controlled Trials and Cohort Studies Criteria

- Initial assembly of comparable groups
- RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Participant selection
- Index tests
- Reference standard
- Flow and timing
- Concerns about applicability

Definition of ratings based on above criteria:

Good:	Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair:	Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients
Poor:	Has a fatal flaw, such as using inappropriate reference standard, improperly administering screening test, using biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

Sources: U.S. Preventive Services Task Force, Procedure Manual, Appendix VI
https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes
Harris et al, 2001[47]

Appendix D Table 1. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool

	Risk of Bias				Concerns About Applicability			Quality Rating
Author, Year	Participant Selection	Index Tests	Reference Standard	Flow and Timing	Participant Selection	Index Tests	Reference Standard	
Hamdani et al, 2018[6]	Unclear	Low	Unclear	Low	High	Low	Low	Fair

Abbreviation: QUADAS=Quality Assessment of Diagnostic Accuracy Studies.

Appendix D Table 2. Individual Study Quality Assessment of Interventional Studies

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-Treat Analysis	Quality Rating
Batisky et al, 2007[76]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Differential: unclear High overall: no	Yes	Fair
Berenson et al, 1983,[89]	Unclear	Unclear	No	Yes	Unclear	No	No	Yes	Differential: no High overall: yes	Yes	Fair
Couch et al, 2008[90]	Unclear	Unclear	Yes	Yes	Yes	Not applicable	Not applicable	Yes	Differential: no High overall: no	Yes	Fair
Ewart et al, 1987[95]	Unclear	Unclear	Yes	Yes	Yes	Not applicable	Not applicable	Yes	Differential: no High overall: yes	No	Fair
Flynn et al., 2004[88]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	No	Fair
Hansen et al, 1991[92]	Unclear	Unclear	Yes	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: no	Unclear	Fair
Hazan et al, 2010[85]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Differential: no High overall: no	Yes	Fair
Howe et al, 1991[93]	Unclear	Unclear	Yes	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: no	No	Fair
Li et al, 2004[81]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: yes	Unclear	Fair
Li et al, 2010[86]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	Differential: no High overall: no	Yes	Fair
Shahinfar et al, 2005[84]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Fair
Sinaiko et al, 1993[94]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	Differential: unclear High overall: unclear	No	Fair
Soffer et al., 2003[83]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Fair
Son et al, 2017[91]	Yes	Yes	Yes	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: no	Yes	Fair
Sorof et al, 2002[80]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: yes	No	Fair

Appendix D. U.S. Preventive Services Task Force Quality Rating Criteria

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-Treat Analysis	Quality Rating
Trachtman et al, 2003[78]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	Unclear	Fair
Trachtman et al, 2008[77]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Fair
Wells et al, 2002[82]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Fair
Wells et al, 2010[79]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: yes	Yes	Fair
Wells et al, 2011[87]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Differential: no High overall: no	Yes	Fair

Appendix D Table 3. Quality Assessment of Meta-Analyses

Author, Year	Concerns regarding specification of study eligibility criteria	Concerns regarding methods used to identify and/or select studies	Concerns regarding methods used to collect data and appraise studies	Concerns regarding the synthesis	Did the interpretation of findings address all of the concerns identified in Domains 1 through 4?	Was the relevance of identified studies to the review's research question appropriately considered?	Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Risk of bias in the review
Burrello et al, 2019[75]	Some concerns	Low	Low	Some concerns	Some concerns	Probably yes	Probably yes	Fair

Appendix E Table 1. Diagnostic Accuracy of Screening for Elevated Blood Pressure in Children and Adolescents (KQ2)

Study, Year	Screening Test	Reference Standard	Definition of a Positive Screening Exam	Population	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Quality Rating
Hamdani et al, 2018[6]	Clinic BP, 6 BPs obtained by auscultation over 2 visits 1 to 2 weeks apart	ABPM measurement every 20 minutes for 26 hours	Elevated BP: BP reading ≥90th percentile and <95th percentile for age, sex, and height; or 120 to 129/<80 mmHg for adolescents ≥13 years old Hypertension: BP >95th percentile for age, sex, and height; or ≥130/80 mmHg for adolescents ≥13 years old	247 adolescents aged 11 to 19 years Median age (IQR): 15.7 (14.3 to16.9), % male: 54% Race: 63% White, 26% Black, 5% Asian, 6 % Other, 16% Hispanic Median BMI (IQR): 25.7 (22.0 to 32.0)	2017 CPG 90th percentile: 81.6% Elevated SBP: 86.8% 120 mmHg: 86.8%	2017 CPG 90th percentile: 70.3% Elevated SBP: 47.9% 120 mmHg: 49.3%	NR	NR	Fair

Abbreviations: BMI=body mass index; BP=blood pressure; CI=confidence interval; CPG= clinical practice guidelines; IQR=interquartile range; KQ=key question; NR=not reported; SBP=systolic blood pressure.

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Unnamed Cohort						
Gillman et al, 1993[55]	Prospective cohort, United States, Harvard General Internal Medicine and Faculty Development Scholarship Program and Andrew Mellon Clinical Epidemiology Fellowship at Harvard Medical School, and NHLBI, Charles H. Hood Foundation, RGK Foundation, and Sawyer Foundation grants	NR/NR/339	School children age 8 to 15 years at a single school in East Boston, Massachusetts	12 years	Mean of six measurements on right arm (three with Hawksley random-zero sphygmomanometers and three with standard mercury sphygmomanometers without removing cuff) in seated position with 5-minute rest taken at four visits each 1 week apart	BP above the 90th percentile within study (SBP males: 113 mmHg, SBP females: 114 mmHg, DBP males: 71 mmHg, DBP females: 71 mmHg)
Fels Longitudinal Study						
Beckett et al, 1992[56]	Longitudinal cohort, United States, NIH grants	976/523/501	Fels Longitudinal Study participants with at least 10 serial BP readings	20 years	Mean of last two of three measurements (standard mercury sphygmomanometer) in seated position at a single visit	Not defined (DBP 80 mmHg described as 90th percentile within study)
Sun et al, 2007[10]	Longitudinal cohort, United States, NIH grants	NR/NR/493	Fels Longitudinal Study participants with serial BP readings from age 2 years to adulthood	NR (compares childhood BP at age 5 to 18 years to adult BP at mean age of 38.4 years)	Mean of last two of three measurements (standard mercury sphygmomanometer) in seated position measured every 6 months	Least-squares means determined according to age and gender (absolute values NR)
Bogalusa Heart Study						
Shear et al, 1987[60]	Longitudinal cohort, United States, NHLBI and National Research and Demonstration Center-Arteriosclerosis grant	4, 238/1,501/ 1,501	Bogalusa Heart Study participants with data from 1976-77, 1978-79, and 1988-91; age 2 to 14 years at baseline	8 years	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	NR

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Bao et al, 1995[57]	Longitudinal cohort, United States, NHLBI grants	NR/1,505/ 1,505	Bogalusa Heart Study participants with data in 1973-74 and 1988-91; age 5 to 14 years at baseline and age 20 to 31 years at followup	15 years	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	BP above the 80th percentile within study (absolute values NR)
Hoq et al, 2002[58]	Longitudinal cohort, United States, National Institute on Aging and NHBLI grants	NR/NR/ 2,122	Bogalusa Heart Study participants with data from 1973-74, 1976-77, 1988-91, and 1995-96. Exclusion criteria: protein or blood in urine; albumin-creatinine ratio >30 mg/mmol; pregnancy; use of oral drugs or insulin for diabetes or glucose level ≥126 mg/dL; current us of antihypertensives	16.1 years	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	BP above the 90th percentile for age, ethnicity, and sex
Li et al, 2003[59]	Prospective cohort, United States, NHLBI, National Institute on Aging, National Institute of Child Health and Human Development, and AHA grants	NR/NR/486	Bogalusa Heart Study participants with adults CIMT measurements who were examined 3 or more times since childhood	Median 22.2 years	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	NR

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Xi et al, 2017[61]	Longitudinal cohort, United States, National Institutes on Aging, Environmental Health Sciences, and Health, National Natural Science Foundation of China, and AHA grants	NR/1,225/ 1,225	Bogalusa Heart Study participants with data from 1976-77, 1978-79, and 1988-91	NR (compares childhood BP at age 6 to 17 years to adult BP at mean age of 27.1 years)	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	Simplified definition Prehypertension, age 6 to 11 years: SBP≥110 and/or DBP≥70 mmHg and SBP<120 and DBP<80 mmHg Prehypertension, age 12 to 17 years: SBP≥120 and/or DBP≥80 mmHg SBP<130 and DBP<85 mmHg Hypertension, age 6 to 11 years SBP≥120 and/or DBP≥80 mmHg Hypertension, age 12 to 17 years: SBP≥130 and/or DBP≥85 mmHg Complex definition, based on the Fourth Report Prehypertension, all ages: Above 90th percentiles (or ≥120/80 mmHg) and below 95th percentiles Hypertension, all ages: Above the 95th percentiles by sex, age, and height

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Du et al., 2019[7]	Longitudinal cohort, United States, National Institutes of Health, Natural Science Foundation of China	3,940/ 3,437/1,760 enrolled for this analysis	Bogalusa Heart Study participants with measures of waist circumference, SBP, DBP, total cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, fasting plasma glucose, and echocardiography conducted between 2000 and 2016 to measure left ventricular hypertrophy	Mean: 25 years	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	AAP 2017, Elevated BP SBP/SBP percentile, age 1 to 13 years: ≥90th-<95th, or if BP exceeds 120/80 mmHg, even if <90th, up to <95th ≥95th to <95th + 12 mmHg or 130/80-139/89 mmHg (whichever is lower) Absolute threshold, age ≥13 years: 120/<80 to 129/<80 mmHg Hypertension SBP/SBP percentile, age 1 to 13 years: ≥95th + 12 mmHg or ≥140/90 mmHg (whichever is lower) Absolute threshold, age ≥13 years: ≥140/90

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Cardiovascular Risk in Young Finns Study						
Raitakari et al, 2003[64]	Prospective cohort, Finland, Academy of Finland, the Social Insurance Institution of Finland, Tampere and Turku University Hospitals, the Turku University Foundation, the Juho Vainio Foundation, the Finnish Foundation of Cardiovascular Research, the Lydia Maria Julin Foundation, Research Foundation of Orion Corporation and the Finnish Cultural Foundation, Helsinki	4,320/ 3,596/2, 229 enrolled in this analysis	Cardiovascular Risk in Young Finns participants, Finnish children age 3, 6, 9, 12, 15, and 18 years randomly chosen from a national register that participated in the followup visits in 2001	21 years	Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position	BP above the 80th percentile

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Juhola et al, 2011[12] and Juonala et al, 2004[65]	Prospective cohort, Finland, Academy of Finland, the Social Insurance Institution of Finland, the Turku University Foundation, Kuopio, Tampere, and Turku University Hospital Medical Funds, Emil Aaltonen Foundation, the Juho Vainio Foundation, Yrjo Jahnsson Foundation, the Finnish Foundation of Cardiovascular Research, and the Finnish Cultural Foundation	4,320/ 3,596/2, 204 enrolled in this analysis	Cardiovascular Risk in Young Finns participants, Finnish children age 3, 6, 9, 12, 15, and 18 years randomly chosen from a national register that participated in the followup visits in 2007	27 years	Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position	BP above the 95th percentile
Juhola, 2012[11]	Longitudinal cohort, Finland Supported by 10 different organizations (e.g., academies, institutes, foundations)	4,320/3,596/ 2,625 enrolled in this analysis	Cardiovascular Risk in Young Finns participants, Finnish children age 3, 6, 9, 12, 15, and 18 years randomly chosen from a national register that participated in the followup visits in 2001 or 2007	21 to 27 years	Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position (only systolic BP measured by ultrasound was used for participants age 3)	SBP or DBP above the 90th percentile for age, ethnicity and sex as defined according to the National High Blood Pressure Education Program
Oikonen, 2016[66]	Longitudinal cohort, Finland, Supported by 16 different organizations (e.g., academies, institutes, foundations)	4,320/3,596/ 1,927 enrolled in this analysis	Cardiovascular Risk in Young Finns participants, Finnish children age 3, 6, 9, 12, 15, and 18 years randomly chosen from a national register that participated in the followup visits in 2001, 2007, and/or 2011	21 to 31 years	Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position (only systolic BP measured by ultrasound was used for participants age 3)	SBP above the 90th percentile or DBP above the 95th percentile for age, ethnicity and sex as defined according to the National High Blood Pressure Education Program

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
Aatola, 2017[67]	Longitudinal cohort, Finland, Academy of Finland, Social Insurance Institution of Finland, Universities, Foundations	4,320/3,596/ 1,540 for this analysis	Risk in Young Finns participants, Finnish children age 3, 6, 9, 12, 15, and 18 years randomly chosen from a national register that participated in the followup visits in 2007	27 years	Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position	SBP or DBP above the 90th percentile for age, ethnicity and sex as defined according to the National High Blood Pressure Education Program
Dunedin Multidisciplinary Health and Development Study						
Theodore, 2015[68]	Prospective cohort, New Zealand, Health Research Council of New Zealand, U.S. National Institutes of Health, British Medical Research Council	1,037/NR/ 975 for this analysis	Dunedin participants, children in the greater Dunedin area born at the Queen Mary Maternity Hospital in 1972-73 with at least 3 age BP measurements	Up to 31 years (compares BP at age 7, 11, 18, 26, 32, and 38 years)	Mean of two or three measurements (standard mercury sphygmomanometer) on right arm in seated position	SBP or DBP above the 90th percentile for age, ethnicity and sex as defined according to the National High Blood Pressure Education Program
Muscatine Study						
Lauer et al, 1989[62]	Longitudinal cohort, United States, NIH, NHLBI, Specialized Center of Research in Atherosclerosis, and Specialized Center of Research in Hypertension grants	NR/NR/2,445	Adult Muscatine Study participants, school children of Muscatine, Iowa	Unclear; range 13 to 23 years based on study initiation at age 7 and followup at age 20 to 30; few participants had measure at age 7	Second of two measurements (Baumanometer mercury sphygmomanometer) on right arm in seated position	Unclear; results reported for BP above the 90th percentile
Lauer et al, 1993[63]	Longitudinal cohort, United States, NIH, NHLBI, Specialized Center of Research in Atherosclerosis, and Specialized Center of Research in Hypertension grants	NR/NR/ 2,445	Adult Muscatine Study participants, school children of Muscatine, Iowa	Unclear; range 13 to 23 years based on study initiation at age 7 and followup at age 20 to 30; few participants had measure at age 7	Second of two measurements (Baumanometer mercury sphygmomanometer) on right arm in seated position	Unclear; results reported for BP above the 90th percentile

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
The International Childhood Cardiovascular Cohort Consortium						
Juhola, 2013 The International Childhood Cardiovascular Cohort Consortium[69]	Regression analysis of 4 prospective cohort studies: United States (Bogalusa Heart Study, Muscatine Study), Finland (Cardiovascular Risk in Young Finns Study), and Australia (Childhood Determinants of Adult Health [CDAH] study)	NR/NR/4, 210 Bogalusa Heart Study: 586 Cardiovascular Risk in Young Finns Study: 2223 CDAH study: 680 Muscatine Study: 721	Bogalusa Heart Study participants with data from 1981-1983, 1984-85, or 1987-88 and 2001-02 or 2003-07 Cardiovascular Risk in Young Finns participants, Finnish children age 3, 6, 9, 12, 15, and 18 years randomly chosen from a national register that participated in the followup visits in 2001 or 2007 CDAH: Participants with data from 1985 and 2004-06 Muscatine Study: Adult Muscatine Study participants, school children of Muscatine, with data from 1970-81 and 1996-99	Overall: 23 years Bogalusa Heart Study: 21.4 years Cardiovascular Risk in Young Finns Study: 26.0 years CDAH: 19.9 years Muscatine Study: 24.0 years	Bogalusa Heart Study: Mean of six measurements (mercury sphygmomanometer) on right arm in seated position Cardiovascular Risk in Young Finns Study and Muscatine Study: Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position CDAH: Mean of two measurements (standard mercury sphygmomanometer) on left arm in seated position Muscatine Study: Second of two measurements (mercury sphygmomanometer) on right arm in seated position	SBP or DBP above the 90th percentile for age, ethnicity, and sex as defined according to the National High Blood Pressure Education Program

Appendix E Table 2. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 1

Author, Year	Study Design, Country, Funding	Number Screened/ Eligible/ Enrolled	Eligibility and Exclusion Criteria	Length(s) of Followup	BP Measurement Method in Children	Definition of Hypertension in Children
The i3C Consortium Study						
Koskinen et al, 2019[70] Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, and the Childhood Determinants of Adult Health study, the Insulin Study, and the Kaunas Study	Pooled longitudinal cohort, United States (Bogalusa Heart Study, Muscatine Study), Finland (Cardiovascular Risk in Young Finns Study), and Australia (Childhood Determinants of Adult Health [CDAH] study, Insulin Study), Eastern Europe (Kaunas Study)	NR/NR/5,925 Young Finns Study: 2,554 Bogalusa: 1,300 CDAH: 695 Muscatine: 721 Insulin: 294 Kaunas: 361	Participants in pooled cohorts with BP data from childhood (ages 3–18) and ultrasound data from adulthood (ages 19–51)	Mean: 25.8 years	Bogalusa Heart Study: Mean of six measurements (mercury sphygmomanometer) on right arm in seated position Cardiovascular Risk in Young Finns Study and Muscatine Study: Mean of three measurements (standard mercury sphygmomanometer) on right arm in seated position CDAH: Mean of two measurements (standard mercury sphygmomanometer) on left arm in seated position Muscatine Study: Second of two measurements (mercury sphygmomanometer) on right arm in seated position Insulin Study: Mean of 2 measurements on right arm Kaunas Study: Mean of 3 measurements on right arm	Either SBP or DBP ≥90th percentile for age, sex, and height

Abbreviations: AAP= American Academy of Pediatrics; AHA=American Heart Association; BP=blood pressure; CDAH=Childhood Determinants of Adult Health; DBP=diastolic blood pressure; KQ=key question; NIH=National Institutes of Health; NHLBI=National Heart, Lung, and Blood Institute; NR=not reported; SBP=systolic blood pressure.

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
Unnamed Cohort						
Gillman et al, 1993[55]	Similar to child measurements, though most measurements taken in homes, two or three visits instead of four, and more variability in number of days between visits	Above the 90th percentile within study (SBP males: 139 mmHg, SBP females: 124 mmHg, DBP males: 84 mmHg, DBP females: 78 mmHg)	Mean age: NR (range 8 to 18 years) Sex: 56% (177/316) female Race: NR	Mean SBP (mmHg) Males: 107 Females: 102 Mean DBP (mmHg) Males: 64 Females: 62.5	NR	6% (20/337) attrition
Fels Longitudinal Study						
Beckett et al, 1992[56]	Unclear; likely the same method as in childhood	DBP>90 mmHg	Mean age: NR (32% age 0 to 4; 63% age 5 to 9; 4% 10 to 14; 1% 15 to 17 years) Sex: 50% (259/523) female Race: 99% (518/523) white, 1% (5/523) other	NR	NR	No loss (cohort selected based on availability of data)
Sun et al, 2007[10]	Mean of last two of three measurements (standard mercury sphygmomanometer) in seated position measured every 2 years	SBP>130 mmHg and/or DBP>85 mmHg	Mean age: NR Sex: 51% (253/493) female Race: NR	Reported in figures of least-squares means and standard deviations	NR	8% loss to followup in Fels Longitudinal Study overall
Bogalusa Heart Study						
Shear et al, 1987[60]	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	≥140/90 mmHg	Mean age: NR (37% age 2 to 5 years, 37% age 6 to 9 years, 26% age 10 to 14 years) Sex: 51% (764/1,501) female Race: 59% (879/1,501) white, 41% (622/1,501) black	Mean BP (mmHg): 99/62	NR	No loss (cohort selected based on availability of data)

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
Bao et al, 1995[57]	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	SBP >140 mmHg or DBP >90 mmHg or ever treated for hypertension	Mean age: NR (43% age 5 to 9 years; 57% age 10 to 14 years) Sex: 56% female (346/1,505) Race: 65% white (978/1,505), 35% black (527/1,505)	Mean SBP (mmHg) Black males: 95 Black females: 94 White males: 97 White females: 95 Mean DBP (mmHg) Black males: 60 Black females: 59 White males: 58 White females: 59	99% of hypertensive patients at followup had previously received treatment for hypertension	No loss (cohort selected based on availability of data)
Hoq et al, 2002[58]	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	Above the 90th percentile for age, ethnicity, and sex	Mean age: 10 (SD, NR) Sex: 57% (1, 207/2, 122) female Race: 68% (1,444/2, 122) white, 32% (678/2, 122) black	Mean SBP (mmHg) Black males: 101 (SD, 11) Black females: 99 (SD, 10) White males: 101 (SD, 10) White females: 99 (SD, 10) Mean DBP (mmHg) Black males: 63 (SD, 9) Black females: 62 (SD, 9) White males: 62 (SD, 8) White females: 62 (SD, 8) Mean BMI (kg/m^2) Black males: 17.5 (SD, 3.4) Black females: 17.8 (SD, 3.8) White males: 17.9 (SD, 3.4) White females: 17.6 (SD, 3.4)	Unclear; currently treated patients excluded, but study reports inclusion of data from hypertensive subjects (defined as those currently taking antihypertensives) did not alter results	No loss (cohort selected based on availability of data)
Li et al, 2003[59]	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	NR	Mean age: NR (range 4 to 17 years) Sex: 61% (295/486) female Race: 71% (344/486) white, 29% (142/486) black	Mean SBP (mmHg) Black males: 105 (SD, 13) Black females: 101 (SD, 11) White males: 101 (SD, 10) White females: 101 (SD, 10) Mean BMI (kg/m^2) Black males: 17.8 (SD, 3.9) Black females: 18.5 (SD, 3.8) White males: 18.1 (SD, 3.5) White females: 18.3 (SD, 3.7)	NR	NR

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
Xi et al, 2017[61]	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	≥140/90 mmHg or taking antihypertensive medicine	Mean age: 10.9 (SD, 3.3) Sex: 60.1% (352/586) female Race: 35.7% (209/586) black (white NR)	Mean SBP (mmHg) Children: 97 (SD, 10) Adolescents: 112 (SD, 12) Mean DBP-K4 (mmHg) Children: 60 (SD, 8) Adolescents: 70 (SD, 9) Mean DBP-K5 (mmHg) Children 45 (SD, 11) Adolescents: 54 (SD, 13)	NR	No loss (cohort selected based on availability of data)
Du et al., 2019[7]	Mean of six measurements (mercury sphygmomanometer) on right arm in seated position	AHA guidelines SBP ≥130 mmHg, DBP ≥80 mmHg or taking antihypertensive medicine Joint National Committee 7th Report SBP ≥140 mmHg DBP ≥ 90 mmHg	Mean age (SD) Normotensive: 10 (3) Elevated BP: 10 (3) Hypertension: 9 (3) Sex (% male) Normotensive: 42% Elevated BP: 60% Hypertension: 47% Race (% white) Normotensive: 67% Elevated BP: 59% Hypertension: 49%	Mean SBP (mmHg) Normotensive: 98 (SD, 9) Elevated BP: 105 (SD, 10) Hypertension: 114 (SD, 13) Mean DBP (mmHg) Normotensive: 51 (SD, 9) Elevated BP: 54 (SD, 10) Hypertension: 56 (SD, 11) Mean BMI (kg/m^2) Normotensive: 17 (SD, 3) Elevated BP: 18 (SD, 4) Hypertension: 19 (SD, 5)	NR	No loss (cohort selected based on availability of data)
Cardiovascular Risk in Young Finns Study						
Raitakari et al, 2003[64]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	BP above the 80th percentile	Mean age: NR (range 3 to 8 years) Sex: 51% (1,832/3,596) female Race: NR	Mean SBP (mmHg) Female: 112 (SD, 11.2) Male: 114 (SD, 12.9) Mean DBP (mmHg) Female: 68 (SD, 9.5) Male: 69 (SD, 9.6) Mean BMI (kg/m^2) Female: 17.9 (SD, 3.0) Male: 18.0 (SD, 3.1)	3.1% (n=NR) taking anti-hypertensive medication	38.0% (1,367/3596) lost to followup by 21 years

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
Juhola et al, 2011[12] and Juonala et al, 2004[65]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	SBP ≥140 mmHg or DBP ≥90 mmHg or taking antihypertensive medication	Mean age: NR (range 3 to 18 years) Sex: 51% (1,832/3,596) female Race: NR	Mean SBP (mmHg) Female: 112 (SD, 11.2) Male: 114 (SD, 12.9) Mean DBP (mmHg) Female: 68 (SD, 9.5) Male: 69 (SD, 9.6) Mean BMI (kg/m^2) Female: 17.9 (SD, 3.0) Male: 18.0 (SD, 3.1)	6.66% (152/2283) taking anti-hypertensive medications	38.7% (1,392/3,596) lost to followup by 27 years
Juhola, 2012[11]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	SBP≥130 mmHg or DBP≥85 mmHg or self-reported use of antihypertensive medication	Mean age: 10.6 (SD, 5.0) Sex: 54% (1,430/2,625) female Race: NR	Mean SBP (mmHg) Female: 111 (SD, 11.2) Male: 114 (SD, 12.9) Mean DBP (mmHg) Female: 68.5 (SD, 9.4) Male: 68.9 (SD, 9.9) Mean BMI (kg/m^2) Female: 17.8 (SD, 3.0) Male: 17.9 (SD, 3.1)	NR	NR
Oikonen, 2016[66]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	≥140/90 mmHg, use of reimbursed antihypertensive medication, or the self-reported use of antihypertensive medication	Mean age: 12.8 (SD, 4.9) Sex: 54.4% (N NR) female Race: 100% (1,927/1,927) white	Mean SBP (mmHg) 115 (SD, 12) Mean DBP (mmHg) 66 (SD, 10) Mean BMI (kg/m^2) 18.7 (3.3)	4.2% (80/1,927) participants were reimbursed for antihypertensive medication	NR
Aatola, 2017[67]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	SBP≥120 mmHg or DBP≥80 mmHg or self-reported use of antihypertensive medication	Mean age: 12.1 (SD, 4.1) Sex: 55.3% (853/1,540) female Race: 100% white	Normal BP: 816 (53%) Elevated BP: 724 (47%)	NR	38% (1,357/3,596) lost to followup and 2% (76/3,596) died

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
Dunedin Multidisciplinary Health and Development Study						
Theodore, 2015[68]	Mean of two or three measurements (random zero sphygmomano-meter) on right arm in seated position	Prehypertension defined as SBP 120 to 139 mmHg Hypertension defined as SBP≥140 mmHg or taking anti-hypertensive medications	Mean age: NR Sex: 48% (N NR) female Race: NR	NR	NR	6.0% (62/1037)
Muscatine Study						
Lauer et al, 1989[62]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	SBP or DBP above the 90th percentile within study	Mean age: NR Sex: NR Race: NR	NR	NR	"The subjects we describe constitute 63% of those eligible for reexamination"
Lauer et al, 1993[63]	Mean of three measurements (random zero sphygmomano-meter) on right arm in seated position	SBP or DBP above the 90th percentile within study	Mean age: NR Sex: NR Race: NR	NR	NR	No loss (cohort selected based on availability of data)

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
The International Childhood Cardiovascular Cohort Consortium						
Juhola, 2013 The International Childhood Cardiovascular Cohort Consortium[69]	Bogalusa Heart Study: Mean of six measurements (mercury sphygmomanometer) on right arm in seated position Cardiovascular Risk in Young Finns Study and Muscatine Study: Mean of three measurements (random zero sphygmomanometer) on right arm in seated position CDAH: Mean of three measurements (digital autonomic monitor) on right arm in seated position Muscatine Study: Mean of three measurements (random zero sphygmomanometer) on right arm in seated position	SBP≥120 mmHg or DBP≥80 mmHg or taking antihypertensive medication	Bogalusa Heart Study: Mean age: 12.5 (SD, 3.4) Sex: 60.1% (352/586) female Race: 35.7% (209/586) black Cardiovascular Risk in Young Finns Study: Mean age: 12.0 (SD, 4.2) Sex: 54.8% (1219/2223) female Race: NR CDAH: Mean age: 11.9 (SD, 2.4) Sex: 56.7% (365/680) female Race: NR Muscatine Study: Mean age: 14.6 (SD, 1.9) Sex: 52.1% (376/721) female Race: NR	Bogalusa Heart Study: Mean BP mmHg (SD) SBP, 106.9 (10.8) DBP, 55.9 (11.6) Blood pressure, N (%) Normal: 534 (91.1%) Elevated: 52 (8.9%) Cardiovascular Risk in Young Finns Study: Mean BP mmHg (SD) SBP, 114.1 (11.3) DBP, 68.7 (9.6) Blood pressure, N (%) Normal: 1151 (51.8%) Elevated: 1072 (48.2%) CDAH: Mean BP mmHg (SD) SBP, 109.3 (12.9) DBP, 66.4 (11.8) Blood pressure, N (%) Normal: 456 (67.1%) Elevated: 224 (32.9%) Muscatine Study: Mean BP mmHg (SD) SBP, 116.9 (12.7) DBP, 68.8 (10.9) Blood pressure, N (%) Normal: 437 (60.6) Elevated: 284 (39.4%)	NR	NR

Appendix E Table 3. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 2

Author, Year Study Name	BP Measurement Method in Adults	Definition of Hypertension in Adults	Baseline Population (Mean Age, Sex, Race)	Baseline Population Characteristics	% Treated, Treatment Duration	% Attrition/Loss to Followup
The i3C Consortium Study						
Koskinen et al, 2019[70] Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, and the Childhood Determinants of Adult Health study, the Insulin Study, and the Kaunas Study	Bogalusa Heart Study: Mean of six measurements (mercury sphygmomanometer) on right arm in seated position Cardiovascular Risk in Young Finns Study and Muscatine Study: Mean of three measurements (random zero sphygmomanometer) on right arm in seated position CDAH: Mean of three measurements (digital autonomic monitor) on right arm in seated position Muscatine Study: Mean of three measurements (random zero sphygmomanometer) on right arm in seated position Insulin Study: Mean of 2 measurements on right arm Kaunas Study: Mean of 3 measurements on right arm	NR	Pooled cohort Mean age (SD):12(4) % male: 54%	Pooled cohort Mean SBP (SD): 109 (13) Mean DBP IV (SD): 72 (11) Mean DBP V (SD): 62 (15) BMI kg/m^2 (SD): 18.4 (3.6)	NR	No loss (cohort selected based on availability of data)

Abbreviations: BMI=body mass index; BP=blood pressure; CDAH=Childhood Determinants of Adult Health; DBP=diastolic blood pressure; KQ=key question; NR=not reported; SBP=systolic blood pressure; SD=standard deviation.

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
No study name			
Gillman et al, 1993[55]	NA	PPV, sensitivity, and specificity of BP at age 10 predicting BP >90th percentile at age 20 (SBP males: 139 mmHg, SBP females: 124 mmHg, DBP males: 84 mmHg, DBP females: 78 mmHg) SBP, males, >75th percentile (108 mmHg): 0.26, 0.59, 0.80 SBP, males, >90th percentile (113 mmHg): 0.35, 0.33, 0.93 SBP, males, >95th percentile (117 mmHg): 0.44, 0.17, 0.97 SBP, males, >99th percentile (123 mmHg): 0.58, 0.04, >0.99 SBP, females, >75th percentile (108 mmHg): 0.27, 0.66, 0.79 SBP, females, >90th percentile (114 mmHg): 0.39, 0.36, 0.94 SBP, females, >95th percentile (118 mmHg): 0.48, 0.20, 0.98 SBP, females, >99th percentile (125 mmHg): 0.65, 0.04, >0.99 DBP, males, >75th percentile (68 mmHg): 0.21, 0.34, 0.82 DBP, males, >90th percentile (71 mmHg): 0.24, 0.16, 0.93 DBP, males, >95th percentile (73 mmHg): 0.27, 0.08, 0.97 DBP, males, >99th percentile (77 mmHg): 0.34, 0.01, >0.99 DBP, females, >75th percentile (67 mmHg): 0.19, 0.49, 0.77 DBP, females, >90th percentile (71 mmHg): 0.24, 0.23, 0.92 DBP, females, >95th percentile (74 mmHg): 0.30, 0.10, 0.98 DBP, females, >99th percentile (78 mmHg): 0.38, 0.02, >0.99	NR
Fels Longitudinal Study			
Beckett et al, 1992[56]	NA	Risk ratio of different DBP vs. 60 mmHg at age 15 and presence of hypertension at age 35 80 mmHg vs. 60 mmHg: Males: 3.0 (CI, NR) Females: 4.5 (CI, NR) 85 mmHg vs. 60 mmHg: Males: 3.9 (CI, NR) Females: 6.6 (CI, NR) 90 mmHg vs. 60 mmHg: Males: 4.9 (CI, NR) Females: 9.0 (CI, NR)	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Sun et al, 2007[10]	NA	OR of hypertension at >30 years of age given SBP exceeding criterion values at single examination in childhood 5- to 7-year-old males: 3.8 (95% CI, 1.5 to 9.7) 5- to 7-year-old females: 4.5 (95% CI, 1.1 to 17.7) 8- to 13-year-old males: 3.5 (95% CI, 1.5 to 8.3) 8- to 13-year-old females: 2.7 (95% CI, 1.0 to 7.1) 14- to 18-year-old males: 1.1 (95% CI, 0.5 to 2.4) 14- to 18-year-old females: 3.8 (95% CI, 1.2 to 12.7)	NR
Bogalusa Heart Study			
Bao et al, 1995[57]	Logistic regression Age, race, sex, SBP, DBP, BMI, change in BMI	Hypertension at followup, baseline highest SBP quintile vs. other SBP quintiles: 18% (54/301) vs. 5% (60/1204); RR 3.6 (95% CI, 2.5 to 5.1) Hypertension at followup, baseline highest DBP quintile vs. other DBP quintiles: 15% (45/301) vs. 6% (72/1204); RR 2.5 (95% CI, 1.8 to 3.6) Baseline SBP at baseline, highest quintile (mean 107 mmHg) vs. lowest quintile (mean 93 mmHg) and hypertension at followup: OR, 2.0 (95% CI, NR)(p≤0.001) Subgroups Black males: OR, 1.3 (95% CI, NR) (p≤0.05) Black females: OR, 2.3 (95% CI, NR) (p≤0.05) White males: OR, 2.6 (95% CI, NR) (p≤0.05) White females: OR, 1.7 (95% CI, NR)(p=NS) Baseline DBP at baseline, highest quintile (mean 68 mmHg) vs. lowest quintile (mean 57 mmHg) and hypertension at followup: OR, 1.5 (95% CI, NR) (p≤0.05) Subgroups (only reported for white males) White males: OR, 2.1 (95% CI, NR; p=NS)	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Hoq et al, 2002[58]	Logistic regression Sex, childhood age, BMI, BP, annual change in BP	NR	Microalbuminuria Childhood SBP, regression coefficient African Americans: 0.016 (p=0.05) Whites: 0.002 (p=0.78) Annual change in SBP from childhood to adulthood, regression coefficient African Americans: 0.315 (p=0.002) Whites: 0.045 (p=0.55) Childhood DBP, regression coefficient African Americans: 0.026 (p=0.012) Whites: 0.002 (p=0.761) Annual change in DBP from childhood to adulthood, regression coefficient African Americans: 0.292 (p=0.016) Whites: 0.063 (p=0.5)
Li et al, 2003[59]	Logistic regression Age, race, sex	NR	CIMT in upper quartile given SBP risk factor Childhood (14 to 17 years): OR, 1.00 (95% CI, 0.80 to 1.25); correlation coefficient 0.103; p=0.02

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Shear et al, 1987[60]	NA	SBP ≥80th percentile at years 1, 4, and 6 and hypertensive at followup: Sensitivity: 0.27 Specificity: 0.95 DBP ≥80th percentile at years 1, 4, and 6 and hypertensive at followup: Sensitivity: 0.33 Specificity: 0.96 SBP ≥90th percentile at years 1, 4, and 6 and hypertensive at followup: Sensitivity: 0.13 Specificity: 0.99 DBP ≥90th percentile at years 1, 4, and 6 and hypertensive at followup: Sensitivity: 0.07 Specificity: 0.99 SBP ≥95th percentile at years 1, 4, and 6 and hypertensive at followup: Sensitivity: 0.07 Specificity: 1.0 DBP ≥95th percentile at years 1, 4, and 6 and hypertensive at followup: Sensitivity: 0.0 Specificity: 1.0	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Xi et al, 2017[61]	Cox regression Sex, age, race, childhood BMI	Childhood prehypertension, simple definition HR, 2.82 (95% CI, 2.04 to 3.89), p<0.001 Childhood prehypertension, complex definition HR, 2.91 (95% CI, 1.99 to 4.26), p<0.001 Childhood hypertension, simple definition HR, 3.11 (95% CI, 1.83 to 5.26), p<0.001 Childhood hypertension, complex definition HR, 3.17 (95% CI, 1.99 to 5.04), p<0.001	Childhood prehypertension, simple definition High PWV: HR, 2.66 (95% CI, 1.82 to 3.89), p<0.001 High CIMT: HR, 2.79 (95% CI, 1.96 to 3.97), p<0.001 LVH: HR, 1.92 (95% CI, 1.19 to 3.10), p=0.007 Any subclinical CVD: HR, 2.55 (95% CI, 1.97 to 3.31), p<0.001 Childhood prehypertension, complex definition High PWV: HR, 2.55 (95% CI, 1.58 to 4.12), p<0.001 High CIMT: HR, 3.03 (95% CI, 1.99 to 4.61), p<0.001 LVH: HR, 2.45 (95% CI, 1.40 to 4.28), p=0.002 Any subclinical CVD: HR, 3.03 (95% CI, 2.20 to 4.18), p<0.001 Childhood hypertension, simple definition High PWV: HR, 3.51 (95% CI, 1.74 to 7.07), p<0.001 High CIMT: HR, 3.07 (95% CI, 1.70 to 5.56), p<0.001 LVH: HR, 3.41 (95% CI, 1.70 to 6.84), p=0.001 Any subclinical CVD: HR, 3.21 (95% CI, 2.07 to 4.96), p<0.001 Childhood hypertension, complex definition High PWV: HR, 2.22 (95% CI, 2.22), p=0.010 High CIMT: HR, 2.03 (95% CI, 1.15 to 3.58), p=0.015 LVH: HR, 2.97 (95% CI, 1.57 to 5.61), p=0.001 Any subclinical CVD: HR, 2.20 (95% CI, 1.47 to 3.30), p<0.001

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Du et al., 2019[7]	Poisson regression) Age, sex, race, childhood BMI, and length of followup	2004 NIH/NHLBI Guidelines Childhood prehypertension or elevated blood pressure Adult hypertension: RR, 1.49 (95% CI, 1.34 to 1.65), p <0.001 Childhood hypertension Adult hypertension: RR, 1.71 (95% CI, 1.48 to 1.98), p <0.001 2017 AAP Guidelines Childhood prehypertension or elevated blood pressure Adult hypertension: RR, 1.45 (95% CI, 1.30 to 1.61), p <0.001 Childhood hypertension Adult hypertension: RR, 1.66 (95% CI, 1.47 to 1.87), p <0.001 Adult Hypertension by JNC7 & 2004 NIH/NHLBI Guidelines Childhood prehypertension or elevated blood pressure Adult Hypertension: RR, 1.53 (95% 1.28 to 1.82) Childhood hypertension Adult hypertension: RR, 1.95 (95% CI, 1.55 to 2.46) Adult Hypertension by JNC7 & 2017 AAP guidelines Childhood prehypertension or elevated blood pressure Adult Hypertension: RR, 1.62 (95% 1.35 to 1.95) Childhood hypertension Adult hypertension: RR, 1.98 (95% CI, 1.45 to 2.39)	2004 NIH/NHLBI Guidelines Childhood prehypertension or elevated blood pressure Adult LVH: RR, 1.30, (95% CI, 1.05 to 1.60), p = 0.0151 Childhood hypertension Adult LVH: RR, 1.52, (95% CI, 1.18 to 1.84), p = 0.001 2017 AAP Guidelines Childhood prehypertension or elevated blood pressure Adult LVH: RR, 1.31, (95% CI, 1.05 to 1.63), p = 0.0155 Childhood hypertension Adult LVH: RR, 1.59, (95% CI, 1.27 to 1.99), p < 0.001
Cardiovascular Risk in Young Finns Study			
Raitakari et al, 2003[64]	Logistic regression Age, sex	NR	Relationship between SBP >80th percentile at age 12 to 18 (mean age 14.9 years) and CIMT 21 years later regression coefficient 0.013 (SE 0.003); p<0.001

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Juhola et al, 2011[12] and Juonala et al, 2004[65]	Linear regression Age, sex, race, study year	Odds ratio of prehypertension or hypertension in adulthood given BP ≥95th percentile as child Female, age 6 and 9 years: 2.4 (95% CI, 1.1 to 5.2) Female, age 12, 15, and 18 years: 2.3 (95% CI, 1.6 to 3.5) Males, age 6 and 9 years: 2.8 (95% CI, 1.5 to 5.1) Males, age 12, 15, and 18 years: 2.1 (95% CI, 1.5 to 3.1) PPV, sensitivity, specificity of BP >95% percentile in childhood and hypertension in adulthood Age 6: 0.11, 0.05, 0.95 Age 9: 0.5, 0.18, 0.97 Age 12: 0.58, 0.12, 0.97 Age 15: 0.56, 0.09, 0.97 Age 18: 0.46, 0.97, 0.06 All ages 6 to 18: 0.44, 0.1, 0.97	NR
Juhola, 2012[11]	Odds ratio Age, sex	Odds of adult hypertension among children with hypertension, OR, (95% CI): 2.12 (1.82 to 2.61) p<0.0001	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Oikonen, 2016[66]	Pearson correlation, AUC Age, sex, Z-scores (year specific for above 90th or 95th percentile)	Adult hypertension defined by BP measurements Number of observations of abnormal BP in childhood resulting in adult hypertension Never: 14% (203/1407) Once: 27% (39/144) Twice: 29% (55/188) Three times: 38% (71/188) AUCs of very young (3 to 9 years) with abnormal BP in childhood resulting in adult hypertension as defined by BP measurements Once: 0.62 ref Twice: 0.64 p=0.19 Three times: 0.65 p=0.15 AUCs of young (12 to 18 years) with abnormal BP in childhood resulting in adult hypertension as defined by BP measurements: Once: 0.59 ref Twice: 0.63 p=0.004 Three times: 0.63 p=0.004 AUCs of very young (age 3 to 9 years) vs. young (age 12 to 18 years) age groups at baseline for predicting hypertension in adulthood 0.63 vs. 0.59, p=0.002 Pearson correlation coefficient between measurements of SBP in childhood predicting SBP in adulthood Once: 0.35 ref (p<0.001 for coefficient) Twice: 0.44 p=0.0009 (p<0.001 for coefficient) Three: 0.46 p<0.0001 (p<0.001 for coefficient) Pearson correlation coefficient between measurements of DBP in childhood predicting DBP in adulthood Once: 0.17 ref (p<0.001 for coefficient) Twice: 0.35 p<0.0001 (p<0.001 for coefficient) Three times: 0.32 p<0.0001 (p<0.001 for coefficient)	Number of observations of abnormal BP in childhood resulting in adult high risk CIMT: Never: 12% (137/1149) Once: 19% (23/120) Twice: 21% (33/154) Three times: 14% (21/147) Two childhood observations of abnormal BP compared to one for predicting adult high risk CIMT: SBP, r=0.44 vs. 0.35, p<0.001 DBP, r=0.35 vs. 0.17, p<0.001 Excluding 3-year-olds from the analyses did not change the results. AUCs of very young (3 to 9 years) with abnormal BP in childhood resulting in high risk CIMT: Once: 0.58 ref Twice: 0.59 p=0.37 Three times: 0.59 p=0.43 AUCs of young (12 to 18 years) with abnormal BP in childhood resulting in high-risk CIMT: Once: 0.62 ref Twice: 0.62 p=0.17 Three times: 0.63 p=0.002 Pearson correlation coefficient between measurements of SBP in childhood predicting CIMT in adulthood Once: 0.12 ref (p<0.001 for coefficient) Twice: 0.16 p=0.30 (p<0.001 for coefficient) Three times: 0.16 p=0.24 (p<0.001 for coefficient) Pearson correlation coefficient between measurements of DBP in childhood predicting CIMT in adulthood Once: 0.06 ref (p<0.05 for coefficient) Twice: 0.04 p=0.49 Three: 0.06 p=0.86 (p<0.05 for coefficient)

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Oikonen, 2016[66] (continued)		Adult hypertension defined by reimbursed antihypertensive medications Number of observations of abnormal BP in childhood resulting in adult hypertension Never: 2% (34/1401) Once: 4% (6/143) Twice: 8% (15/188) Three times: 8% (25/187) AUCs of very young (3 to 9 years) with abnormal BP in childhood resulting in adult hypertension Once: 0.69 ref Twice: 0.71 p=0.50 Three times: 0.73 p=0.27 AUCs of young (12 to 18 years) with abnormal BP in childhood resulting in adult hypertension Once: 0.64 ref Twice: 0.67 p=0.10 Three times: 0.68 p=0.05	
Aatola, 2017[67]	Linear regression Age, sex, adult BMI	Elevated BP resolved in adulthood: 35.8% (259/724) Elevated BP persistent in adulthood: 64.2% (465/724) Subgroups Normal weight Elevated BP resolved in adulthood: 13.2% (20/152) RR 1.19 (95% CI, 0.67 to 2.11) p=0.57 Elevated BP continued in adulthood: 30.0% (50/169) RR 2.91 (95% CI, 1.82 to 4.65) p<0.001 Sensitivity (calculated): 0.55 Specificity (calculated): 0.63 PPV (calculated): 0.53 Overweight/obese Elevated BP resolved in adulthood: 11.2% (12/107) RR 1.26 (95% CI, 0.60 to 2.65) p=0.54 Elevated BP continued in adulthood: 28.0% (83/296) RR 3.40 (95% CI, 1.99 to 5.82) p<0.001 Sensitivity (calculated): 0.56 Specificity (calculated): 0.64 PPV (calculated): 0.73	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Muscatine Study			
Lauer et al, 1989[62]		Adult hypertension (above the 90th percentile) among children who were ever hypertensive, N (%): NR (24%), "2.4 times the expected," p<0.001 Adult hypertension (above the 80th percentile) among children who ever had SBP above the 90^{h} percentile, N (%): NR (39%), "1.9 times the expected," p<0.001 Adult DBP above the 90th percentile among children who ever had DBP above the 90th percentile, N (%): NR (17%), "1.7 times the expected," p<0.001 Adult DBP above the 80th percentile among children who ever had DBP above the 90th percentile, N (%): NR (32%), "1.6 times the expected," p<0.001 Adult SBP above the 90th percentile among children who ever had SBP above the 90th percentile by number of occurrences, N (%): None: NR (6%) Once: NR (17%) Twice or more: NR (24%) X^2=51.1, p<0.001 Adult DBP above the 90th percentile among children who ever had DBP above the 90th percentile by number of occurrences, N (%): None: NR (7%) Once: NR (9%) Twice or more: NR (25%) X^2=38.0, p<0.001 Children with BP above the 90th percentile had 2 to 4 times greater risk of having high adult SBP readings than children at the 50th percentile (0.14 vs. 0.07 in females and 0.27 vs. 0.07 in males) Children with BP above the 90th percentile had two times greater risk of having high adult DBP readings than children at the 50th percentile (0.18 vs. 0.09, gender differences not statistically significant)	

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Lauer et al, 1993[63]	NA	Children with SBP >90th percentile and SBP >90th percentile in adulthood 24% (N NR) RR, 2.4 (95% CI, NR) (p<0.001) Children with SBP >90th percentile and SBP >80th percentile in adulthood 39% (N NR) RR, 1.9 (95% CI, NR) (p<0.001) Children with DBP >90th percentile and DBP >90th percentile in adulthood; 17% (N NR) RR, 1.7 (95% CI, NR) (p<0.001) Children with DBP >90th percentile and DBP >80th percentile in adulthood 32% (N NR) RR, 1.5 (95% CI, NR) (p<0.001)	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Dunedin Multidisciplinary Health and Development Study			
Theodore, 2015[68]	Group-based trajectory modeling Early life factors (maternal hypertension, birthweight, birth order, gender, family history of high BP, breastfeeding, early childhood socioeconomic status) and effect modifiers (BMI, alcohol consumption, cigarette smoking)	Prehypertension or hypertension at age 7 and hypertension at age 38: AUC, 0.68 (Sensitivity 36.6%, Specificity 86.8%, PPV, 21.3%, NPV, 93.4%) Prehypertension or hypertension at age 11 and hypertension at age 38: AUC, 0.70 (Sensitivity 8.1%, Specificity 97.6%, PPV, 26.3%, NPV, 91.1%) Prehypertension or hypertension at age 18 and hypertension at age 38: AUC, 0.76 (Prehypertension: Sensitivity 89.0%, Specificity 50.1%, PPV, 14.9%, NPV, 97.9%; Hypertension: Sensitivity 19.2%, Specificity 97.8%, PPV, 46.7%, NPV, 92.5%) Prehypertension or hypertension at age 7 and hypertension at age 38: AUC, 0.64 (Sensitivity 21.0%, Specificity 90.1%, PPV, 66.4%, NPV, 55.2%) Prehypertension or hypertension at age 11 and hypertension at age 38: AUC, 0.66 (Sensitivity 4.7%, Specificity 98.8%, PPV, 78.9%, NPV, 51.9%) Prehypertension or hypertension at age 18 and hypertension at age 38: AUC, 0.74 (Prehypertension: Sensitivity 73.4%, Specificity 64.1%, PPV, 64.3%, NPV, 73.2%; Hypertension: Sensitivity 7.3%, Specificity 99.5%, PPV 93.3%, NPV 54.9%) OR, (95% CI) for risk factors for membership in hypertension trajectory group age 7 to 38: Maternal hypertension vs. none: 0.92 (0.15 to 5.51) Firstborn vs. others: 2.95 (1.00 to 8.69) Male vs. female: 109.5 (26.8 to 467) Breastfeeding <4 weeks vs. 4 weeks: 0.49 (0.20 to 1.20) Low SES vs. others: 0.72 (0.17 to 3.12) Birthweight (kg): 0.36 (0.16 to 0.83) Proportion of relatives with HBP: 43.2 (5.27 to 355) Shift in trajectory per unit change in variable (95% CI) for effect modifiers for membership in hypertension trajectory group age 7 to 38: BMI: 1.70 (1.25 to 2.15) Average weekly alcohol consumption: 0.06 (-0.11 to 0.23) Number of cigarettes per day in last month: 0.23 (-0.07 to 0.53)	NR

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
The International Childhood Cardiovascular Cohort Consortium			
Juhola, 2013 The International Childhood Cardiovascular Cohort Consortium[69]	Logistic regression, Poisson regression Age, sex, adult BMI, length of followup, race	Overall: Childhood (ages 4 to 18 years) BP status to BP status in adulthood (ages 23 to 46), N (%): Normal to elevated: 1092 (42.4%) Elevated to elevated: 986 (60.4%) Bogalusa Heart Study: Childhood (ages 4 to 18 years) BP status to BP status in adulthood (ages 23 to 46), N (%): Normal to elevated: 233 (43.6%) Elevated to elevated: 31 (59.6%) Cardiovascular Risk in Young Finns Study: Childhood (ages 4 to 18 years) BP status to BP status in adulthood (ages 23 to 46), N (%): Normal to elevated: 533 (46.3%) Elevated to elevated: 691 (64.5%) CDAH: Childhood (ages 4 to 18 years) BP status to BP status in adulthood (ages 23 to 46), N (%): Normal to elevated: 196 (43.0%) Elevated to elevated: 123 (54.9%) Muscatine Study: Childhood (ages 4 to 18 years) BP status to BP status in adulthood (ages 23 to 46), N (%): Normal to elevated: 130 (29.8%) Elevated to elevated: 141 (49.7%)	Overall: Risk for high left common CIMT, RR (95% CI): Resolution vs. control: 1.09 (0.61 to 1.97) Persistent vs. control: 1.76 (1.21 to 2.56) Overall: Risk of high CIMT (≥90th percentile) by BP in childhood versus adulthood groups, RR (95% CI): For participants 4 to 11 years Resolution: 1.07 (0.63 to 1.82) p=0.80 Persistent: 1.63 (1.08 to 2.48) p=0.02 For participants 12 to 18 years Resolution: 1.29 (0.89 to 1.86) p=0.18 Persistent: 1.96 (1.45 to 2.63) p<0.001 Males Resolution: 1.33 (0.74 to 2.39) p=0.34 Persistent: 1.99 (1.34 to 2.96) p=0.001 Females: Resolution: 1.20 (0.85 to 1.71) p=0.31 Persistent: 1.79 (1.29 to 2.47) p<0.001 Bogalusa Heart Study: High risk for CIMT, RR (95% CI): Resolution vs. control: 2.94 (0.87 to 9.93) Persistent vs. control: 3.60 (1.38 to 9.40) Cardiovascular Risk in Young Finns Study: High risk for CIMT, RR (95% CI): Resolution versus control: 1.27 (0.83 to 1.96) Persistent versus control: 1.93 (1.36 to 2.75)

Appendix E Table 4. Tracking Hypertension and Other Outcomes From Childhood to Adulthood (KQ 4)—Part 3

Author, Year Study Name	Statistical Analysis and Variables Adjusted for in Analysis	HTN Association in Adulthood (OR, RR, Correlation Coefficient, etc.)	Intermediate Outcome Association in Adulthood (OR, RR, Correlation Coefficient, etc.)
Juhola, 2013 The International Childhood Cardiovascular Cohort Consortium[69] (continued)			CDAH: High risk for CIMT, RR (95% CI): Resolution vs. control: 0.80 (0.37 to 1.72) Persistent vs. control: 1.02 (0.54 to 1.91) Muscatine Study: High risk for CIMT, RR (95% CI): Resolution vs. control: 1.09 (0.61 to 1.97) Persistent vs. control: 1.75 (1.03 to 2.97)
The i3C Consortium Study			
Koskinen et al, 2019[70] Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, and the Childhood Determinants of Adult Health study, the Insulin Study, and the Kaunas Study	Logistic regression Age, sex	NR	Childhood BP with high CIMT in adulthood SBP: OR, 1.24 (95% CI, 1.13 to 1.37), p<0.0001 DBP IV: OR, 1.07 (95% CI, 0.97 to 1.17), p=0.16 DBP V: OR, 1.01 (95% CI, 0.92-1.10), p=0.88)

Abbreviations: AAP=American Academy of Pediatrics; AUC=area under the curve; BMI=body mass index; BP=blood pressure; CDAH=Childhood Determinants of Adult Health; CI=confidence interval; CIMT=carotid intima-media thickness; CVD=cardiovascular disease; DBP=diastolic blood pressure; HR=hazard ratio; HTN=hypertension; JNC7= Joint National Commission's 7th Report; KQ=key question; LVH=left ventricular hypertrophy; N=number of patients; NA=not applicable; NIH=National Institutes of Health; NHLBI=National Heart, Lung, and Blood Institute; NPV=negative predictive value; NR=not reported; NS= not significant; OR=odds ratio; PPV=positive predictive value; PWV=pulse wave velocity; ref=reference; RR=relative risk ratio; SBP=systolic blood pressure; SE=standard error; SES=socioeconomic status; vs.=versus.

Appendix E Table 5. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 1

Author, Year, Quality *Study Name (If Applicable)*	Study Design Setting Country Funding	Study Duration	Eligibility Criteria	Number Screened/ Eligible/Enrolled
Pharmacologic Interventions				
Batisky et al, 2007[76] Fair	RCT Clinical trial from 28 centers U.S. AstraZeneca LP	4-week dose-ranging study; 52-week safety study	Children age 6-16 years with newly or previously diagnosed primary hypertension, whether or not currently receiving treatment (1-2 week run-in period), with persistent sitting SBP and/or sitting DBP >95th percentile adjusted for age, sex, height, but not to exceed >20mmHg SBP and/or <1 0mmHg DBP above the 95th percentile Excluded if secondary hypertension, type 1 DM, impaired liver function, asthma, contraindication to beta blockers	204 enrolled (60 patients [29%] due to not completing eligibility criteria) 144 randomized 140 analyzed in dosing study 100 analyzed in safety study
Burrello et al, 2018[75] Unclear or some concerns	Meta-analysis NA NR The European Union's Horizon 2020	Median followup of 35 days Placebo-controlled periods limited to 2 to 4 weeks	Placebo-controlled RCTs with >50 patients and followup ≥4 weeks testing a pharmacological treatment of hypertension	2,378 randomized across 13 studies
Flynn et al, 2004[88] Fair *Pediatric use of Amlodipine in the Treatment of Hypertension (PATH) 1 Study*	Crossover Clinical trial from 49 centers in North and South America	Phase 1: 4 weeks, randomized to either 2.5 or 5 mg amlodipine daily Phase 2: at week 4, subjects randomly allocated to continue receiving amlodipine or withdrawn to placebo for 4 weeks	Children ages 6 to 16 years with seated SBP >95th percentile for age, sex, and height on 3 occasions and absence of transient, malignant, or accelerated hypertension, residual aortic coarctation with an upper-to-lower extremity BP gradient of >30 mmHg, or unstable chronic renal, hepatic, hematologic, endocrine, or neurologic disease. History of prior or ongoing treatment with >2.5 mg amlodipine per day were excluded; others included 2 week washout period	344 enrolled 268 randomly assigned (84 have primary hypertension)
Hazan, 2010[85] Fair	RCT Clinical trial at 61 sites U.S. Daiichi Sankyo, Inc.	2-week washout period Phase 1: 3-week dosing study Phase 2: 2-week withdrawal study	Hypertensive primary hypertension in 128 + 97/302; Patients with clinically significant medical condition or chronic disease, malignant hypertension, or severe hypertension excluded	422 screened 302 randomized to 2 cohorts

Appendix E Table 5. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 1

Author, Year, Quality *Study Name (If Applicable)*	Study Design Setting Country Funding	Study Duration	Eligibility Criteria	Number Screened/ Eligible/Enrolled
Li, 2004[81] Fair	RCT Clinical trial in 78 clinical centers U.S., Russia, Israel Bristol-Myers Squibb	Phase A: 10-day run-in Phase B: 4-week dose ranging Phase C: 2-week withdrawal vs. placebo Phase D: 1-year open-label safety phase	Children ages 6-16 years with hypertension (3 sequential SBP and DBP measurements >95th percentile for gender, age, and height) or high normal BP (SBP or DBP >90th percentile but ≤ 95th percentile) and with an associated clinical condition such as diabetes mellitus	376 screened 255 eligible 253 randomized
Li et al, 2010[86] Fair	RCT Clinical trial in 43 centers in the U.S., India, South Africa, Russia, and Dominican Republic Pfizer	Phase 1: 6 week dosing study (no placebo) Phase 2: 4 week placebo-controlled study	Children ages 4-16 years and a history of seated SBP >95th percentile for age, sex, and height. Excluded if body weight <20 kg, unstable hypertension, concomitant therapy with potassium sparing diuretic (subjects were allowed to be taking another "necessary" concomitant antihypertensive medication), clinically unstable underlying disease, a National Kidney Disease Outcomes Initiative CKD classification of >3, potassium level >5.5 mEq/L	394 screened 304 randomized
Shahinfar, 2005[84] Fair	RCT 43 clinical centers North and South America (including U.S.), Europe, Africa Merck	36 days	Children ages 6-16 years weighing ≥20 kg with mean siting DBP >95th percentile by gender, height, and age, and an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2	175 randomized
Soffer, 2003 #3577 Fair	RCT Multisite (number and location NR) Merck	Phase 1 randomized to 3 different doses, Phase 2 randomized washout	Children ages 6 to 16 years weighing ≥20 kg with an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 with documented hypertension defined as BP >95th percentile by age, gender, and height	115 randomized
Sorof et al, 2002[80] Fair *Ziac Pediatric Hypertension Study*	RCT Clinical trial from 22 centers in U.S. and Brazil NR	2-week run-in, 6-week titration period, 4-week dose maintenance period, 2-week tapering period	Children ages 6-17 years with mean sitting SBP and/or DBP >95th percentile, and current antihypertensive medications stopped 1 week prior to study entry. Exclude severe hypertension (>99th percentile), correctable secondary hypertension, hypertensive encephalopathy or neurovascular event within the past 6 months, resting bradycardia or any cardiac arrhythmia, renal impairment, and concomitant medication that might induce BP elevation	140 enrolled 94 randomized (62 treatment + 32 placebo)

Appendix E Table 5. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 1

Author, Year, Quality *Study Name (If Applicable)*	Study Design Setting Country Funding	Study Duration	Eligibility Criteria	Number Screened/ Eligible/Enrolled
Trachtman et al, 2003[78] Fair *Plendil Pediatric Clinical Trial*	RCT Clinical trial at 30 sites in the U.S. NR	1 to 3-week screening period, 2- to 3-week dose titration period, 3-week maintenance study	Children age 6 to 16 years with BP >95th percentile for age, sex, and height. Excluded if SBP >20 mmHg or DBP >10mmHg above 95th percentile, evidence of a secondary cause of hypertension, glomerular filtration rate was <40 ml/min/1.73m^2, recipients of a kidney transplant, concomitant illness such as liver disease or congestive heart failure	168 screened 133 randomized 128 completed treatment
Trachtman et al, 2008[77] Fair *Candesartan in Children with Hypertension (CINCH) program*	RCT Clinical trial at 42 sites in U.S. and Europe AstraZeneca LP	4-week trial and 1-year open-label study	Children age 6 to 17 years with newly diagnosed and previously diagnosed hypertension, with SBP or DBP >95th percentile for age and gender, but not exceeding the 95th percentile by >20/10 mmHg. Excluded if known secondary hypertension, bilateral renal artery stenosis, uncompensated nephrotic syndrome, insulin-dependent diabetes mellitus, and glomerular filtration rate <50 mL/min/1.73m^2	240 randomized
Wells, 2002[82] Fair	RCT Multicenter (number and location NR) Merck	2-week dose ranging phase and 2-week placebo-controlled washout phase	Children ages 6 to 16 years weighing ≥20 kg with hypertension (DBP >95th percentile for age, gender, and height on repeated measures) and an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 Excluded children with secondary hypertension, severe or symptomatic hypertension, or other significant systemic diseases.	110 enrolled
Wells et al, 2010[79] Fair	RCT Clinical trial at 16 centers in U.S., Brazil, and Mexico Boehringer Ingelheim Pharmaceuticals, Inc.	4 weeks, after 2-week washout period	Children age 6 to 18 years with SBP >95th percentile for age, height, and gender, weighing 20-120 kg, and had to be able to discontinue any current medications without undue risk. Excluded if had symptoms or signs of central nervous system injury within 6 months, SBP ≥20 mmHg or DBP ≥10 mmHg above 99th percentile, congestive heart failure, valvular disease, cardiac arrhythmia, renal artery stenosis, or uncorrected coarctation of the aorta, chronic renal disease, hepatic dysfunction or abnormal liver function tests, or bone marrow or solid organ transplantation	115 enrolled 77 randomized

Appendix E Table 5. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 1

Author, Year, Quality *Study Name (If Applicable)*	Study Design Setting Country Funding	Study Duration	Eligibility Criteria	Number Screened/ Eligible/Enrolled
Wells, 2011[87] Fair	RCT 55 centers in 9 countries in U.S., Latin America, Europe Novartis	2-week dose ranging phase, 2-week placebo controlled washout phase, 52-week open label extension phase	Children ages 6 to 16 years with mean sitting SBP ≥95th percentile for age, sex, and height. Excluded children with severe hypertension, hypertensive neurologic injury; estimated creatinine clearance of <40 mL/min/1.73 m^2 or other health, severe arrhythmias; coarctation of the aorta; bilateral renal artery stenosis (unilateral for children with a single kidney); or concurrent treatment with medications known to have a significant effect on BP	261 randomized
Pharmacologic Intervention with Lifestyle Intervention				
Berenson et al, 1983,[89] Berenson et al, 1990,[96] Fair *Franklinton Blood Pressure Intervention Study, ADAPT*	RCT of complex intervention with additional comparison group School based, U.S. NHLBI grant	6 months	Children ages 8 to 18 years with BP ≥90th percentile for height, Control group with BP <80th percentiles and the 50-60th percentile for comparison (based on centiles derived from study) Excluded children with evidence of secondary hypertension	1,804 eligible 1,604 screened 443 assessed and 150 selected in phase 2; received informed consent from 150 (100 with BP >90th percentile randomized to treatment group) (50, of whom 47 included) and comparison group (50, of whom 47 included), a further 50 (of whom 47 included) children with midrange BP (<80th percentile) provided further comparison group)
Berenson et al, 1983,[89] Berenson et al, 1990,[96] Fair *Franklinton Blood Pressure Intervention Study, ADAPT*	Same as above	30 months	Same as above	Same as above

Appendix E Table 5. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 1

Author, Year, Quality *Study Name (If Applicable)*	Study Design Setting Country Funding	Study Duration	Eligibility Criteria	Number Screened/ Eligible/Enrolled
Lifestyle Interventions				
Couch et al, 2008,[90] Fair	RCT Cincinnati Children's Hospital Medical Center U.S. AHA Ohio Valley Affiliate	3 month-long intervention; 6 months followup	Adolescents ages 11 to 18 years with a clinical diagnosis of prehypertension (3 persistent SBP and/or DBP measurements between 90th and 95th percentile for age, gender, and height) or Stage 1 hypertension (SBP and/or DBP between 95th and 99th percentile for age, gender, and height), newly enrolled in the Cincinnati Children's Hypertension Center between Sept 2003 and Dec 2005. Exclude secondary hypertension, prior use of BP altering medications, unwilling to discontinue current vitamins	206 screened 99 invited 57 randomized (29 treatment, 28 routine care)
Ewart et al, 1987[95] Fair	RCT 2 large Baltimore City public high schools, U.S. NHLBI grant	9 months	SBP or DBP between 85th and 95th percentiles, after 2 screenings; Students in grade 9 and 10 SBP ≥121 mmHgDBP ≥74 mmHg	1,654 eligible 1,400 screened 299 met criteria on 1st screen 159 met criteria on 2nd screen and were randomized (79 treatment, 80 control)
Hansen et al, 1991[92] Fair *Odense Schoolchild Study*	RCT Odense, Denmark School-based Danish Health Insurance Foundation the Danish Health Services Development Foundation, the Danish Heart Foundation the Health Insurance Foundation of Denmark, the Danish Medical Research Council, the Funen Prevention Council, the Danish Sports Research Council, and the Rosalie Petersen Foundation.	8 months	Children in the Odense, Denmark school system ages 9-11 years with a mean BP ≥95th percentile (hypertensive group) or <95th centile (normotensive group)	1,369 screened 137 randomized (69 hypertensive vs. 68 normotensive)

Appendix E Table 5. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 1

Author, Year, Quality *Study Name (If Applicable)*	Study Design Setting Country Funding	Study Duration	Eligibility Criteria	Number Screened/ Eligible/Enrolled
Howe et al, 1991[93] Fair	RCT crossover School-based Adelaide, Australia Channel 7 Children's Research Foundation of South Australia Inc.	2 phases of 4 weeks each	Children age 11-14 years representing top (>90th), middle (45-55th), and bottom (<10%) deciles of the BP range attending two schools in Adelaide, Australia	692 screened 103 enrolled
Sinaiko et al, 1993[94] Fair	RCT St. Paul and Minneapolis public schools, U.S. NIH grant	3 years	Adolescents in 5th to 8th grade in St. Paul and Minneapolis public schools with BP screened to be in the upper 85th percentile	19,452 screened 3, 223 eligible 210 randomized to 3 arms: (70 low sodium diet + 71 potassium chloride + 69 control)
Son et al, 2017[91] Fair	RCT NR South Korea NR	12 weeks	Adolescent girls (Tanner 2 to 3 stage, age 14 to 16 years) categorized as obese with prehypertension (SBP between 120 and 140 mmHg and DBP between 80 and 90 mmHg), hyperinsulinemia (>12.0 μU/ml) and abdominal obesity (waist >80 cm). All participants were sedentary, defined as having less than 1 hour of regular exercise training per week, and were not on a weight loss diet within the last 6 months. Exclusion criteria included pulmonary, cardiovascular, renal, adrenal, pituitary, severe psychiatric, thyroid diseases, and any medication use.	40 randomized

Abbreviations: ADAPT=Dietary/Exercise Alteration Program Trial; AHA=American Heart Association; BP=blood pressure; CINCH=Candesartan in Children with Hypertension; DBP=diastolic blood pressure; DM=diabetes mellitus; KQ=key question; NIH=National Institutes of Health; NHLBI=National Heart, Lung, and Blood Institute; NA=not applicable; NR=not reported; RCT=randomized, controlled trials; SBP=systolic blood pressure; U.S.=United States; vs.=versus.

Appendix E Table 6. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 2

Author, Year, Quality *Study Name (if Applicable)*	Withdrawals or Loss to Followup; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Pharmacologic Interventions			
Batisky et al, 2007[76] Fair	Two patients randomized incorrectly and two patients had no postbaseline BP measures	Mean age (SD): 12.5 ± 2.8 years Mean baseline BP: 132/78 ± 9/9 mmHg % Male: 70% % Black: 25.7% % Previously treated for hypertension: 22.9% % BMI >95% percentile: 74.3%	4 week dosing trial of ER metoprolol succinate: A: 0.2 mg/kg B: 1.0 mg/kg C: 2.0 mg/kg D: Placebo 52-week safety study: Start at 25 mg or 12.5 mg once daily at investigator discretion; increase every 2 weeks until maximum of 200 mg once daily
Burrello, 2019[75] Unclear or some concerns	NR	Mean age (95% CI): 12.1 (11.8 to 12.3) % male: 60% Baseline SBP (95% CI): 130 (128.0 to 133.7) Baseline DBP (95% CI): 83 (74.2 to 88.1)	Pooled treatment arms regardless of dose for studies testing valsartan, eplerenone, olmesartan, telmisartan, metoprolol, losartan, amlodipine, fosinopril, lisinopril, felodipine, bisoprolol + HCTZ, enalapril
Flynn et al, 2004[88] Fair *Pediatric use of Amlodipine in the Treatment of Hypertension (PATH) 1 Study*	12 excluded from analysis	Mean age: 12.1 + 3.3 years mean baseline BP: 137.9 + 12.7/74.2 + 11.6 mmHg % primary hypertension: 31.3% (n=84) % prior medication: 44% (n=118)	2 phases, 4 weeks each Phase 1: A: Amlodipine 2.5 mg/day (n=127) B: Amlodipine 2.5 mg/day for 1st 2 weeks, then uptitrated to 5.0 mg/day for weeks 3 & 4 (n=141) Phase 2: C: Amlodipine 2.5 mg/day (n=84) D: Amlodipine 5.0 mg/day (n=94) E: Placebo (n=90)
Hazan, 2010[85] Fair	Cohort A 3 withdrew due to AE 1 missing 4 protocol violations Cohort B: 1 SeSBP/SeDBP criteria 1 lost to followup 1 other 1 investigator judgment 1 noncompliance	Cohort A: Mean age (SD): 12.2 (2.97) % male: 64.2% Race: 62.1% white, 18.4% black, 10% Asian, 0.5% Hawaiian, 13.2% other Mean BMI (SD): 28.9 (10.93) Primary hypertension: 67.4% Mean SeSBP (SD): 129.3 (8.70) Mean SeDBP (SD):77.2 (8.16) Cohort B: Mean age (SD): 12.5 (2.64) % male: 50.9% Race: 100% black Mean BMI: 26.7 (9.67) Primary hypertension: 86.6% Mean SeSBP (SD): 131.2 (9.40) Mean SeDBP (SD): 79.3 (8.09)	Olmesartan medoxomil low dose (2.5 mg for participants weighing >20 kg and <35 kg or 5.0 mg for participants weighing ≥ 30 kg) or high dose (20 mg for participants weighing >20 kg and <35 kg or 40 mg for participants weighing ≥ 30 kg) Placebo

Appendix E Table 6. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 2

Author, Year, Quality *Study Name (if Applicable)*	Withdrawals or Loss to Followup; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Li, 2004[81] Fair	13 did not complete Phase B and 13 did not complete Phase C Overall study withdrawals across all 4 phases of study due to AEs: 5/253 (2%)	Mean age (SD): 12.1 (2.6) % male: 65.6% Race: 60.1% white, 20.6% black, 2.0% Asian, 13.8% Hispanic, 0.4% Native American, 3.2% Other % high-normal BP: 14.2% % hypertension: 85.8%	Phase A: Fosinopril 0.1 mg/kg test dose Phase B: Fosinopril low (0.1 mg/kg), medium (0.3 mg/kg), and high (0.6 mg/kg) for 4-weeks Phase C: A maximum 2-week randomized placebo withdrawal phase Phase D: 52-week open-label safety study
Li et al, 2010[86] Fair	27 not rerandomized into phase, 24 withdrawals	Age <12 years: 52.6% Race: 35% black, 57% white, 11% Hispanic, 8% Asian % male: 63% % primary hypertension: 56% % etiology of hypertension obesity: 22% % etiology of hypertension renal disease: 17% % receiving antihypertensives prior to study: 30%	Eplerenone 25 mg once daily, 25 mg twice daily, or 25 mg twice daily for 2 weeks, then 50 mg twice daily for 4 weeks Placebo
Shahinfar, 2005[84] Fair	Withdrawals due to AEs: 1/175 (<1%)	Mean age (SD): 12.0 (3.1) Race: 55% white, 21%, Hispanic, 11% African American, 12% Other % male: 56% Mean DBP (SD): 88.6 (6.9) Mean SBP (SD): 129.7 (13.1)	Losartan low (2.5 mg or 5.0 mg), middle (25 mg or 50 mg), high (50 mg or 100 mg) dose over 36 days for children weighing for children weighing <50 kg or ≥50 kg, respectively.
Soffer, 2003[83] Fair	Withdrawals due to AEs: 1/115 (<1%)	N (%) age <6 to 12: 54 (47.0%) 13 to 16: 61 (53.0%) Race: 44.3% white, 10.4% black, 0.9% Asian, 44.3% Hispanic SiDBP mean (SD): 89.8 (8.4) SiSBP mean (SD): 129.9 (12.9)	Lisinopril low (0.625 mg or 1.25 mg), middle (2.5 mg or 5 mg), or high (20 mg dose or 40mg) dose daily for children weighing <50 kg or ≥50 kg, respectively.
Sorof et al, 2002[80] Fair *Ziac Pediatric Hypertension Study*	None	Treatment, placebo groups: Mean age: 13.8 years (3.1 SD), 14.0 years (2.7 SD) % male: 56%, 59% % black: 40%, 44% % White: 45%, 38% % Hispanic: 11%, 19% Mean BMI: 28.0 kg/m^2, 28.9 kg/m^2	Bisoprolol fumarate/hydrochlorothiazide combination (B/HT) (n=62): for 4 weeks B 2.5 mg/HT 6.25 mg B 5 mg/HT 6.25 mg B 10 mg/HT 6.25 mg Placebo (n=32)

Appendix E Table 6. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 2

Author, Year, Quality *Study Name (if Applicable)*	Withdrawals or Loss to Followup; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Trachtman et al, 2003[78] Fair *Plendil Pediatric Clinical Trial*	Five discontinued treatment	Mean age: 12.1 ± 2.7 years % male: 60% % black: 39% % nonblack: 61% Mean weight: 171 ± 65 lbs Mean duration of increased BP: 2.1 ± 1.9 years	ER felodipine 2.5 mg (n=33), 5 mg (n=340, or 10 mg (n=31), titrated to target dose over 2-3 weeks, depending on dosage Placebo (n=35)
Trachtman et al, 2008[77] Fair *Candesartan in Children with Hypertension (CINCH) program*	11 patients discontinued 233 included in intention to treat analysis	4-week phase 1 trial: % age ≥12: 70.8% % male: 70.8% % black: 47.1% % white: 45.0% BMI ≥95th percentile: 68.8% Duration of hypertension <1 year: 64.2% 52 week open label study: % age >12: 70.8% % male: 71.2% % black: 43.8% % white: 47.6% BMI >95th percentile: 67.0% Duration of hypertension <1 year: 64.8%	4 week trial: Candesartan doses 2, 8, and 16 mg/day for those <50 kg, and 4, 16, and 32 mg/day for those ≥50 kg Placebo Open-label study: Candesartan at 4 or 8 mg/day to start, but later adjusted to control BP. For this study, other hypertensives, except for other angiotension receptor blockers, were permitted
Wells, 2002[82]	9 excluded for missing data 13 withdrawals	Mean age (SD): 11.6 (3.1) % male: 58.2% % black: 20.9% % white: 39.1% % Hispanic: 40.0% Hypertension: 44.5%	Enalapril low (0.625 mg or 1.25 mg), middle (2.5 mg or 5 mg), or high (10 mg dose or 20 mg) dose daily for children weighing <50 kg or ≥50 kg, respectively.
Wells et al, 2010[79] Fair	13 withdrawals	Mean age: 14 years (2.5 years) % male: 56.6% % white: 50.5% % black: 36.8%	Telmisartan low dose (1 mg/kg/day) (n=29) and high dose (1 mg/kg/day titrated up to 2 mg/kg/day after 1 week) (n=31) Placebo (n=16) 4-week study duration
Wells, 2011[87] Fair	Phase I: 16 withdrawals Phase 2: 13 withdrawals	Mean age (SD): 11.4 (2.87) % male: 60.5% % black: 48.7%	Valsartan low (10 mg or 20 mg), middle (40 mg or 80 mg), or high (80 mg dose or 160 mg) dose daily for children weighing <35 kg or ≥35 kg, respectively.

Appendix E Table 6. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 2

Author, Year, Quality *Study Name (if Applicable)*	Withdrawals or Loss to Followup; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Pharmacologic Intervention With Lifestyle Intervention			
Berenson et al, 1983,[89] Berenson et al, 1990,[96] Fair *Franklinton Blood Pressure Intervention Study, ADAPT*	1st 6 months completed by 133 children (88.6%); 5 had secondary hypertension and were excluded from analyses	NR	A: high BP intervention group received propranolol/ chlorthalidone + ADAPT program consisting of nutrition education and promotion of modification to children and parents (educational materials, cooking classes for parents, individual dietary consultations, pledges, t-shirt rewards); expanded community availability of low-sodium foods in grocery stores, restaurants, and school lunches; and a school-based exercise component B: high BP control group C: midrange BP comparison group Propranolol 20 mg/day for children <40kg 40 mg/day for those >40 kg Chlorthalidone (given simultaneously) 6.25 mg per day for child <40kg 12.5 mg/ per for those >40 kg
Berenson et al, 1983,[89] Berenson et al, 1990,[96] Fair *Franklinton Blood Pressure Intervention Study, ADAPT*	At 30 months, retained 59% of treatment and 60% of high BP comparison group (note: some children graduated from school)	Treatment, high BP comparison: % male: 54.2%, 55.3% % white: 47.9%, 46.8% Mean age: 12.3 years, 12.0 years Mean SBP, 116.9 mmHg, 118.5 mmHg Mean DBP, 77.8 mmHg, 78.5 mmHg	Same as above Children apparently continued to be maintained in original treatment and control groups for 30 months

Appendix E Table 6. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 2

Author, Year, Quality *Study Name (if Applicable)*	Withdrawals or Loss to Followup; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Lifestyle Interventions			
Couch et al, 2008,[90] Fair	3-month retention (83% treatment, 79% routine care) 6-month retention (62% treatment, 64% routine care)	DASH vs. routine care: Mean age: 14.3 years (2.1 years SD), 14.4 years (2.1 years SD) % ≥14 years old: 69%, 68% % male: 62%, 64% % black: 28%, 32% % white: 72%, 68% BMI: 29.1 kg/m^2, 29.4 km/m^2 % hypertensive: 72%, 39%, p<0.01 % prehypertensive: 28%, 61%, p<0.01	A: DASH-type diet modified for adolescent population: 60 minute face-to-face counseling session; 10 module illustrated manual; encouragement to make gradual dietary changes to include 8 servings/day of fruits and vegetables, 3 servings/day of low fat dairy foods, 2 servings/day of DASH-unfriendly foods; food diary of servings, but not calorie tracking; 8 weekly and 2 biweekly phone counseling by trained interventionists; biweekly mailings; small, weekly monetary incentives not to exceed $50 for the entire program vs. B: Routine nutrition counseling provided by Cincinnati Children's Hypertension Center: 60-minute face-to-face counseling session with dietitian and pamphlet *Eat Right to Lower Blood Pressure*
Ewart et al, 1987[95] Fair	Participated treatment: 51/79 (65%) Control: 59/80 (74%) Withdrawals in both groups significantly more likely to have lower grades and higher rates of school absence. Analyzed, due to criteria SBP, treatment: 22, control: 27 DBP, treatment: 40, control: 40 SBP and DBP, treatment: 9,control: 9	Mean age: 14.7 years (range 13-17 years) Black treatment 28/51, control 33/59 Male: treatment 29/51, control 37/59 BMI range: 19.0-31.2 kg/m^2	Progressive muscle relaxation (12 weeks, 15-20 minutes, 4 days per week) occurring supine on mats for first 6 weeks then while sitting, including assuming relaxed posture, muscle relaxation, slow diaphragmatic breathing, and hand warming, plus informational instruction on BP and CPR and emergency first aid (16 weeks, 50 minutes, 5 days per week) provided in class for academic credit (PMR provided within existing course) vs. control Schools A and B both had treatment and control groups.Treatment group also received additional interventions: relaxation tapes and asked to practice daily at home, taught to graph finger temperature and received a thermometer ring, and appeared to receive additional monitoring of relaxation techniques during the intervention period.

Appendix E Table 6. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 2

Author, Year, Quality *Study Name (if Applicable)*	Withdrawals or Loss to Followup; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Hansen et al, 1991[92] Fair *Odense Schoolchild Study*	64/69 (93%) hypertensive 68/68 (100%) normotensive Note: 5 children in the hypertensive group and 17 children in the normotensive group did chose to not participate, which were replaced with other children from the population by a "randomized reselection procedure"	Ages 9-11 years Other details NR	Three extra lessons per week of an ordinary school physical education program (for a total of 5 lessons per week) for 8 months. Each lesson was approximately 50 minutes long, including 10 minutes of warming up, and included organized games, gymnastics, and exercises. The intervention occurred at 6 different schools by 6 different teachers. The placebo group received usual physical education 2 days per week.
Howe et al, 1991[93] Fair	100/103 (97%)	Mean age: 13.3 ± 0.1 years Mean SBP, 115 ± 1 mmHg Mean DBP, 60.1 ± 0.6 mmHg	Low sodium (<75 mmol/day) or high sodium (>150 mmol/day) diet for 4 weeks, then changed to the alternate diet for an additional 4 weeks, plus weekly visits for individual dietary counselling and urinary sodium analysis, and diet diaries
Sinaiko et al, 1993[94] Fair	NR	Low sodium, potassium, placebo: Mean age: 13.2 ± 0.1 years, 13.3 ± 0.1 years, 13.4 ± 0.1 years % male: 50%, 51%, 49% BMI: 22.5 ± 0.5 kg/m^2, 22.3 ± 0.5 kg/m^2, 22.2 ± 0.5 kg/m^2 SBP, 113.6 ± 1.0 mmHg, 114.2 ± 0.9 mmHg, 113.7 ± 1.0 mmHg DBP, 63.4 ± 1.5 mmHg, 66.6 ± 1.3 mmHg, 65.3 ± 1.4 mmHg	A: Low sodium diet: <70 mmol/day; families met with nutritionist 7 times during 1st 3 months of study for instruction/information on reducing sodium intake; reinforcement sessions every 3 months thereafter; regular phone support B: Potassium chloride supplementation: participants' normal diet + 1 mmol/kg body weight per day, not to exceed 80 mmol/dayC: Placebo: participant's normal diet + placebo Measured every 3 months for 3 years
Son et al, 2017[91] Fair	NR	Control, exercise Mean (SE) age: 15 ± 1 years, 15 ± years % male: 0%, 0% Mean (SE) BMI: 30.31 ± 0.76 kg/m^2, 30.36 ± 0.69 kg/m^2 Mean (SE) SBP, 130.2 ± 1.4 mmHg, 134 ± 2.41 mmHg Mean (SE) DBP, 82.2 ± 2.45 mmHg, 76.3 ± 3.63 mmHg	Participants in the exercise group trained using combined resistance and aerobic exercise (CRAE) for 12 weeks, 3 days per week, 60 minutes each day. This CRAE program was divided into warm-up (5 minutes), the main exercise (30 minutes of various exercises and 20 minutes of playing badminton), and cool-down (5 minutes). Intensity of the exercise was gradually increased from 40 to 50% heart rate reserve (HRR) and rated perceived exertion (RPE) 11 to 12 within the first 1 to 4 weeks to 60 to 70% HRR and RPE 15 to 16 in 9 to 12 weeks.

Abbreviations: ADAPT=A Dietary/Exercise Alteration Program Trial; AE=adverse event; BMI=body mass index; B/HT=bisoprolol fumarate/hydrochlorothiazide; BP=blood pressure; CINCH=Candesartan in Children with Hypertension; CPR=cardiopulmonary resuscitation; CRAE=combined resistance and aerobic exercise; DASH=dietary approaches to stop hypertension; DBP=diastolic blood pressure; ER=extended release; HCTZ= hydrochlorothiazide; HRR=heart rate reserve ; KQ=key question; N=number; NR=not reported; PATH=Pediatric use of Amlodipine in the Treatment of Hypertension; PMR=progressive muscle relaxation; RCT=randomized, controlled trial; RPE=rated perceived exertion; SBP=systolic blood pressure; SD=standard deviation; SE=standard error; SeDBP= seated diastolic blood pressure ; SeSBP= seated systolic blood pressure .

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Pharmacologic Interventions					
Batisky et al, 2007[76] Fair	Cuff At each visit, BP was measured at least 6 times, 3 sitting and 3 standing. 3 consecutive BP measurements were used to calculate the mean BP for each visit	All treatment groups pooled: 46% (95% CI, 37 to 55) Placebo: 26% (95% CI, 8 to 44)	Mean change from baseline (95% CI) A: SBP -5.2 (-7.7 to -2.6) (p=0.145) DBP -3.1 (-5.7 to -0.5) (p=0.655) B: SBP -7.7 (-11.3 to -4.0) (p=0.027) DBP -4.9, 95% CI (-8.6 to -1.3) (p=0.280) C: SBP -6.3, (-8.7 to -3.8) (p=0.049) DBP -7.5 (-10.0 to -5.0)(p=0.017) D: SBP -1.9 (-5.5 to 1.8) DBP -2.1 (-5.7 to 1.5) All metoprolol ER groups pooled: SBP -6.1 (-7.7 to -4.5) (p=0.035) DBP -5.3 (-6.9 to -3.7) (p=0.119)	NR	NR
Burrello, 2019[75] Unclear or some concerns	NR	NR	Mean reduction of SBP (95% CI) ACEIs -4.38 (12.16 to -7.27) ARBs -3.07 (-1.44 to -4.99) β-blockers -3.2 (+2.23 to -8.69) CCBs -3.1 (+0.45 to -6.52) MRAs -0.12 (+3.46 to -3.69)	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Flynn et al, 2004[88] Fair *Pediatric use of Amlodipine in the Treatment of Hypertension (PATH) 1 Study*	Oscillometric device, cuff Seated BP 4 BP measurements taken 24 hours after last dose of study drug at each study visit; the mean of the last 3 readings was calculated and recorded	SBP 33.3% DBP 45% SBP and DBP 8.3%	Outcome data not provided for the children with primary hypertension only (n=84). Distribution between the two treatment groups and control groups not always reported. Results for all causes combined (authors state that response to reduction in SBP and DBP did not differ significantly according to underlying cause of hypertension (data NR): Phase I (from baseline): Mean SBP reduction for 2.5 mg group: -7.3 + 11.4 mmHg; mean SBP reduction for 5.0 mg group: -9.0 + 11.4 mmHg; mean DBP reduction for 2.5 mg group: -3.7 + 9.2 mmHg; mean DBP reduction for 5.0 mg group: -4.4 + 8.3 mmHg. Phase 2 (compared with placebo): Mean SBP reduction for 2.5 mg group: -6.9 +12.5 mmHg; significantly greater than placebo group (values not NR), p=0.045 mean SBP reduction for 5.0 mg group: -8.7 +13.3 mmHg vs. placebo group -3.6+12.7 mmHg, p=0.005 mean DBP reduction for 2.5 mg group: NR Mean DBP reduction for 5.0 mg group: NR	NR	NR
Hazan, 2010[85] Fair	Validated electronic BP measuring instrument or clinical sphygmomanometer, seated cuff SBP and DBP, 3 measurements taken at least 1 minute a part	NR	BP at end of Period 1 Cohort A treatment: Mean SeSBP (SD): 120.4 (11.91) Mean SeDBP (SD): 70.1 (10.34) Placebo Mean SeSBP (SD): 118 (13.25) Mean SeDBP (SD): 69.1 (10.23) Cohort B treatment: Mean SeSBP (SD): 123.4 (12.86) Mean SeDBP (SD): 73.4 (8.09) Placebo Mean SeSBP (SD): 123.8 (11.81) Mean SeDBP (SD): 73.7 (10.18)	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Li, 2004[81]	Device for indirect noninvasive automatic mean arterial pressure	NR	Change in withdrawal phase placebo vs. any fosinopril Mean (95% CI) SBP: -3.7 (-6.6, -0.8), p=0.0132 DBP: -1.6 (-3.5, 0.3), p=0.1036	NR	NR
Li et al, 2010[86] Fair	Dinamap automated device BP measured every 2 minutes for 8 minutes. Mean of last 3 measurements was recorded.	NR	Phase 1: No placebo group Phase 2: 4 weeks Least squares mean change in SBP from baseline of Phase 2: Eplerenone 50 mg twice daily vs. placebo: -2.76 mmHg (95% CI, -5.5 to 0), p=0.048 No other doses or DBP received statistical significance. No other doses or DBP achieved statistical significance.	NR	NR
Shahinfar, 2005[84] Fair	Mercury sphygmomanometer on BP measured 3 times at least one minute apart	Phase 1 Low: 20.0% Middle: 37.5% High: 42.2%	Mean change (95% CI) in withdrawal phase DBP Low/low vs. low/placebo: 0.9 (-3.5, 5.1) Middle/middle vs. middle/placebo: 6.7 (0.8, 12.6) High/high vs. high/placebo: 5.3 (0.1, 10.4) SBP Low/low vs. low/placebo: -0.8 (-5.7, 4.2) Middle/middle vs. middle/placebo: 5.3 (-0.8, 11.3) High/high vs. high/placebo: 9.3 (4.0, 14.7)	NR	NR
Soffer, 2003[83] Fair	Mercury sphygmomanometer Mean of 3 measurements taken at least 1 minute apart	NR	Mean change (95% CI) in withdrawal phase DBP Low/low vs. low/placebo: -0.2 (-6.7, 6.3) Middle/middle vs. middle/placebo: 9.7 (3.3, 16.1) High/high vs. high/placebo: 9.1 (3.8, 14.3) SBP Low/low vs. low/placebo: -1.7 (-8.8, 5.4) Middle/middle vs. middle/placebo: 10.4 (1.7, 19.0) High/high vs. high/placebo: 12.2 (7.4, 17.0)	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Sorof et al, 2002[80] Fair *Ziac Pediatric Hypertension Study*	Standard mercury manometer cuff 3 resting, seated measurements taken a 2-minute intervals in each arm; average of 3 measurements recorded	NR	Measured baseline (week 3) and week 8: Overall: B/HT decreased SBP greater than placebo (absolute reduction 9.3 mmHg vs. 4.9 mmHg, p=0.045) B/HT decreased DBP greater than placebo (absolute reduction 7.2 mmHg vs. 2.7 mmHg, pp=0.012)	Stratified by age: 6- to 12-year-olds (n=28): B/HT decreased SBP greater than placebo (absolute reduction 10.0 mmHg vs. 1.2 mmHg, p=0.03) B/HT decreased DBP greater than placebo (absolute reduction 8.5 mmHg vs. 2.7 mmHg, p=0.038) 13- to 17-year-olds (n=66): SBP, p=ns DBP, p=ns Stratified by severity of hypertension: SBP or SBP >5 mmHg above 95th percentile (n=57): B/HT decreased SBP greater than placebo (absolute reduction 11.1 mmHg vs. 1.9 mmHg, p=0.003)	NR
Sorof et al, 2002[80] Fair *Ziac Pediatric Hypertension Study (continued)*				B/HT decreased DBP greater than placebo (absolute reduction 7.9 mmHg vs. 1.4 mmHg, p=0.012) SBP or SBP <5 mmHg above 95th percentile (n=37): SBP, p=ns DBP, p=ns	

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Trachtman et al, 2003[78] Fair *Plendil Pediatric Clinical Trial*	Mercury manometer, cuff 3 BP measurements (sitting, standing, supine) obtained at 1-minute intervals, averaged and recorded	Proportions achieving sitting DBP and SBP <90th percentile was 11.4% placebo vs. 15.2%, 17,6%, and 19.4%, in the felodine ER 2.5 mg, 5.0 mg, and 10 mg groups, respectively. Results for changes in SBP NR	Felodipine ER 5 mg reduced trough sitting, supine, and standing DBP compared to placebo, -4.64 mmHg (95% CI, -9.18 to 0.09), -5.06 (95% CI, -9.68 to -0.45), and -5.09 (95% CI, -9.53 to -0.65), respectively, p<0.05 Felodine ER 2.5 mg vs. placebo, p=ns Felodine ER 10 mg vs. placebo, p=ns	NR	NR
Trachtman et al, 2008[77] Fair *CINCH program*	Cuff 3 resting BP measurements were averaged and recorded	Proportion of participants achieving BP <95th percentile: All doses (low 54%, medium 62%, and high 65%) vs. placebo (31%), p<0.05 (significance of individual dose groups vs. placebo NR)	4-week trial: BP declined with all active treatment doses vs. placebo. Adjusted mean SBP reduction for all active doses combined vs. placebo: -10.22 mmHg vs. -3.666 mmHg, p<0.0001 Adjusted mean DBP reduction for all active doses combined vs. placebo: -6.56 mmHg vs. 1.80 mmHg, p=0.0029 52-week study: no random allocation between the treatment vs. control groups, so not reported here.	Reduction in BP less for blacks than nonblacks, SBP 4.8 mmHg vs. 7.9 mmHg and DBP 3.9 mmHg vs. 6.7 mmHg, respectively (all active doses pooled)	NR
Wells, 2002[82] Fair	Auscultatory method, sitting DBP, measured 24 hours after last dose	NR	Mean change (95% CI) in withdrawal phase SBP Low/low vs. low/placebo: 3.9 (-2.2, 10.0) Middle/middle vs. middle/placebo: 9.9 (0.2, 19.7) High/high vs. high/placebo: 11.2 (4.4, 18.0) DBP Low/low vs. low/placebo: 0.5 (-5.9, 6.9) Middle/middle vs. middle/placebo: 6.8 (-0.3, 13.8) High/high vs. high/placebo: 11.0 (5.2, 18.0)	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Wells et al, 2010[79] Fair	NR	Achievement of <95th percentile for both SBP and DBP, High dose vs. placebo: age 6 to <12 years, 85.7% vs. 33.3%, 12 to <18 years, 79.2% vs. 27.3%, p=0.10 overall presumably (individual comparisons' significance levels NR) Low dose vs. placebo: age 6 to <12 years, 50.0% vs. 33.3%, age 12 to <18 years, 68.2% vs. 27.3%, p=0.032 overall presumably (individual comparisons' significance levels NR)	SBP adjusted mean difference from placebo: High dose: -8.5 mmHg (SE, 2.7; 95% CI, -14 to -3.0, p=0.0027) Low dose: -3.6 mmHg (SE, 2.8; 95% CI, -9.2 to 1.9, p=ns) DBP adjust mean difference from placebo: High dose: -4.8 mmHg (SE, 2.4; 95% CI, -9.7 to 0, p=0.051) Low dose: -4.5 mmHg (SE, 2.5; 95% CI, -9.5, 0.4, p=ns)	NR	NR
Wells, 2011[87] Fair	NR	NR	Mean (SD) BP end of Phase 1 SBP Valsartan: 122.2 (12.07) Placebo: 122.2 (11.51) DBP Valsartan: 70.7 (11.26) Placebo: 71.8 (10.04) Mean (SD) BP end of Phase 2 SBP Valsartan: 123.3 (13.05) Placebo: 126.1 (12.09) DBP Valsartan: 71.2 (11.30) Placebo: 75.3 (10.83)	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Pharmacologic Intervention With Lifestyle Intervention					
Berenson et al, 1983,[89] Berenson et al, 1990,[96] Fair *Franklinton Blood Pressure Intervention Study, ADAPT*	Mercury manometer or automatic recording device 3 resting, seated BP measurements averaged and recorded	NR	Mean SBP mmHg (SD), baseline, 6-month followup A: (n=46) 116.6 ± 2.6, 109.0 ± 2.7 vs. B: (n=44) 118.5 ± 3.1, 115.5 ± 2.7, p<0.0001 C: (n=47) 103.4 ± 2.5, 103.0 ± 2.3 Mean DBP mmHg (SD), baseline, followup A: (n=46) 77.7 ± 1.4, 70.8 ± 1.9 vs. B: (n=44) 78.3 ± 1.9, 74.4 ± 2.0, p<0.01 C: (n=47) 65.8 ± 1.4, 64.1 ± 1.5 Authors report that "the drop in blood pressure in the treated children was associated with the initial use of the drug, with the decrease occurring within the first week of therapy," but no data reported to support this statement	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Berenson et al, 1983,[89] Berenson et al, 1990,[96] Fair *Franklinton Blood Pressure Intervention Study, ADAPT*	Same as above	NR	Adjusted mean difference SBP (mmHg) between treatment (n=47) vs. high BP control group (n=48) at 6, 17, and 30 months: All children: -4.35 ± 1.06 (p<0.01), -3.45 ± 1.12 (p<0.01), -3.59 ± 1.12 (p<0.01) Adjusted mean difference DBP (mmHg) between treatment vs. high BP control group at 6, 17, and 30 months: All children: -2.68 ± 0.91 (p<0.01), -1.70 ± 0.84 (p<0.05), -1.73 ± 0.82 (p<0.05) NOTE: unclear if these are changes from the previous measure, or from baseline (presume former)	Stratified by race: Adjusted mean difference SBP (mmHg) between treatment (n=25) vs. high BP control group (n=25) at 6, 17, and 30 months: Black (n=25 vs. 25): -4.52 ± 1.35 (p<0.01), -3.75 ± 1.48 (p<0.05), -3.96 ± 1.49 (p<0.05) White (n=22 vs. 23): -3.97 + 1.72 (p<0.05), -3.03 ± 1.75 (p=ns), -3.16 ± 1.74 (p=ns) Adjusted mean difference DBP (mmHg) between treatment (n=25) vs. high BP control group (n=25) at 6, 17, and 30 months: Black (n=25 vs. 25): -3.80 +1.14 (p<0.01), -3.30 ± 0.93 (p<0.05), -3.28 ± 0.92 (p<0.01) White (n=22 vs. 23): -1.53 + 1.41 (p=ns), -0.21 ± 1.47 (p=ns), -0.03 ± 1.43 (p=ns)	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Lifestyle Interventions					
Couch et al, 2008,[90] Fair	Manometer BP calculated as mean of all possible measurements at that time point Baseline: 4 measurements taken in clinic 2 weeks apart 3-month and 6-month assessment: 2 measurements	NR	3-month outcomes: Statistically significant reduction of SBP (-2.2 mmHg; p<0.01) and DBP (-2.8 mmHg; p<0.05) Relative change: DASH-type diet reduced SBP compared to routine care, relative change -7.9% vs. -1.5%, p=0.01 DBP, no effect 6 month outcomes: SBP, no effect DBP, no effect Normal BP: 61% DASH-type diet vs. 44% routine care, p=0.36 ITT population (6 month outcomes only) DASH-type diet reduced SBP compared with routine care, relative change -6.8 vs. -2.8, p<0.05	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Ewart et al, 1987[95] Fair	BP obtained at school in a quiet room after 10 minutes of rest (manometer and cuff) 9 measures taken over 20 minutes and averaged	NR	Pooled analysis of both schools, treatment vs. control: 4 months postbaseline: Change in SBP from baseline to 4-month followup: treatment: -7.2 mmHg (SD, 9.2 mmHg) (p<0.01), control: -1.9 mmHg (SD, 9.2 mmHg) (p>0.3) DBP (n=40 vs. 40): Change in SBP from baseline to 4-month followup treatment: -9.6 mmHg (SD, 9.6), p<0.001, control: -13.1 mmHg (SD, 9.6 mmHg) (p<0.001) 9 months post baseline: SBP treatment 20/22, control 22/27 available: treatment group—no significant change from 4 months, control group—SBP decreased significantly from 4-month levels. no effect DBP treatment 35/40, control 28/40 available: treatment group significantly increased from 4 months, control group significantly increased. No significant differences between SBP and DBP between treatment and control groups	NR	None
Hansen et al, 1991[92] Fair *Odense Schoolchild Study*	Manometer One resting, seated BP obtained at each examination	NR	3-month outcomes: No differences in SBP or DBP between groups 8-month outcomes: SBP mean decrease 6.5 mmHg (3.2 to 9.9) in normotensive intervention group and -4.9 mmHg (0.7 to 9.2) in hypertensive intervention group vs. control (values NR), p<0.05 DBP mean decrease 4.1 mmHg (1.7 to 6.6 mmHg) in normotensive intervention group and -3.8 mmHg (0.9 to 6.6 mmHg) in hypertensive training group vs. control (values NR), p<0.05	NR	NR

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Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Howe et al, 1991[93] Fair	Mobile clinic Resting, supine BP testing 2 readings averaged and recorded, after an initial BP test	NR	No significant differences in SBP or DBP between diets	NR	NR
Sinaiko et al, 1993[94] Fair	Manometer Resting, seated BP measured twice and averaged Measured at 12, 24, and 36 months	NR	Boys: No significant effects due to intervention No significant differences in rates of increase in BP over 36 months between the 3 groups (significance level NR) Girls: The low-sodium group was the only group that had rates of increase in BP compared with placebo that were significantly greater than 0 over the 36-month study period (SBP -0.5 ± 0.4 mmHg and DBP 0.1 ± 0.5 mmHg), p<0.01 Boys: All study arms had rates of increase in BP over the 36-month study period that were significantly greater than zero (low sodium group SBP 2.2 + 0.5 mmHg and DBP 1.8 + 0.8 mmHg, p<0.0001; potassium SBP 1.9 + 0.4 mmHg and 1.6 + 0.7 mmHg, p<0.0001; placebo SBP 1.6 + 0.4 mmHg and DBP 3.2 + 0.7 mmHg, p<0.0001 Girls: Only the placebo group had rates of increase in BP over the 36-month study period that were significantly greater than zero (SBP 1.4 + 0.4 mmHg and DBP 1.8 + 0.5 mmHg), p<0.01 No other significant differences in rates of increase in BP over 36 months were found between or within the groups	NR	NR

Appendix E Table 7. Study Characteristics and Results From RCTs Assessing the Effectiveness of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 5)—Part 3

Author, Year, Quality *Study name (if applicable)*	Measurement	BP Outcomes: % Achieving <95th Percentile of BP for Age, Gender, and Height	BP Outcomes: Compared to Baseline and/or Placebo	BP Outcomes: Other	Clinical Outcomes, Including Quality of Life
Son et al, 2017[91] Fair	Resting, seated BP measured twice and averaged Measured at baseline and 12 weeks	NR	Between group difference from baseline to 12 weeks for SBP, -8.3 (SE 2.67), p<0.05 DBP was not significantly different from baseline to 12 weeks in either group Control group Mean (SE) SBP Baseline: 130.2 ± 1.4 mmHg 12 weeks: 130.6 ± 1.39 mmHg Mean (SE) DBP Baseline: 82.2 ± 2.45 mmHg 12 weeks: 82.4 ± 1.99 mmHg Exercise group Mean (SE) SBP Baseline: 134 ± 2.41 mmHg 12 weeks: 123.7 ± 2.13 mmHg p<0.05 for 12 weeks vs. baseline p<0.05 for exercise vs. control Mean (SE) DBP Baseline: 76.3 ± 3.63 mmHg 12 weeks: 79.8 ± 1.48 mmHg	NR	NR

Abbreviations: ADAPT=Dietary/Exercise Alteration Program Trial; ACEI= angiotensin-converting-enzyme inhibitor ; ARB=angiotensin receptor blocker; BP=blood pressure; B/HT=bisoprolol fumarate/hydrochlorothiazide; BMI=body mass index; CCB= calcium channel blockers ; CI=confidence interval; CINCH=Candesartan in Children with Hypertension; DASH=dietary approaches to stop hypertension; DBP=diastolic blood pressure; ER=extended release; ITT=intention to treat; KQ=key question; MRA= Mineralocorticoid receptor antagonist ; n=number; NR=not reported; PATH=Pediatric use of Amlodipine in the Treatment of Hypertension; SBP=systolic blood pressure; SD=standard deviation; SE=standard error; SeDBP= seated diastolic blood pressure ; SeSBP= seated systolic blood pressure; vs.=versus.

Appendix E Table 8. Study Characteristics and Results From RCTs Assessing the Adverse Effects of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 8)

Author, Year, Quality *Study Name (if Applicable)*	Relevancy (Best Information Reported)	Type of Study Setting Duration	Mean Age (SD)	# Randomized or Analyzed	Intervention	Adverse Events (AEs)
Pharmacologic Interventions						
Batisky et al, 2007[76] *Fair*	Inclusion criteria of primary hypertension only	RCT, 28 U.S. centers U.S.,4-week-long dose-ranging study, 52-week-long safety study	12.5 (2.8)	144 randomized in dosing study 100 analyzed in safety study	ER metoprolol succinate 0.2 to 2.0 mg/kg placebo 52-week open-label study: 25 mg or 12.5 mg once daily at investigator discretion; increase every 2 weeks until maximum of 200 mg once daily	4-week placebo-controlled dose-ranging study: 1 withdrawal due to AEs in placebo group 3 cases of fatigue with metoprolol vs. 0 in placebo (2.6% vs. 0%)
Li et al, 2004[81] *Fair*	Hypertensive (20.9% with renal etiology, otherwise not reported), or high-normal BP in the presence of associated clinical condition such as diabetes mellitus	Dose-ranging RCT; 78 clinical centers in U.S., Russia, Israel Phase A: 10-day run-in Phase B: 4-week dose ranging Phase C: 2-week withdrawal vs. placebo Phase D: 1-year open-label safety phase	12.1 (2.6)	376 screened 255 eligible 253 randomized	Fosinopril	2-week placebo-controlled phase: Incidence of AEs similar between placebo (33.9%) and combined fosinopril treatment groups (34.3%)
Sorof et al, 2002[80] *Fair*	Excluded severe hypertension and correctable secondary hypertension	RCT clinical trial from 22 centers in U.S. and Brazil 2-week run-in, 8-week titration period, 4-week dose maintenance period, 2-week tapering period	13.8 (3.1)	94 randomized (62 treatment + 32 placebo)	B/HT (n=62): B 2.5 mg/HT 6.25 mg B 5 mg/HT 6.25 mg B 10 mg/HT 6.25 mg placebo (n=32)	B/HT group had fewer overall AEs than placebo group, 33/62 (53%) vs. 24/32 (75%) (p=0.047) and fewer serious AEs, 1/62 (2%) vs.5/32 (16%) (p=0.016) Most common specific AE (B/HT group vs. placebo): headache (26% vs. 31%) infection (3% vs. 16%) rhinitis (5% vs. 9%) pharyngitis (8% vs. 6%)

Appendix E Table 8. Study Characteristics and Results From RCTs Assessing the Adverse Effects of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 8)

Author, Year, Quality *Study Name (if Applicable)*	Relevancy (Best Information Reported)	Type of Study Setting Duration	Mean Age (SD)	# Randomized or Analyzed	Intervention	Adverse Events (AEs)
Trachtman et al, 2003[78] *Fair*	Excluded secondary hypertension	RCT Clinical trial at 30 sites in the U.S. 1 to 3-week screening period, 2- to 3-week dose titration period, 3-week maintenance study	12.1 (2.7)	133 randomized	ER felodipine 2.5 mg (n=33), 5 mg (n=340, or 10 mg (n=31), titrated to target dose over 2-3 weeks, depending on dosage Placebo (n=35)	1 withdrawal due to "heart racing" in felodipine group; heart rate was 96 bpm and ECG normal Overall AEs (placebo, felodipine ER 2.5 mg, 5.0 mg, and 10 mg groups): 66%, 64%, 56%, and 77% (p not reported) Most common AEs across all groups were headaches (33%), respiratory infections (12%), and nausea (10%)
Trachtman et al, 2008[77] *Fair*	Excluded secondary hypertension; Other hypertensives, except for other angiotension receptor blockers, were permitted	RCT clinical trial at 42 sites in U.S. and Europe 4-week trial and 1-year open-label study	% age >12 years: 70.8%	240 randomized	4-week trial: Candesartan doses 2, 8, and 16 mg/day for those <50 kg, and 4, 16, and 32 mg/day for those >50 kg Placebo open-label study: Candesartan at 4 or 8 mg/day to start, but later adjusted to control BP	3/240 patients discontinued in the 4-week trial due to AEs (no group data reported) Most common AEs: headache, upper respiratory infection, dizziness, cough, and sore throat (no data reported)
Wells et al, 2010[79] *Fair*	Excluded secondary Hypertension	RCT clinical trial at 16 centers in U.S., Brazil, and Mexico 4 weeks, after 2-week washout period	14 (2.5)	115 enrolled 77 randomized	Telmisartan low dose (1 mg/kg/day) (n=30) and high dose (1 mg/kg/day titrated up to 2 mg/k/day after 1 week) (n=31) Placebo (n=16)	Any adverse event: High-dose patients: 41.9% Low-dose patients: 41.7% Placebo patients: 31.3% (significance not reported) 2 patients discontinued due to AEs, both in the high dose group: 1 patient who experienced a serious AE (near syncope and moderate increase in blood urea nitrogen and serum creatinine) who received an excessive dose in error; and 1 patient due to moderate-intensity dizziness, weakness, and headache

Appendix E Table 8. Study Characteristics and Results From RCTs Assessing the Adverse Effects of Treatment of Abnormal Blood Pressure in Children and Adolescents (KQ 8)

Author, Year, Quality *Study Name (if Applicable)*	Relevancy (Best Information Reported)	Type of Study Setting Duration	Mean Age (SD)	# Randomized or Analyzed	Intervention	Adverse Events (AEs)
Pharmacologic Intervention with Lifestyle Intervention						
Berenson et al, 1983[89] *Fair*	BP >90th percentile for height, control group with BP <80th percentiles and the 50 to 60th percentile for comparison (based on centiles derived from study) Excluded children with evidence of secondary hypertension	"Close to clinical trial" School based, 6 months	12	150 (50 high BP treatment group, 50 high BP comparison group, 50 medium BP comparison group)	Group A: Propranolol 20 mg/day for children <40kg, 40 mg/day for those >40 kg + Chlorthalidone 6.25 mg per day for children <40 kg, 12.5 mg/day for those >40 kg + nutrition education and promotion of dietary modification to children and parents Group B (high BP elevation at baseline): No treatment Group C (medium BP elevation at baseline): No treatment	AEs reported as very low incidence with no major complications (no detailed data reported); 1 temporary withdrawal from active treatment due to nightmares

Abbreviations: AE=adverse events; bpm=beats per minute; BP=blood pressure; B/HT=bisoprolol fumarate/hydrochlorothiazide; ECG=electrocardiograph; ER=extended release; KQ=key question; RCT=randomized, controlled trial; SD=standard deviation; U.S.=United States; vs.=versus.

Appendix F Table 1. Studies Included in 2013 AHRQ Report and Excluded From This Review

Key Question	Author (Year)	Exclusion Reason
KQ 2 (Diagnostic Test Accuracy)	Fixler & Laird (1983)[51] Stergiou (2008)[52]	Wrong comparator (two additional hypertension measurements) Poor quality (excluded participants with very high blood pressure during the course of the study)
KQ 3 (Harms of Screening)	Stenn (1981)[53]	Wrong population (control group was students who were screened but normotensive)
KQ 5 (Effectiveness of Interventions)	[142]Gregoski (2011)[54, 86]	Wrong population (needed a resting SBP between the 50th and 95th percentiles)
KQ 6 (Intermediate Outcomes)	Li (2010)[86]	Wrong comparator (dose-ranging studies with no placebo control group)
KQ 8 (Harms of Treatment)	Flynn (2004)[142] Hazan (2010)[85] Shahinfar (2005)[84] Soffer (2003)[83] Wells (2002)[82] Li (2010)[86]	Wrong comparator (dose-ranging studies with no placebo control group) Wrong comparator (dose-ranging studies with no placebo control group) Wrong comparator (dose-ranging studies with no placebo control group) Wrong comparator (dose-ranging studies with no placebo control group) Wrong comparator (dose-ranging studies with no placebo control group) Wrong comparator (dose-ranging studies with no placebo control group)

Abbreviation: KQ=key question; SBP=systolic blood pressure.