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Screening for Hypertension in Children and Adolescents to Prevent Cardiovascular Disease: Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Hypertension in children can be associated with adverse health outcomes and may persist into adulthood, where it presents a significant personal and public health burden. Screening asymptomatic children has the potential to detect hypertension at earlier stages, so that interventions can be initiated which, if effective, could reduce the adverse health effects of childhood hypertension in children and adults.

Purpose: To assess the effects of screening for hypertension in asymptomatic children and adolescents to prevent cardiovascular disease.

Methods: We searched the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews (through July 2012) and MEDLINE (1946–July 9, 2012) and manually reviewed reference lists of included studies. Citations were independently reviewed by two investigators, and data extraction performed by one investigator and checked by a second for accuracy. We included studies of screening for hypertension in asymptomatic children and studies of benefits and harms of treatments for children with hypertension. Diagnostic accuracy studies were included if they used a reference standard and allowed calculation of sensitivity and specificity. We excluded studies focusing on secondary hypertension.

Results: No studies evaluated the effect of screening asymptomatic children for hypertension on subsequent health outcomes, including onset of hypertension. Two studies that assessed accuracy of screening tests for elevated blood pressure found moderate sensitivities (0.65 and 0.72) and specificities (0.75 and 0.92) and low positive predictive values (0.37, 0.17). The association between elevated blood pressure or hypertension in childhood and hypertension in adulthood was assessed in 10 studies, with most studies finding a small but significant association. Seven fair-quality studies found drug interventions were effective at lowering blood pressure after 4 weeks, based on the proportion achieving normotensive status and/or mean reductions in blood pressure. One trial of a drug combined with lifestyle modifications found lower mean blood pressures at 30 months, and one trial of increased exercise found lower mean blood pressures at 8 months, whereas other lifestyle trials found no differences. Of 13 studies assessing harms of interventions, only one study found that adverse event rates were significantly lower for those in the intervention group; all other studies found no difference in adverse events.

Conclusions: Studies are needed to assess whether screening for hypertension in children and adolescents reduces adverse health outcomes or delays the onset of hypertension. Blood pressure screening may be effective at identifying children with hypertension, though evidence is limited and false-positive rates were high. The presence of hypertension in childhood is associated with hypertension in adults, but with limited evidence available for its association with end-organ damage markers in adults. Drug interventions for hypertension may be effective at lowering blood pressure with few serious side effects; however, studies of longer duration are needed to confirm results from short-term studies. Evidence on the effectiveness of childhood combination drug and lifestyle interventions and lifestyle-only interventions is sparse and mixed, with most studies showing no sustained reduction in blood pressure in childhood. Studies are needed to assess whether treating hypertension in childhood affects subsequent intermediate or clinical outcomes in adulthood.

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CHAPTER 1. INTRODUCTION

Purpose and Prior USPSTF Recommendation

The purpose of this systematic evidence review is for the U.S. Preventive Services Task Force (USPSTF) to update its recommendation on screening for high blood pressure in children and adolescents to prevent cardiovascular disease. In 2003, the USPSTF found poor evidence that routine blood pressure measurement accurately identifies children and adolescents at increased risk for cardiovascular disease, and poor evidence to determine whether treatment of elevated blood pressure in children or adolescents decreases the incidence of cardiovascular disease. As a result, the USPSTF could not determine the balance of benefits and harms of routine screening for high blood pressure in children and adolescents, which resulted in an I recommendation.[1, 2]

Recent data from the National Health and Nutrition Examination Survey suggest that mean blood pressure levels are rising steadily in children,[3] as is the prevalence of childhood hypertension.[4] This may be due to the increase in the prevalence of obesity and overweight among children,[4, 5] which is highly correlated with high blood pressure (see Contextual Question 1 below). Screening of asymptomatic children has the potential to detect hypertension at earlier stages, so that interventions can be initiated which, if effective, could reduce the adverse health effects of childhood hypertension in both childhood and adulthood, including cardiovascular disease and end-organ damage.[5] This report summarizes recent and older evidence on screening and diagnostic accuracy of screening tests for high blood pressure in children, the effectiveness and harms of treatment for screen-detected, primary childhood hypertension, and the tracking of hypertension from childhood to adulthood.

Condition Definition

The National High Blood Pressure Education Program (NHBPEP) and the National Heart, Lung, and Blood Institute (NHBLI) define prehypertension and hypertension in children based on centiles according to age, height, and sex.[6-8] Prehypertension is defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP) readings at or above the 90th percentile but less than the 95th percentile. Hypertension is defined as SBP or DBP readings at or above the 95th percentile. Hypertension is categorized as stage 1 (SBP or DBP from the 95th to 99th percentile, plus 5 mm Hg) or stage 2 (SBP or DBP above the 99th percentile, plus 5 mm Hg).[7]

The NHBPEP provides detailed guidance on optimal blood pressure measurement techniques,[6] including recommendations on type of sphygmomanometer and appropriate cuff size. Blood pressure measurement should be performed in a controlled environment after 5 minutes of rest, with the child or adolescent seated with their right arm supported at heart level. Screening programs need to ensure that children and adolescents with elevated blood pressure readings have followup measurements to confirm (or exclude) the presence of hypertension. The NHBPEP also recommends that measurements should be obtained over time at multiple clinic visits, and at least three consistent, elevated readings are required for a diagnosis of prehypertension or hypertension.[6] Children whose blood pressure is elevated on at least three

occasions need to be assessed by a health care provider regarding the need for further investigations and to discuss management strategies.

Prevalence and Burden of Disease

The prevalence of hypertension in the general (asymptomatic) population of children is between 1 and 5 percent,[9, 10] while children with a higher body mass index (BMI) (>95th percentile) have a higher prevalence (about 11%).[11] Younger children with hypertension are more likely to have an underlying condition causing the hypertension (i.e., secondary hypertension, see Contextual Question 2, below), while older children and adolescents are more likely to have primary hypertension.[12, 13]

The prevalence of hypertension in children in the United States has increased by about 1 to 2 percent over recent decades,[4] and longitudinal population-based studies of blood pressure data between 1963 and 2002 suggest that the increase is largely attributable to the rise in childhood obesity.[4, 14] In addition, some authors have suggested that a significant proportion of children with hypertension are not currently diagnosed.[15, 16]

Childhood hypertension, particularly stage 2, is thought to cause damage to end-organs adversely affected by elevated blood pressure, mainly the cardiovascular, renal, and cerebrovascular systems. Children with stage 2 hypertension usually require drug interventions to reduce the risk of end-organ damage.[7]

Etiology and Natural History

Hypertension can be secondary to an underlying disorder or a primary condition (primary hypertension).

Primary hypertension has been linked with numerous potential risk factors, including BMI, parental history of hypertension, nutrition, race, and sex (see Contextual Question 1, below). The proportion of children with primary hypertension whose blood pressure subsequently returns to normal without treatment or other changes in lifestyle is unknown. However, a proportion of children who have elevated blood pressure in childhood will continue to experience elevated blood pressure in adulthood, a phenomenon known as tracking (see Key Question 3, below).

Secondary hypertension can be caused by a large number of underlying conditions in children, most commonly renal parenchymal disease (e.g., glomerulonephritis, renal scarring due to reflux nephropathy, polycystic kidney disease, and chronic renal failure) or renovascular disease (e.g., fibromuscular dysplasia.).[13, 17] Less common causes of secondary hypertension in children include aortic coarctation (10% to 20%) and endocrine disorders (e.g., pheochromocytoma, hyperthyroidism) or are related to medications (e.g., oral contraceptives in adolescents, sympathomimetic drugs, dietary supplements).[13, 17] In children with secondary hypertension, elevated blood pressure is unlikely to be the only clinical manifestation of the underlying disorder, and the type of treatment is directly related to the type of hypertension (and in some

cases, correction of any underlying disorder). In some cases, treatment of the underlying cause may allow blood pressure levels to return to normal levels, while in other cases, elevated blood pressure may track into adulthood.

The clinical sequelae of elevated blood pressure are either due to the effects of sustained blood pressure over a longer period of time or, less commonly, to the presence of extremely high levels of blood pressure for a short period (known as hypertensive emergency). Sustained elevation of blood pressure in adults is an established risk factor for multiple conditions, including cardiovascular and cerebrovascular disorders and renal impairment. However, in children these are remote events, and therefore intermediate measures of target end-organ damage have been proposed, including physical alterations to the structure of vascular walls (e.g., early atherosclerosis, thickening of arteries) and the heart (e.g., increase in left ventricle mass) and altered renal function (e.g., microalbuminuria). The evidence for the independent causal effect of hypertension (over and above obesity, for example) on several of these markers is growing but remains unclear, as does the extent to which these regress when levels of blood pressure are reduced with antihypertensive intervention.[18-23]

The clinical sequelae of extremely high levels of blood pressure elevation over even short periods of time are well known, and include hypertensive encephalopathy, renal impairment, cardiac failure, and cerebrovascular accidents. For this reason, very high levels of blood pressure constitute an urgent situation and may require immediate intervention to correct underlying causes and to lower blood pressure to avoid end-organ damage.

Rationale for Screening/Screening Strategies

The rationale for screening children and adolescents for elevated blood pressure is that if hypertension can be identified at an early stage, then interventions could be initiated to decrease the level of blood pressure in affected individuals, decreasing the rate of progression of hypertension from children to adults, and thus reducing the personal and public health burden of hypertension[24] and the resulting cardiovascular outcomes. In addition, treatment may be beneficial to children during childhood. Because hypertension is often asymptomatic, screening identifies children with elevated blood pressure who may not otherwise have been diagnosed. The same screening tests are used to identify both primary and secondary hypertension.

There are a number of strategies that could be used to screen children and adolescents for elevated blood pressure, including measurement of blood pressure during routine visits to health care facilities, such as for well-child examinations and preparticipation physicals for sports, or during acute-care appointments. Other strategies could include school-based screening programs or screening in other community settings.

Interventions/Treatment

Stage 1 hypertension in children is treated with drug and lifestyle interventions, although drugs are not recommended as first-line therapy.[6] Lifestyle interventions for hypertension include

weight reduction in children who are overweight or obese coupled with increased physical activity and limited salt intake, as well as education and counseling. The NHBPEP recommends drug treatments for children with stage 2 hypertension or for hypertension that does not respond to lifestyle modification.[6] Numerous drug interventions have been approved to treat hypertension in children, including diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and vasodilators (**Table 1**). Interventions for secondary hypertension depend upon the underlying cause and therefore vary greatly.

Current Clinical Practice

Current screening practice for elevated blood pressure typically involves measurement of blood pressure in office-based health care settings as part of well-child or sports preparticipation examinations, often in conjunction with other vital signs and growth parameters. NHBPEP centile charts are then used to interpret SBP and DBP levels and categorize them as normal, prehypertension, or hypertension based on a child's age, height, and sex. A simplified version has been proposed that has only one threshold value of abnormal SBP and DBP by sex, for each year of the child's life from age 3 to 18 years.[25]

As stated earlier, the NHBPEP recommends repeating blood pressure measurements on two more occasions in children in whom a single elevated SBP or DBP reading has been noted. This is to ensure that subsequent clinical actions are taken based on blood pressure values that are truly elevated, rather than values that are falsely elevated due to either measurement error or anxiety and discomfort in the child (known as "white coat hypertension"). Compliance with this practice in clinical settings in the United States is not known. Based on a cohort study of 14,187 children seen in outpatient departments in the United States, of whom 507 (3.6%) had elevated blood pressures, only one quarter of children (131 [26%]) had a diagnosis of hypertension documented in their electronic health record, suggesting that repeat blood pressure measures had not been obtained in the majority to confirm or exclude hypertension.[16]

The subsequent clinical workup of children in whom hypertension has been diagnosed aims to identify possible underlying causes of hypertension, detect comorbid conditions, and determine the presence of any target end-organ damage. The NHBPEP recommends a structured approach to identifying possible underlying causes, with a workup that includes history, physical examination, laboratory testing, and imaging. A more detailed search for underlying causes and evaluation for end-organ damage should be used in children who are at greatest risk of secondary hypertension, including those in younger age groups and those with stage 2 hypertension.[7] The initial management of children with confirmed hypertension is directed at identifying and correcting any underlying causes and controlling or monitoring blood pressure. Clinical decisions regarding initiation of therapy depend on the level of blood pressure, presence of end-organ damage, comorbid conditions, and associated risk factors. Lifestyle intervention options including alterations to diet, exercise, and weight loss are recommended as the initial approach in most children. Several classes of drugs are approved for treatment of hypertension in children. Drugs are usually initiated in children with symptomatic hypertension, end-organ damage, stage 1 hypertension that does not respond to nondrug intervention, and stage 2 hypertension.

Recommendations of Other Groups

Numerous organizations, including the American Heart Association,[26] the NHBPEP,[6] and the NHBLI's Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[8] recommend routine screening of asymptomatic children for high blood pressure during office visits beginning at age 3 years, and confirmation with at least two subsequent measures prior to a diagnosis of hypertension.[6, 8] The American Academy of Family Physicians contend that there is insufficient evidence for or against routine screening for high blood pressure in children and adolescents.[7] The American Academy of Pediatrics does not have a specific policy statement on screening asymptomatic, general-risk children and adolescents for hypertension.

CHAPTER 2. METHODS

Key Questions and Analytic Framework

Using the methods of the USPSTF, which are fully described in **Appendix A**, and with the input of members of the USPSTF, we developed an analytic framework (**Figure**) and key questions to guide our literature search and review.

Key Questions

1. Is screening for hypertension in children/adolescents effective in delaying the onset of or reducing adverse health outcomes related to hypertension?
2. What is the diagnostic accuracy of screening tests for elevated blood pressure in children/adolescents?
3. What is the association between hypertension in children/adolescents and hypertension and other intermediate outcomes in adults?
4. What are the adverse effects of screening for hypertension in children/adolescents, including labeling and anxiety?
5. What is the effectiveness of drug, nondrug, and combination interventions for treating primary hypertension in children/adolescents?
6. What is the effectiveness of drug, nondrug, and combination interventions initiated for the treatment of primary hypertension in children/adolescents for reducing blood pressure and other intermediate outcomes in adults?
7. What is the effectiveness of drug, nondrug, and combination interventions initiated for the treatment of primary hypertension in children/adolescents for reducing adverse health outcomes in adults related to primary hypertension?
8. What are the adverse effects of drug, nondrug, and combination interventions for treating primary hypertension in children/adolescents?

Three contextual questions were also requested by the USPSTF to help inform the report. Contextual questions were not reviewed using systematic review methodology.

Contextual Questions

1. What are the main risk factors for primary hypertension in children/adolescents?
2. What is the prevalence of secondary hypertension in asymptomatic children/adolescents in primary care settings?
3. What are the optimal ages at which to initiate screening and optimal time intervals at which to repeat screening children/adolescents for hypertension?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews (through July 2012) and MEDLINE (1946–July 9, 2012) for relevant studies

and systematic reviews. Complete search strategies are described in **Appendix A1**. We also manually reviewed reference lists of included studies.

Study Selection

We selected studies on the basis of inclusion and exclusion criteria developed for each key question (see **Appendix A2** for details). All citations identified through searches and other sources were imported into EndNote v.X3 and were independently reviewed by two investigators for inclusion/exclusion. Discrepancies regarding inclusion/exclusion of full-text papers were resolved through consensus. We included studies of screening for hypertension in asymptomatic children and adolescents and studies of benefits and harms of interventions for childhood hypertension. For studies of diagnostic accuracy, we required that studies include a reference standard comparison and provide adequate data to reproduce 2 x 2 tables, if not reported. Longitudinal cohort studies were included to address the tracking of hypertension from childhood to adulthood. We excluded studies of interventions for treatment of obesity and lipid disorders in children, as these populations are covered by other USPSTF publications.[27, 28] We also excluded studies focusing on secondary hypertension, both the treatment of elevated blood pressure in these patients and the treatment of the underlying conditions. In addition, we excluded studies with total populations of less than 30 participants. **Appendix A3** shows the results of our literature search and selection process. **Appendix A4** shows studies that were excluded at the full-text level with reasons for exclusion.

Data Abstraction and Quality Rating

One investigator abstracted details about the patient population, study designs, testing methods, analysis, followup, and results, and a second investigator checked data abstraction for accuracy. For studies of interventions, we also abstracted data on dose in drug studies. By using predefined criteria developed by the USPSTF[29] and others for additional criteria for diagnostic accuracy studies,[30] two investigators rated the quality of studies as good, fair, or poor and resolved discrepancies by consensus (**Appendix A5**).

Data Synthesis

We assessed the overall strength of the body of evidence for each key question as good, fair, or poor using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results among studies, and directness of evidence.[29] The limited number of studies and differences in study design and methods precluded us from conducting meta-analyses. Results are presented in narrative format and, where possible, include ranges and 95 percent confidence intervals (CIs). For studies of diagnostic accuracy, we constructed 2 x 2 tables and calculated sensitivity, specificity, predictive values, and 95 percent CIs, if not already reported. Pooling of results from diagnostic accuracy studies was also not possible due to heterogeneity across studies.

External Review

This draft report was reviewed by content experts, USPSTF members, Agency for Healthcare Research and Quality (AHRQ) Project Officers, and AHRQ's collaborative partners (**Appendix A6**).

CHAPTER 3. RESULTS

Key Question 1. Is Screening for Hypertension in Children/Adolescents Effective in Delaying the Onset of or Reducing Adverse Health Outcomes Related to Hypertension?

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.

Key Question 2. What Is the Diagnostic Accuracy of Screening Tests for Elevated Blood Pressure in Children/Adolescents?

Summary

Two studies provided evidence on the sensitivity and specificity of screening tests for elevated blood pressure. The studies employed different reference standards, but reported similar sensitivities (0.65 and 0.72) and specificities (0.75 and 0.92). Positive predictive values for both studies were low (0.37 and 0.17). Twelve other studies that did not meet inclusion criteria due to the inability to construct 2 x 2 tables and/or failure to apply a reference standard reported a wide range of positive predictive values (0.04 to 0.53).

Evidence

We identified one fair-quality study that provided evidence on the diagnostic accuracy of clinic blood pressure measurements compared with ambulatory monitoring (**Table 2**, **Appendixes B1** and **B2**).[31] One hundred and five Greek children and adolescents (mean age, 13 years) who were referred to a specialty hypertension clinic were enrolled in a prospective study that compared the diagnostic accuracy of office, home, and ambulatory blood pressure measurement. For the purposes of this review, only office-based blood pressure was included as the index test, as home blood pressure monitoring is outside the scope of this report. Office blood pressure was measured three times at each of two clinic visits, and hypertension was diagnosed in those children with readings above the 95th percentile, according to published NHBPEP normative values.[6] This was compared with a reference standard of 24-hour ambulatory monitoring at 20-minute intervals. Hypertension was again diagnosed in children with readings above the 95th percentile as a result of ambulatory blood pressure measurement, although authors used different normative values for ambulatory blood pressure measurement than the NHBPEP standards.[32] Compared with ambulatory measurement, office-based blood pressure measurement had a sensitivity of 0.65 (95% CI, 0.45 to 0.80) and a specificity of 0.75 (95% CI, 0.63 to 0.84). The corresponding positive predictive value was 0.37 (95% CI, 0.28 to 0.47) and the negative

predictive value was 0.63 (95% CI, 0.53 to 0.72). This study has some important limitations. All of the participants were referred for evaluation at a specialty clinic, and thus may not be representative of a true screened population of asymptomatic children. In addition, the use of different normative values according to testing method is a potential source of bias.

A second, fair-quality study selected a random sample of 10 percent of children whose initial (i.e., screening) blood pressure test was negative and who went on to have further blood pressure tests to assess if they were true negatives or false negatives (**Table 2**, **Appendixes B1** and **B2**).[33] Among tenth grade students (n = 9,017), the sensitivity and specificity of initial elevated blood pressure for persistent elevation of blood pressure were 0.72 (95% CI, 0.65 to 0.78) and 0.92 (95% CI, 0.91 to 0.92) respectively, but positive predictive value was limited at 0.17 (95% CI, 0.15 to 0.20). The school-based setting for this study may be useful for screening interventions, but the authors' use of a sample of children screening negative rather than the entire population of children screening negative to create the 2 x 2 tables may have caused bias in the diagnostic accuracy values derived from this study.

We identified 12 additional studies that compared one or more index measurements of blood pressure with subsequent reference measurements but failed to apply the reference tests to participants who initially screened negative (**Appendix B3**).[34-45] These studies also did not meet our inclusion criteria for this key question, as they did not provide enough data to recreate 2 x 2 tables (or calculate sensitivity and specificity). Most studies were of school-based screening and were highly variable in defining a positive screening test. For example, some used a conventional cut-off point of greater than the 90th or 95th percentile based on NHBEP centiles to define hypertension, but others used cohort-specific data to define their own normative values.[35, 36] Others used a lower threshold to define a positive screen (e.g., blood pressure greater than the 70th percentile[44]) or used absolute SBP and DBP values rather than percentiles to define a positive screening test.[38, 39, 42, 43] Positive predictive values among the studies ranged from 0.04 to 0.53. The reason for this heterogeneity is unclear and did not appear to be related to the populations, prevalence of hypertension, method of testing, or thresholds used to define positive tests. Considered as a whole, only approximately one quarter (median positive predictive value, 0.26) of children and adolescents who initially screened positive were subsequently diagnosed with hypertension.

Key Question 3. What Is the Association Between Hypertension in Children/Adolescents and Hypertension and Other Intermediate Outcomes in Adults?

Summary

Longitudinal studies provided some evidence on the association between elevated blood pressure or hypertension in childhood and adulthood (seven studies), carotid intima media thickness (two studies), and microalbuminuria (one study). The studies used different thresholds for defining elevated blood pressure and hence hypertension in childhood, and different definitions of hypertension in adults. The sensitivities and specificities of elevated blood pressure or hypertension from childhood to adult hypertension ranged from 0 to 0.66 and 0.77 to 1,

respectively. Positive predictive values (i.e., the probability of adult hypertension given the presence of hypertension in childhood) ranged from 0.19 to 0.65. Four studies reported significant associations between elevated blood pressure in childhood and hypertension in adults, with odds ratios (ORs) ranging from 1.1 to 4.5 and relative risks from 1.5 to 9. The two studies that reported associations between childhood hypertension and carotid intima media thickness in adulthood provided conflicting findings. One found a very weak but not independently significant association, whereas the other found no significant association in 12- to 17-year-olds. Childhood hypertension was significantly associated with microalbuminuria in black adults but not white adults in a single study. We found no evidence for associations between hypertension in childhood and other intermediate or final hypertension-related outcomes in adulthood (e.g., left ventricular hypertrophy and other cardiovascular outcomes).

Evidence

We identified 10 studies that reported on the presence of hypertension (or elevated blood pressure) in children and the presence of hypertension or other intermediate outcomes in adulthood (**Table 3**, **Appendix B4**).[24, 46-54] We did not formally quality-rate these studies, though characteristics related to study quality are included in **Table 3**. Many of the studies had methodological shortcomings, making interpretation and direct comparisons of results difficult. In some studies, it was unclear if blood pressure thresholds in childhood were cohort-specific or based on standardized values.[24, 46, 49, 51, 52, 54] The definition of hypertension in childhood varied among the studies, with threshold values ranging from >80th percentile to >95th percentile, while three of the studies did not provide a definition of childhood hypertension.[47, 52, 54] The studies drew data from five cohorts: the Bogalusa Heart Study,[46, 49, 52, 54] the Muscatine Study,[51] the Fels Longitudinal Study,[24, 47] the Young Finns Study,[50, 53] and a cohort of children in Boston.[48] The studies reported either the association or diagnostic value of elevated childhood blood pressure in predicting hypertension,[24, 46-48, 50, 51, 54] carotid intima media thickness,[52, 53] or microalbuminuria[49] in adults.

Elevated blood pressure or hypertension. The most direct evidence on presence of hypertension in childhood and incidence of hypertension in adulthood comes from analysis of data from the Cardiovascular Risk in Young Finns Study.[50] This well-conducted, longitudinal study enrolled 3,596 children in Finland ages 3 to 18 years and provided followup for 2,204 participants at 30 to 45 years. Prehypertension or hypertension—defined according to NHBPEP charts—at ages 3 to 9 years was significantly predictive of hypertension in adulthood in both men (OR, 2.8 [95% CI, 1.5 to 5.1]) and women (OR, 2.4 [95% CI, 1.1 to 5.2]). Results were similar for measures in older children and adolescents (ages 12 to 18 years). A second, smaller (n=493) analysis of data from the Fels Longitudinal Study used age- and sex-based least squares means (rather than standardized charts) to retrospectively determine the presence of hypertension in childhood and its association with hypertension in adulthood.[24] Results from this study were consistent with the Finnish study, finding that children with blood pressure readings that exceeded study-determined thresholds were significantly more likely to be hypertensive in adulthood. ORs ranged from 3.5 to 3.8 for boys ages 5 to 13 years and from 2.7 to 4.5 for girls ages 5 to 18 years. The exception is for boys ages 14 to 18 years, in whom high blood pressure was not significantly predictive of hypertension in adulthood (OR, 1.1 [95% CI, 0.5 to 2.4]).[24]

Studies used a variety of thresholds to differentiate between normal and elevated blood pressure in childhood and the accuracy of these measures in predicting high blood pressure or hypertension in adulthood. One study of 317 children with blood pressure measures at age 10 years and followup at age 20 years found blood pressure cut-offs between >75th percentile and >99th percentile in childhood provided moderate sensitivity (up to 0.66) and high specificity (up to >0.99), as well as moderate positive predictive value (up to 0.65) for predicting blood pressure >90th percentile in adulthood.[48] Overall, positive predictive values for blood pressure >90th percentile in adulthood ranged from 0.21 (in men) and 0.19 (in women) to 0.58 and 0.65, depending on the cut-off used in childhood in this study. In comparison, a study of data from the Bogalusa Heart Study (a longitudinal study of Louisiana school children)[46] used a cohort-specific cut-off of >80th percentile to define childhood hypertension. An earlier analysis of Bogalusa Heart Study data found that using a blood pressure cut-off of >80th percentile in children provided the best balance of sensitivity and specificity for predicting hypertension in adulthood compared with higher thresholds, though sensitivity was low (range, 0.0 to 0.33 for SBP and DBP) regardless of cut-off.[54]

Three studies reported the incidence of elevated blood pressure in childhood and subsequent risk of hypertension in adulthood.[46, 47, 51] An analysis of Bogalusa Heart Study data found that after 15 years of followup, children (age range, 5 to 14 years; mean age not reported) in the highest quintile of SBP and DBP at baseline were about three times more likely to be hypertensive as adults when compared with children in the lower three quintiles (risk ratio, 3.6 [95% CI, 2.5 to 5.1] and 2.5 [95% CI, 1.8 to 3.6], respectively).[46] Results from two other studies were consistent, finding that higher SBP or DBP in childhood increased risk of hypertension in adulthood, though one study compared a higher with lower DBP at baseline and incidence of hypertension in adulthood,[47] and the other reported absolute rates of elevated blood pressure in adulthood among children with blood pressure readings above the cohort-specific 90th percentile.[51]

Other intermediate outcomes. Two studies reported on incidence of carotid intima media thickness in adulthood and its relationship to blood pressure in childhood.[52, 53] One study (n=3,596) found that SBP >80th percentile in adolescence was very mildly associated with presence of carotid intima media thickness in adulthood (regression coefficient, 0.013; $p<0.001$), though its clinical significance is unclear.[53] The second study (n=486) found no association between an undefined childhood SBP risk and incidence of carotid intima media thickness in adulthood (highest quintile vs. lower three quintiles: OR, 1 [95% CI, 0.8 to 1.25]).[52]

A third study of 2,122 children from the Bogalusa Heart Study examined the association of childhood blood pressure (mean age, 10 years) with microalbuminuria in adulthood (mean age, 26 years).[49] In black participants, regression modeling found that SBP, DBP, and the annual change in SBP and DBP from childhood to adulthood were independent predictors of development of microalbuminuria. However, neither SBP, DBP, nor annual changes in these measures were significantly associated with microalbuminuria in white participants.

We identified no studies analyzing associations between elevated blood pressure or hypertension in childhood and other intermediate outcomes in adulthood (e.g., left ventricular hypertrophy and other cardiovascular outcomes).

Key Question 4. What Are the Adverse Effects of Screening for Hypertension in Children/Adolescents, Including Labeling and Anxiety?

We identified one good-quality study meeting inclusion criteria for Key Question 4.[56] In this comparative, prospective study in Ontario, Canada, 85 children ages 10 to 18 years with SBP at or above the 85th percentile for their age and sex were enrolled. These children were identified as having elevated blood pressure after repeat screening of a population-based cohort. Eighty-five age- and sex-matched children from the same community were identified as controls. Rates of school absenteeism did not change significantly in the year after the children were identified as having elevated blood pressure compared with preidentification rates and also when compared with the control group (both total and illness days increased in both groups; $p>0.05$ for between-group differences). Personality testing (assertiveness and type A characteristics) of a subset of the study subject pairs did not predict change in absenteeism. No other measures of adverse effects associated with screening were reported in this study.

Key Question 5. What Is the Effectiveness of Drug, Nondrug, and Combination Interventions for Treating Primary Hypertension in Children/Adolescents?

Summary

Fourteen randomized, controlled trials (RCTs) of interventions for hypertension in children and adolescents met inclusion criteria, including seven drug trials, one trial of a drug combined with a lifestyle intervention, and six trials of lifestyle interventions. All of the drug trials, none of which examined the same drugs, reported short-term reductions in the absolute level of blood pressure and/or increased proportions of children achieving blood pressure <95th percentile for their age, sex, and height. The antihypertensive effects were of variable magnitude and not consistently present for a given agent, varied for SBP and DBP, and were not always significantly different from placebo (or this difference was not reported). None of the drug trials were longer than 4 weeks in duration. The one trial of a drug combined with a lifestyle modification in a school setting showed long-term effectiveness, but was an intensive intervention. Lifestyle modification was largely ineffective among the trials, although one school-based trial of increased number of physical education classes demonstrated statistically significant reductions in blood pressure when compared with untreated controls. A full review of the effectiveness of treatment for the individual causes of secondary hypertension is beyond the scope of this review; therefore, this key question focuses on the treatment of primary hypertension.

Evidence

Fourteen RCTs (in 15 publications) of treatment for hypertension in children and adolescents met inclusion criteria (**Appendix B5**),[35, 57-70] including seven drug trials (**Table 4**), one trial of a

drug combined with a lifestyle intervention (two publications; **Table 5**), and six trials of lifestyle interventions (**Table 6**). We did not identify any observational studies that met our inclusion criteria. All trials were rated fair-quality; however, the majority of the studies were on the lower end of the continuum of fair-quality studies, mainly due to inadequate reporting of randomization, concealment of treatment allocation, and lack of information about blinding of outcome assessors and/or care providers (**Appendix B6**). None of the trials had a fatal flaw that would downgrade them to poor quality. The proportion of children with primary hypertension reported in the included studies ranged from 31[61] to 56 percent.[65] Other included studies attempted to exclude participants with secondary hypertension, but most failed to report the proportion of participants with primary or secondary hypertension.[35, 57, 58, 60, 63, 64, 66, 68-70]

Table 7 summarizes the effect of treatment on blood pressure as the mean difference from baseline and/or placebo, as reported, for all intervention types.

Drug interventions. The seven included trials of drug interventions all examined different drugs (**Tables 4** and **7**; **Appendix B5**), therefore meta-analysis was not possible. Drugs included extended-release metoprolol succinate,[57] candesartan,[69] telmisartan,[70] amlodipine,[61] extended-release felodipine,[68] eplerenone,[65] and bisoprolol fumarate/hydrochlorothiazide combination.[67] The included studies typically involved two phases, an initial RCT lasting up to 4 weeks in which the active drug (in different doses) was compared with placebo, followed in some trials by a longer period of up to 1 year of observation providing only safety data. None of the studies provided outcomes of efficacy beyond 4 weeks. The number of participants in the studies ranged from 77 to 304, and all studies were conducted in clinic settings in various countries; most, but not all, included at least one site in the United States.

Percentage achieving normotensive blood pressure. Overall ranges for children achieving normotensive status (based on varying definitions) ranged from 15 to 86 percent in patients taking drug treatments and 11 to 48 percent in patients taking placebo. The following studies reported the percentages of participants achieving blood pressure <95th percentile (or the <90th percentile[68]) for their age, sex, and height: extended-release metoprolol succinate, 46 percent (compared with placebo, 26%; p values not reported);[57] amlodipine: SBP, 33.3 percent, DBP, 45 percent for primary hypertension (compared with placebo: SBP, 29.4%, DBP, 47.6%; p-values not reported);[61] 15.2 to 19.4 percent for various doses of extended-release felodipine (compared with 11.4% for placebo; p-values not reported);[68] candesartan, 54 to 65 percent for various doses (compared with placebo, 33.3%; $p<0.05$);[69] and telmisartan, 79.2 to 85.7 percent for high dose (compared with placebo, 27.3% to 33.3%; $p=0.10$) and 50.0 to 68.2 percent for low dose (compared with placebo but values not reported; $p=0.325$), depending on the child's age.[70]

Mean reductions in blood pressure. With the exception of one outlier, the results of the included studies showed significant reductions with some doses of some drugs in mean SBP ranging from 2 to 10 mm Hg, and from 0.4 to 8 mm Hg mean DBP, from baseline to followup. Similarly, SBP reductions were 0 to 9 mm Hg and DBP reductions were 0.5 to 10 mm Hg between intervention and placebo groups. One study of eplerenone 50 mg per day reported a small mean increase in SBP and no change in DBP, and for all studies, some doses of active interventions were not effective and various drugs were only effective for SBP and not DBP, or vice versa.

Drug combined with lifestyle interventions. One trial (in two publications) examined an intervention that combined education, support, and dietary change with a propranolol/chlorthalidone drug combination[58, 59] (**Tables 5** and **7**; **Appendix B5**).

The school-based ADAPT (A Dietary/Exercise Alteration Program Trial), which included a propranolol/chlorthalidone drug combination, was the only trial identified that showed effectiveness in reducing blood pressure over a long followup period.[58, 59] The intervention included a program consisting of nutrition education and promotion of diet modification to children and parents (i.e., 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. Berenson et al. found that both SBP and DBP decreased significantly between baseline and 6-month followup (SBP, -7.6 mm Hg [$p<0.0001$]; DBP, -6.9 mm Hg [$p<0.01$]) compared with the control group. These results were not sustained 30 months after treatment, at which time SBP had increased from baseline values in both the intervention (+1.4 mm Hg) and control groups (+3.5 mm Hg), though DBP values remained lower than baseline values (-4.2 and -3.3 mm Hg, respectively).

The trial had methodologic flaws, including unclear loss to followup.[58, 59]

Lifestyle interventions. Six trials of lifestyle interventions were identified, the majority of which included support related to the interventions (e.g., regular check-ins) in addition to dietary, exercise, meditation, and progressive muscle relaxation[35, 60, 62-64, 66] (**Tables 6** and **7**; **Appendix B5**) only one of which demonstrated statistically significant reductions in blood pressure when compared with untreated controls.[63]

One small school-based trial from Denmark compared the effects of three classes of physical education in addition to the existing two physical education classes (i.e., total of five classes per week) for a period of 8 months. Hypertensive children randomized to the additional exercise group had a significant SBP decrease of 4.9 mm Hg and a DBP decrease of 3.8 mm Hg compared with the usual level of physical education classes after 8 months ($p<0.05$ for both).[63]

Another trial comparing children randomized to a low-sodium diet combined with personalized support and/or potassium chloride supplementation or usual care found that the low-sodium portion of the intervention was only effective in reducing blood pressure for girls compared with placebo, but not for boys at 36-month followup.[66]

Other studies of dietary changes,[60, 64] meditation,[62] and progressive muscle relaxation[35] reported no difference in blood pressure changes between intervention and control groups.

Key Question 6. What Is the Effectiveness of Drug, Nondrug, and Combination Interventions Initiated for the Treatment of Primary Hypertension in Children/Adolescents for Reducing Blood Pressure and Other Intermediate Outcomes in Adults?

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.

Key Question 7. What Is the Effectiveness of Drug, Nondrug, and Combination Interventions Initiated for the Treatment of Primary Hypertension in Children/Adolescents for Reducing Adverse Health Outcomes in Adults Related to Primary Hypertension?

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

Key Question 8. What Are the Adverse Effects of Drug, Nondrug, and Combination Interventions for Treating Primary Hypertension in Children/Adolescents?

Summary

Drug interventions for treating primary hypertension in children appear to be well-tolerated, though high-quality data are lacking in this population, as most studies enrolled a mixture of children with primary and secondary hypertension. Across one good-quality and 10 fair-quality studies, there were no significant differences between treated and untreated children in either the proportion experiencing an adverse event or in withdrawals due to adverse events, and serious adverse events were rarely reported. One additional fair-quality trial noted that a combination of bisoprolol and hydrochlorothiazide was associated with lower adverse event rates than placebo. Pooled data from numerous RCTs found no difference between active treatments and placebo groups in incidence of specific harms, including headache, cardiac events, gastrointestinal events, and cough. Evidence on adverse events associated with interventions that combined drug and lifestyle modifications is extremely limited. A study of a combination of drug and lifestyle interventions reported no serious adverse events in the active treatment group compared with untreated children. We identified no studies reporting on harms associated with nondrug treatments.

Evidence

Drug interventions. Eleven RCTs[57, 61, 65, 68-70, 73-77] of drug monotherapy and one trial of combination drug therapy[67] reported safety data (**Table 8**). One study was rated good-quality;[73] the remainder were of fair-quality, primarily due to failure to adequately report method of randomization and allocation concealment and lack of details about blinding (**Appendix B6**). All were dose-ranging studies that included a placebo arm or a placebo washout phase. Four of the studies included only primary hypertension patients,[57, 68-70] while the other studies enrolled a mix

of patients with primary and secondary hypertension.[61, 65, 67, 73-77] The number of children enrolled in the studies ranged from 76 to 304, mean ages ranged from 12 to 17 years, and duration of followup for harms data ranged from 4 weeks to 1 year (in studies with open-label phases).

Adverse event data were often poorly reported, and many did not include data from placebo arms/phases but rather reported longer-term data on active treatments only from open-label study phases. Five studies of monotherapy reported similar proportions of patients experiencing any adverse event between active treatment (range, 27% to 77%) and placebo (range, 25% to 66%) arms.[65, 68, 70, 73, 74] One study of a combination of bisoprolol plus hydrochlorothiazide compared with placebo found that children taking bisoprolol plus hydrochlorothiazide had lower overall rates of any adverse events compared with children taking placebo (53% vs. 75%; p=0.05) after 12 weeks of followup.[67] Withdrawals due to adverse events ranged from 0 to 7 percent in children receiving active treatments[57, 61, 67-70, 73-77] and 0 to 6.2 percent in placebo groups,[57, 67, 69, 70, 73, 74] though, again, not all studies reported events in placebo groups/phases. Serious harms were rarely reported. One study reported two cases of patients with serious harms (pneumonia and metometrorrhagia) taking metoprolol[57] and one study reported one serious adverse event (near syncope and elevated creatinine) in a patient who received an incorrect dose of telmisartan. A third study reported eight cases of serious adverse events in 304 patients, though none were considered to be treatment related.[65] A fourth study reported fewer serious adverse events, most commonly severe hypertension, in the active treatment group than the placebo group (2% vs. 16%; p=0.02).[67] No deaths were reported in any of the studies.

Headache was described as the most common specific adverse event in most studies, with rates ranging from 2 to 33 percent in children receiving active treatments among the studies that reported data.[57, 67, 68, 70, 74, 77] Only two studies included comparative rates for placebo, with no incidence of headache noted in those patients compared with 11 percent of active treatment patients in one study[70] and 31 versus 26 percent (placebo vs. combination treatment) in another study.[67] Other commonly reported adverse events associated with active treatments were cough, upper respiratory infection, and gastrointestinal events, including nausea and diarrhea, though specific rates were not always reported.[57, 61, 67-70, 74-77]

More detailed data on specific adverse events associated with drug treatments for childhood hypertension are available from two analyses of trials submitted to the U.S. Food and Drug Administration (FDA) over a 7-year period. Neither study met criteria for systematic review and conclusions from included data are potentially subject to bias, as there was inadequate reporting of searches, inclusion criteria, quality rating, and methods used to pool data. One study provided an analysis of a series of patient-level data from 1,707 children (mean age, 12 years; 62% male) from 10 placebo-controlled RCTs submitted to the FDA.[78] Event rates were pooled for all active treatments—including amlodipine, benazepril, enalapril, felodipine, fosinopril, irbesartan, lisinopril, losartan, quinapril, and ramipril—and compared with placebo rates. Overall adverse event rates were similar between active treatment groups and placebo groups among the included studies (0.83 vs. 0.76 per patient, respectively; p=0.37). There were no significant differences between active treatments and placebo for any adverse event, including headache (47% vs. 48%; p=0.68), cardiac events (16% vs. 8%; p=0.5), gastrointestinal events (24% vs. 23%; p=0.51), syncope (8% vs. 6%; p=0.35), asthma (12% vs. 11%; p=0.58), and elevated liver function tests

(7% vs. 7%; p=0.51).[78] The second FDA study compared the incidence of cough in hypertensive children (mean age, 13 years; 61% male) treated with active interventions (n=748) or placebo (n=551).[79] Based on data from eight placebo-controlled trials, there was no difference in incidence of cough between active treatment (3% of patients) or placebo groups (3% of patients; p=0.86) among the included studies.

Drug combined with lifestyle interventions. One fair-quality trial (ADAPT) reported no adverse events in children treated with propanolol plus chlorthalidone in addition to lifestyle intervention focusing on dietary modification and exercise compared with untreated children[58] **(Table 8**).

Lifestyle interventions. We did not identify any studies of lifestyle modification interventions that reported adverse events.

CHAPTER 4. DISCUSSION

Summary of Review Findings

A summary of the evidence is provided in **Table 9**.

No studies addressed Key Question 1 to determine whether screening for hypertension in children and adolescents was effective at delaying the onset of or reducing the risk of health outcomes related to hypertension in children. In addition, no studies addressed Key Question 6 or 7 to provide evidence on the effectiveness of interventions for treating primary childhood hypertension for reducing blood pressure levels or other intermediate or clinical health outcomes in adulthood.

Only two studies provided evidence on the diagnostic accuracy of blood pressure screening (Key Question 2), with sensitivities of 0.65 and 0.72, specificities of 0.75 and 0.92, and positive predictive values of 0.37 and 0.17. One study involved children referred to a hypertension clinic in Greece and therefore may not be applicable to primary care settings in the United States. The other study involved school-based screening of 10th grade children, and therefore may not be generalizable to clinical settings or other age groups. Twelve additional studies provide data on the positive predictive value of screening for elevated blood pressure, which ranged widely from 4 to 53 percent. Taken together, these findings suggest that the sensitivity of blood pressure measurement to detect hypertension is moderate, and that a significant proportion of children who screen positive are likely to have normal blood pressure (i.e., the majority of children screened positive will be false positives). In addition to false-positive rates, the only evidence that explicitly examined the adverse effects of screening (Key Question 4) was obtained from a small study reporting that rates of school absenteeism did not change after children were identified as having elevated blood pressure. We found no evidence that examined other potential adverse effects of screening for hypertension.

Ten longitudinal studies provided evidence on the association between elevated blood pressure in childhood and hypertension, carotid intima media thickness, or microalbuminuria in adulthood (Key Question 3). All but two of the studies were based on longitudinal data from the United States, although methods to measure blood pressure and definitions of childhood and adult hypertension differed between studies. Although elevated blood pressure in childhood was significantly associated with hypertension in adults in four studies, with ORs ranging from 1.1 to 4.5 and relative risks from 1.5 to 9, the two studies that reported sensitivities and specificities of hypertension in childhood for adult hypertension provided widely differing estimates of 0.0 to 0.66 and 0.77 to 1.0, respectively. Only three studies examined the association between childhood hypertension and other intermediate outcomes related to hypertension in adults. The association of childhood hypertension and carotid intima media thickness was not clear from two studies. A single study found childhood hypertension was significantly associated with microalbuminuria in black adults but not white adults. We found no evidence for associations between hypertension in childhood and other intermediate or final hypertension-related outcomes in adulthood (e.g., left ventricular hypertrophy and other cardiovascular outcomes).

Fourteen studies provided evidence on the effectiveness of interventions to reduce blood pressure in young adolescents (Key Question 5); seven RCTs of monotherapy with drug interventions were small, of very short duration (≤4 weeks), on the lower spectrum of fair-quality, and were mostly limited to those with primary hypertension. All of the drug trials reported reductions in the absolute level of blood pressure and/or increased proportions of children achieving blood pressure <95th percentile for their age, sex, and height. However, the antihypertensive effects were of variable magnitude, were not consistently present for a given agent across both SBP and DBP, and were not always significantly different from placebo or baseline (or this difference was not reported). Moreover, none of the drugs were evaluated in more than one study. The mean age in the majority of the studies was 12 years, so generalizability of results to younger children is unknown. The only trial of combined drug and various lifestyle components that demonstrated evidence of sustained reduction of blood pressure after 6 months was an intensive, school-based intervention. Of six trials that assessed lifestyle interventions, only one, a small Danish school-based trial of increased number of exercise classes, reported a significant decrease in blood pressure after 8 months.

Drugs for treating primary hypertension in children were well-tolerated, with one of 13 studies showing significant differences in rates of adverse events and serious adverse events between active drug and placebo (Key Question 8). Harms studies were limited by quality and generalizability, as most enrolled a mixture of children with primary and secondary hypertension, used open-label periods to examine side effects, and had limited power to identify rare adverse events. We identified no studies reporting on harms associated with lifestyle interventions alone.

Contextual Questions

Contextual Question 1. What Are the Main Risk Factors for Primary Hypertension in Children/Adolescents?

According to evidence identified from a large number of epidemiological studies, numerous factors, both modifiable and not modifiable, have been linked with increased risk of primary hypertension in children, including obesity, low birth weight, lack of breastfeeding, sex, ethnicity, and family history of hypertension.[4, 10, 11, 14, 80-82] The evidence for the strength and independence of these associations varies markedly.

The association of increased BMI with hypertension has been established in several large epidemiologic studies.[11, 40, 80, 83-86] The most robust evidence comes from a large study by Rosner and colleagues who analyzed data from 11 separate studies with a total of 58,698 children and adolescents ages 1 to 17 years, of whom 59 percent were white, 31 percent black, and 11 percent Hispanic.[83] The prevalence of systolic hypertension (≥95th percentile) in children who had normal weight (i.e., BMI <85th percentile) was 4.8 to 6.5 percent in boys and 4.8 to 5.3 percent in girls (depending on ethnic group), but in overweight children (BMI ≥85th percentile), hypertension was two to three times more frequent, occurring in 14 to 18 percent of boys and 13 to 16 percent of girls.[83] A further study from primary care practices of 18,618 children ages 2 to 19 years, in whom 20 percent were overweight (BMI ≥95th percentile), found higher blood

pressure was significantly associated with BMI in all age groups and both sexes, including those in the youngest age group.[80] For example, the proportion of boys ages 2 to 5 years with SBP and/or DBP ≥95th percentile was 6 percent in those with BMI <85th percentile and 8 percent in those with BMI >95th percentile. In boys ages 6 to 10 years, corresponding proportions were 5 and 11 percent, 7 and 20 percent in boys ages 11 to 15 years, and 10 and 19 percent in boys ages 16 to 19 years. Sorof and colleagues reported that the prevalence of hypertension in adolescents was strongly and independently associated with increased BMI in 5,102 adolescents (mean age, 14 years); the prevalence of hypertension increased from 2 percent in those with BMI ≤5th percentile to 11 percent in those with BMI ≥95th percentile.[11]

The Rosner study also provides the most robust evidence on the associations between ethnicity and hypertension, as they were able to adjust for BMI and sex.[83] In boys, the prevalence of elevated SBP (≥95th percentile) was not significantly different between black and white boys (OR, 0.96 [95% CI, 0.87 to 1.05]; p=0.39). In comparison, Hispanic boys had significantly higher SBP than white boys (OR, 1.49 [95% CI, 1.31 to 1.68]; p<0.001). For girls, both blacks and Hispanics had significantly higher rates of SBP than white girls (OR, 1.16 [95% CI, 1.06 to 1.28]; p=0.001 and OR, 1.24 [95% CI, 1.08 to 1.43]; p=0.003, respectively). After adjusting for BMI, Hispanic boys continued to have significantly higher rates of SBP (OR, 1.29 [95% CI, 1.14 to 1.47]; p<0.001), whereas there remained no significant difference between black and white boys. After adjusting for BMI in girls, neither black nor Hispanic children had significantly different rates of SBP elevation. In boys, the prevalence of elevated DBP (≥95th percentile) was significantly greater in black boys (OR, 1.16 [95% CI, 1.04 to 1.30]; p=0.008) and Hispanic boys (OR, 1.32 [95% CI, 1.12 to 1.55]; p<0.001) than white boys, and both remained significant after adjusting for BMI (OR, 1.13 [95% CI, 1.01 to 1.26] and OR, 1.19 [95% CI, 1.01 to 1.40], respectively; p=0.04 for both comparisons). The crude rates of DBP were also significantly higher in black girls than white girls (OR, 1.15 [95% CI, 1.04 to 1.28]; p=0.008), but there was no significant difference between Hispanic girls and white girls (OR, 1.05 [95% CI, 0.88 to 1.24]; p=0.59), and adjusting for BMI did not alter these associations.

It is unclear whether having one or both parents with hypertension increases the risk of hypertension in childhood or adolescence. Some small, cross-sectional studies have noted this association,[87-90] while others have not.[91, 92] Based on current evidence, an association, if present, would be small. The largest study we identified (N=864) was a community-based study of young people ages 16 to 24 years who were screened for blood pressure some 8 years after their parents had been screened for blood pressure. A total of 29 percent of adolescents who had at least one parent with blood pressure in the top 10 percent of the distribution had a blood pressure score in the top 20 percent of distribution, resulting in a sensitivity of 0.27 and specificity of 0.84 for predicting elevated blood pressure.[93] The implications of this study are limited because NHBPEP definitions of hypertension were not used.

Breastfeeding has been shown to be protective against elevated blood pressure in several studies. A prospective cohort study of 7,276 children examined the association between type of infant feeding and blood pressure at age 7 years.[94] Breastfeeding was associated with lower SBP (0.8 mm Hg [95% CI, 0.1 to 1.5]) and DBP (0.6 mm Hg [95% CI, 0.1 to 1.0]) after adjusting for multiple confounders. An association was also noted between breastfeeding in premature, low birth weight infants (<1850 g) and lower blood pressure when measured in adolescence. A

similar association was reported in a another study of 301 children, in whom SBP at age 7 years was significantly higher in children who were exclusively bottle fed compared with those who received breast milk (mean, 94.2 mm Hg [range, 93.5 to 94.9] vs. 90.7 mm Hg [range, 89.9 to 91.7], respectively).[95]

Contextual Question 2. What is the Prevalence of Secondary Hypertension in Asymptomatic Children/Adolescents in Primary Care Settings?

Evidence on the prevalence of secondary hypertension is dependent on the populations of children studied, and there appears to be no accurate prevalence rates for asymptomatic children in ambulatory settings. Most evidence comes from children referred to pediatric specialty clinics following the detection of hypertension by screening or incidentally, or in children diagnosed with other conditions (e.g., renal abnormalities) in whom hypertension had also been noted. Among these populations, the prevalence of secondary hypertension varies inversely with age.[13, 17] In grade school-aged children (i.e., up to age 12 years), secondary hypertension accounts for 70 to 85 percent of cases.[12, 13, 17] In children younger than age 12 years, up to 85 percent diagnosed with secondary hypertension have underlying renal disease, most commonly one of the renal parenchymal diseases (e.g., glomerulonephritis, renal scarring due to reflux nephropathy, polycystic kidney disease, and chronic renal failure) or renovascular diseases (e.g., fibromuscular dysplasia.).[13, 17] Less common causes of secondary hypertension in children include aortic coarctation and endocrine disorders (e.g., phaeochromocytoma, hyperthyroidism) or relation to medications (e.g., oral contraceptives in adolescents, sympathomimetic drugs, dietary supplements).[13, 17] By the time a child reaches adolescence, hypertension is predominantly primary (85% to 95% of cases); the prevalence of secondary hypertension in adolescents is about 5 percent.[13, 96]

Contextual Question 3. What Are the Optimal Ages at Which to Initiate Screening and the Optimal Time Intervals at Which to Repeat Screening Children/Adolescents for Hypertension?

We identified no evidence on the optimal ages at which to initiate screening for hypertension or on ideal screening intervals. The American Academy of Family Physicians and other organizations recommend beginning routine screening at age 3 years,[6, 7] but this recommendation is not based on empirical evidence.

Limitations of the Review

We excluded nonEnglish-language articles, which could result in language bias. We did not search for studies published only as abstracts and could not formally assess for presence of publication bias with graphical or statistical methods because of small numbers of studies for each key question and differences in study design, populations, and outcomes assessed. We included observational studies for some key questions where trials were not available, which are more susceptible to bias and confounding than well-conducted randomized trials. When evidence

from settings more applicable to practice in the United States was sparse or unavailable, we included studies conducted in other countries, which could limit applicability. We included some studies that enrolled a small-to-moderate proportion of individuals with secondary hypertension, as many studies did not clearly report the populations with primary and secondary hypertension.

Emerging Issues/Next Steps

In adults, there is growing evidence for ambulatory blood pressure measurement and self-measured blood pressure (otherwise known as home monitoring) in diagnosis and monitoring in ambulatory and community settings. In adults, the importance of home monitoring is increasing, and these devices are now recommended in some settings for diagnosis of hypertension and monitoring of response to intervention. Advances in technology and electronic transmission of data also offer the potential to transmit blood pressure readings between patients' homes and clinicians' offices.

The evidence for the role of these devices in children is at an early stage. Approximately two thirds of pediatric nephrologists report that they use ambulatory blood pressure measurement in management of children with hypertension,[97] and one study found that valid readings of ambulatory blood pressure measurement can be obtained in the majority (84%) of children ages 3 to 18 years.[98] However, the current use and feasibility of ambulatory blood pressure measurement in pediatric practice in ambulatory settings is not known.

Ambulatory blood pressure measurement and home monitoring offer several potential advantages over clinic measures, such as the opportunity to gather a larger number of readings, and provide readings that are more representative of a child's blood pressure, at multiple points during the day and night and over multiple days. These readings may facilitate identifying children with patterns of blood pressure that may have diagnostic or prognostic significance, which cannot easily be identified with clinic-only measurements.[99-102]

White coat hypertension occurs when blood pressure readings obtained in a clinic setting are elevated, but readings obtained out of the clinic are normal. This has been reported to occur in between 1 and 62 percent of children. However, there is some evidence in adults to suggest that white coat hypertension may not be a benign condition, but may reflect underlying increased activity of the sympathetic nervous system and greater risk of cardiovascular outcomes than in those with normal blood pressure.[103] In children, there are no data on long-term outcomes, and the association between ambulatory blood pressure measurement and intermediate outcomes, such as carotid intima media thickness and left ventricular hypertrophy, is uncertain at this time.[101]

A second condition that has been identified using multiple blood pressure readings is masked hypertension (also known as reverse white coat hypertension, or white coat normotension), which occurs when clinic blood pressure is normal, but blood pressure measured using ambulatory blood pressure measurement or home devices is elevated. The prevalence in children is estimated at 7 to 10 percent.[102, 104] In adults, there is some evidence to suggest that masked hypertension is associated with elevated risk for cardiovascular outcomes,[105] while in children,

small studies suggest a possible association with intermediate outcomes, such as left ventricular hypertrophy, but there is no evidence on long-term outcomes.[102, 104]

The use of ambulatory blood pressure measurement or home monitoring could also potentially be useful for monitoring children with confirmed hypertension, including more accurate and more rapid titration of antihypertensive intervention and determining whether side effects of interventions are associated with levels of blood pressure.[101] Its role in children is unknown, however, and there are currently several problems with obtaining and interpreting measurements from these devices. Few ambulatory blood pressure measurement and home devices have been validated for use in children, raising concerns regarding accuracy,[101, 106] particularly at the lower levels of SBP and DBP.[106] In addition, the measurements and pattern of readings from ambulatory blood pressure measurement and home devices need to be interpreted and compared with normative data. Unlike adults, in whom normative data for ambulatory blood pressure measurement have been correlated with end-organ damage and cardiovascular outcomes, the normative data on ambulatory blood pressure measurement in children are limited, may not be representative of current ambulatory blood pressure measurement devices, and are not from children in the United States.[32, 106, 107] In addition, blood pressure norms may be changing due to the increasing prevalence of overweight and obesity in children and adolescents.

Future Research

We suggest that large observational studies include blood pressure measures and other cardiovascular risk factors obtained in children and adolescents, and have followup periods of many decades, given the time needed to develop clinical sequelae of hypertension, such as cardiovascular disease.

Further evidence is needed on the effectiveness and comparative effectiveness of drug and lifestyle interventions to reduce blood pressure in children with primary hypertension. There is a major gap on the effectiveness of all currently available medications approved by the FDA for hypertension in children, including older medications. Given that most children with primary hypertension will potentially require blood pressure lowering intervention for decades, such studies should include longer followup periods to determine effectiveness in these populations, including those followed in primary care rather than specialty settings, and include drug monotherapy and combinations of antihypertensive drugs (such as stepped care regimens), including measures of long-term compliance. Improving the evidence for the safety of antihypertensive medications also requires further studies of all FDA-approved medications. Our finding of mixed outcomes of lifestyle interventions suggests the need for further studies, particularly in U.S. settings. Some of the lifestyle interventions included numerous components, so study designs that take account of such complex interventions and identify the components that provide the greatest relative benefit are needed. Given the link between BMI and hypertension, the rising levels of overweight and obese children suggest this is an urgent priority.

A further major gap in the evidence is the effectiveness of interventions for primary childhood hypertension for reducing the level and or proportion of blood pressure or other intermediate outcomes in adulthood, or for subsequent reduction of adverse health outcomes in adults.

Determining the effects of interventions to reduce blood pressure on adverse health outcomes (e.g., cardiovascular outcomes) would require extended followup periods and, again, would be logistically challenging. However, it would be possible to assess the effects of interventions on blood pressure in young adults and on intermediate outcomes, such as structural changes in the heart or vasculature.

The lack of data on diagnostic accuracy of blood pressure devices represents a major gap in the current evidence base. First, studies of the diagnostic accuracy of blood pressure screening in primary care or community settings (e.g., schools) of nonreferred populations, with wide age ranges and varying characteristics are needed, that follow both children who screen positive and those who screen negative in order to calculate all measures of diagnostic accuracy. In addition, evidence is needed on the number and frequency of readings needed to make a diagnosis, and the comparative effectiveness of different types of devices to measure blood pressure, including newer devices that obtain multiple readings in one visit, home-based devices, and ambulatory blood pressure measurement. As noted above, ambulatory blood pressure measurement offers several potential advantages over clinic-based devices, but evidence of its value and comparative effectiveness over other screening devices is lacking. Given the importance of identifying children with secondary hypertension during screening, the use of blood pressure screening devices that distinguish primary and secondary hypertension based on level or pattern of blood pressure are needed. Such studies should also assess the adverse effects of screening, including the immediate effects—such as parent/clinic time and discomfort for the child—as well as adverse effects of children with false-positive screening results, such as labeling, effects on school or sports participation, and need for followup due to a positive screening result.

Finally, the centiles used to define hypertension in children and adolescents are based on normative values, unlike in adults, where they are based on cardiovascular risk. We identified some evidence that elevated blood pressure levels in childhood are associated with increased risk of hypertension in adults, but evidence for its association with other markers of hypertension-related end-organ damage were very limited. Adequately-sized cohort studies with long followup periods might allow refinement of these centiles to define thresholds of blood pressure in children that are associated with different levels of risk for adverse health outcomes, permitting more accurate risk assessment.

Conclusions

There is no direct evidence that screening for hypertension in children and adolescents reduces adverse health outcomes or delays the onset of hypertension. Blood pressure screening may be effective at identifying children with hypertension, though evidence is limited and false-positive rates were high. The presence of hypertension in childhood is associated with hypertension in adults, but with limited evidence for its association with end-organ damage markers in adults. Drug interventions for hypertension may be effective at lowering blood pressure with few serious side effects; however, studies of longer duration are needed to confirm results from short-term studies. Evidence on the effectiveness of combination drug and lifestyle interventions and lifestyle-only interventions is mixed, with most studies showing no sustained reduction in blood pressure. There is no evidence on whether treating hypertension in childhood affects subsequent

intermediate or clinical outcomes in adulthood.

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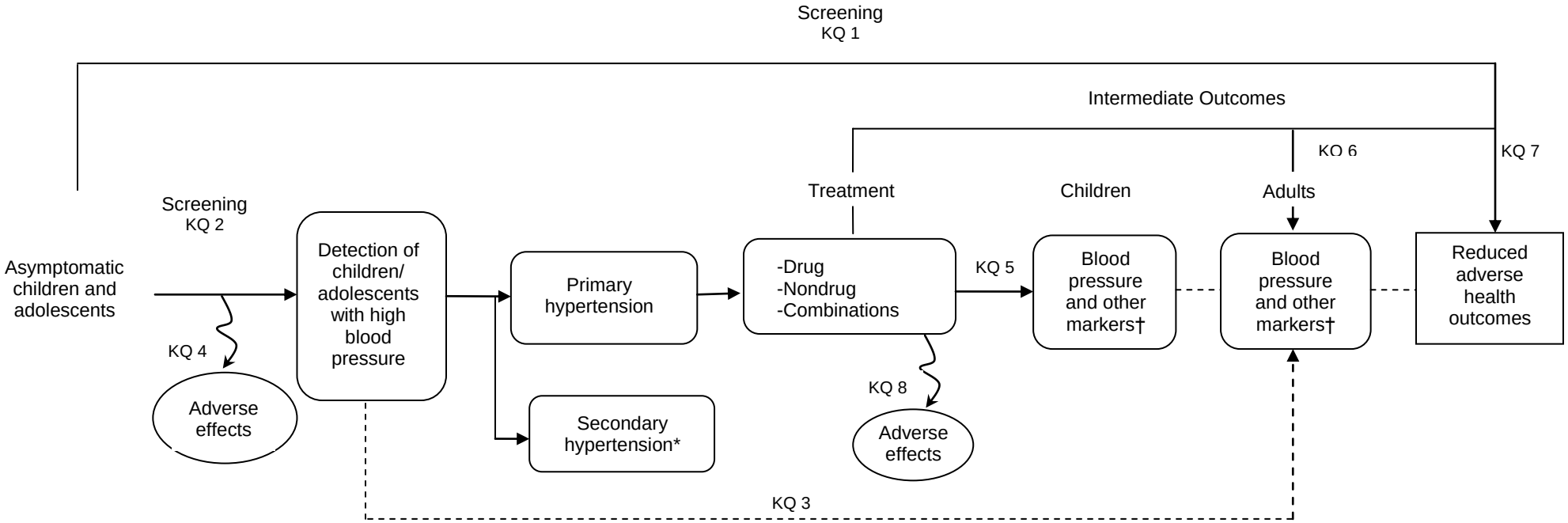
Figure. Analytic Framework



Abbreviation: KQ = key question.
*The assessment and treatment of secondary hypertension is beyond the scope of this review.
†Includes left ventricular hypertrophy, urinary albumin excretion (microalbuminuria), intima media thickness (measured at carotid and/or femoral arteries), and retinal vascular changes.

Table 1. Drug Interventions for Hypertension in Children and Adolescents

Drug class	Drug	Dosing
ACE inhibitors	Benazepril	Starting dose: 0.2 mg/kg/day up to 10 mg/day Maximum dose: 0.6 mg/kg/day up to 40 mg/day
	Enalapril	Starting dose: 0.08 mg/kg/day up to 5 mg/day Maximum dose: 0.6 mg/kg/day up to 40 mg/day
	Fosinopril	Weight >50 kg: 5-10 mg/day, maximum 40 mg/day
	Lisinopril	Starting dose: 0.07 mg/kg/day up to 5 mg/day Maximum dose: 0.6 mg/kg/day up to 40 mg/day
ARBs	Irbesartan	Age 6-12 years: 75-150 mg/day Age ≥13 years: 150-300 mg/day
	Losartan	Starting dose: 0.7 mg/kg/day up to 50 mg/day Maximum dose: 1.4 mg/kg/day up to 100 mg/day
Beta blockers	Propanolol	Starting dose: 1-2 mg/kg/day Maximum dose: 4 mg/kg/day up to 640 mg/day
	Amlodipine	Age 6-17 years: 2.5-5 mg/day
Central alpha-agonists	Clonidine	0.2-2.4 mg/day
Diuretics	HCTZ	1-3 mg/kg/day; maximum 50 mg/day
Vasodilator	Hydralazine	0.75-7.5 mg/kg/day; maximum 200 mg/day
	Minoxidil	Age <12 years: 0.2 mg/kg/day; maximum 50 mg/day Age ≥12 years: 5 mg/day; maximum 100 mg/day

Source: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004.[6]
ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.

Table 2. Diagnostic Accuracy of Screening for Elevated Blood Pressure in Children and Adolescents

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
Fixler and Laird, 1983[33]	Three measures with mercury manometer measured at least 4 weeks apart	Initial screening results compared to subsequent measures	Systolic or diastolic blood pressure ≥95th percentile based on normative levels for the study population	n=9,017; 8th graders with followup at 10th grade Mean age not reported; all were in 8th grade at time of initial screening 53% male 44% Black 42% White 14% Hispanic	Initial positive screen vs. subsequent screens: 0.72 (0.65 to 0.78)	Initial positive screen vs. subsequent screens: 0.92 (0.91 to 0.92)	Initial positive screen vs. subsequent screens: 0.17 (0.15 to 0.2)	Initial positive screen vs. subsequent screens: 0.993 (0.991 to 0.994)	Fair
Stergiou et al, 2008[31]	Three averaged measurements with mercury sphygmomanometer, measured in nondominant arm in sitting position after 5 minutes at rest	24-hour ambulatory measurements	Systolic or diastolic blood pressure ≥95th percentile based on U.S. normative blood pressure tables	n=102; 100% referred for screening Mean age 13 years (SD 3; range 6-18) 63% male Race not reported	Positive ambulatory result vs. positive clinic result: 0.65 (0.45 to 0.80)	Positive ambulatory result vs. positive clinic result: 0.75 (0.63 to 0.84)	Positive ambulatory result vs. positive clinic result: 0.37 (0.28 to 0.47)	Positive ambulatory result vs. positive clinic result: 0.63 (0.53 to 0.72)	Fair

CI = confidence interval; SD = standard deviation; U.S. = United States.

Table 3. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name Followup	Definition of HTN in childhood	Definition of HTN in adulthood	Outcomes	Quality considerations			
				Enrollment	Attrition: % with complete data, % of original N at followup	Measurement method stated for both time periods?	Statistical analysis and adjusted variables
Blood Pressure Outcomes							
Bao et al, 1995[46] Bogalusa Heart Study 15 years	>80th percentile	SBP >140 mmHg or DBP >90 mmHg or ever treated for hypertension	Hypertension at followup, baseline highest SBP quintile vs. other SBP quintiles: 18% (54/301) vs. 5% (60/1204); Risk ratio 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); Risk ratio 2.5; 95% CI 1.8 to 3.6	Unclear; data from 1,505 subjects who completed baseline and followup surveys (of 3,865 at baseline)	No loss (cohort selected based on availability of data; 39% of original cohort completed both surveys)	Yes	Logistic regression Age, race, sex, SBP, DBP, BMI, change in BMI
Beckett et al, 1992[47] Fels Longitudinal Study 20 years	SBP not defined DBP >80 mmHg described as >90th percentile	DBP >90 mmHg	DBP 80 mmHg vs. 60 mmHg at age 15 and presence of hypertension at age 35: Males: Risk ratio 3.0; Females: Risk ratio 4.5 DBP 85 mmHg vs. 60 mmHg at age 15 and presence of hypertension at age 35: Males: Risk ratio 3.9; Females: Risk ratio 6.6 DBP 90 mmHg vs. 60 mmHg at age 15 and presence of hypertension at age 35: Males: Risk ratio 4.9; Females: Risk ratio 9.0	Unclear; data from 523 subjects who completed baseline and followup surveys (of 976 at baseline)	No loss (cohort selected based on availability of data; 54% of original cohort completed both surveys)	No	N/A
Gillman et al, 1993[48] Study not named 12 years	>90th percentile (SBP: 113 mmHg, within study)	>90th percentile (SBP: 139 mmHg, within study)	Positive predictive value, sensitivity, and specificity of BP at age 10 predicting BP>90th percentile at age 20: SBP, males: >75th percentile (108 mmHg): 0.26, 0.59, 0.80 >90th percentile (113 mmHg): 0.35, 0.33, 0.93 >95th percentile (117 mmHg): 0.44, 0.17, 0.97 >99th percentile (123 mmHg): 0.58, 0.04, >0.99 SBP, females: >75th percentile (108 mmHg): 0.27, 0.66, 0.79 >90th percentile (114 mmHg): 0.39, 0.36, 0.94 >95th percentile (118 mmHg): 0.48, 0.20, 0.98 >99th percentile (125 mmHg): 0.65, 0.04, >0.99 DBP, males: >75th percentile (68 mmHg): 0.21, 0.34, 0.82 >90th percentile (71 mmHg): 0.24, 0.16, 0.93 >95th percentile (73 mmHg): 0.27, 0.08, 0.97 >99th percentile (77 mmHg): 0.34, 0.01, >0.99 DBP, females: >75th percentile (67 mmHg): 0.19, 0.49, 0.77 >90th percentile (71 mmHg): 0.24, 0.23, 0.92 >95th percentile (74 mmHg): 0.30, 0.10, 0.98 >99th percentile (78 mmHg): 0.38, 0.02, >0.99	Children from a single school in East Boston, Massachusetts; sampling method unclear	6% (20/337) attrition	Yes	N/A

Table 3. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name Followup	Definition of HTN in childhood	Definition of HTN in adulthood	Outcomes	Quality considerations			
				Enrollment	Attrition: % with complete data, % of original N at followup	Measurement method stated for both time periods?	Statistical analysis and adjusted variables
Juhola et al, 2011[50] Cardio-vascular Risk in Young Finns Study 27 years Other publication: Juonala et al, 2004[55]	≥95th percentile	Unclear	Prehypertension or hypertension in adulthood and BP ≥95th percentile in childhood: Female, ages 6 and 9: OR 2.4 (95% CI 1.1-5.2) Female, ages 12, 15, and 18: OR 2.3 (95% CI 1.6-3.5) Males, ages 6 and 9: OR 2.8 (95% CI 1.5-5.1) Males, ages 12, 15, and 18: OR 2.1 (955 CI 1.5-3.1) PPV, sensitivity, specificity of BP >95% percentile in childhood and hypertension in adulthood – All ages 6-18: 0.44; 0.1; 0.97	Finnish children and adolescents aged 3, 6, 9, 12, and 15 randomly sampled from 5 cities	38.7% (1,392/3596) lost to followup by 27 years	Yes	Linear regression Age, sex, race, study year
Lauer et al, 1993[51] Muscatine Study Duration of followup unclear	Unclear; results reported for >90th percentile	SBP or DBP >90th percentile (cohort specific)	24% of children with BP >90th percentile had BP >90th percentile in adulthood; risk ratio 2.4 (p<0.001) 39% of children with SBP >90th percentile had SBP >80th percentile in adulthood; risk ratio 1.9 (p<0.001) 17% of children with DBP >90th percentile had DBP >90th percentile in adulthood; risk ratio 1.7 (p<0.001) 32% of children with DBP >90th percentile had DBP >80th percentile in adulthood; risk ratio 1.5 (p<0.001)	Unclear; data from 2,445 subjects who completed baseline and followup surveys (number at baseline NR)	No loss (cohort selected based on availability of data)	Yes	N/A
Shear et al, 1987[54] Bogalusa Heart Study 8 years	Not reported	≥140/90 mmHg	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	Data from 1,501 subjects who completed baseline and followup surveys (of 4,238 subjects at baseline)	No loss (cohort selected based on availability of data; 35% of original subjects completed both surveys)	Yes	N/A
Sun et al, 2007[24] Fels Longitudinal Study Duration of followup unclear	Least-squares means determined according to age and sex (absolute values not	SBP >130 mmHg and/or DBP >85 mmHg	Odds of hypertension at >30 years of age given SBP exceeding criterion values at single examination in childhood: 5-7 year old males: 3.8 (95% CI 1.5-9.7) 5-7 year old females: 4.5 (95% CI 1.1-17.7) 8-13 year old males: 3.5 (95% CI 1.5-8.3) 8-13 year old females: 2.7 (95% CI 1.0-7.1) 14-18 year old males: 1.1 (95% CI 0.5-2.4)	Unclear; data from 493 subjects who completed baseline and followup surveys (of 976 at baseline)	8% loss to follow-up in Fels Longitudinal Study overall; data from 51% of original	Yes	N/A

Table 3. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name Followup	Definition of HTN in childhood	Definition of HTN in adulthood	Outcomes	Quality considerations			
				Enrollment	Attrition: % with complete data, % of original N at followup	Measurement method stated for both time periods?	Statistical analysis and adjusted variables
	reported)		14-18 year old females:3.8 (95% CI 1.2-12.7)		subjects		
Other Outcomes							
Hoq et al, 2002[49] Bogalusa Heart Study 16 years	≥90th percentile for age, ethnicity and sex	≥90th percentile for age, ethnicity and sex	Microalbuminuria: Childhood SBP - Blacks: regression coefficient 0.016 (p=0.05); Whites: regression coefficient -0.002 (p=0.78) Annual change in SBP from childhood to adulthood - Blacks: regression coefficient 0.315 (p=0.002); Whites: regression coefficient -0.045 (p=0.55) Childhood DBP- Blacks: regression coefficient 0.026 (p=0.012); Whites: regression coefficient -0.002 (p=0.761) Annual change in DBP from childhood to adulthood - Blacks: regression coefficient 0.292 (p=0.016); Whites: regression coefficient 0.063 (p=0.5)	Unclear; data from 2,122 subjects who completed baseline and followup surveys (of 3,865 at baseline)	Cohort selected based on availability of data; data from 55% of original subjects	Yes	Logistic regression Sex, childhood age, BMI, BP, annual change in BP
Li et al, 2003[52] Bogalusa Heart Study 22 years	Not reported	Not reported	Odds of carotid intima media thickness in upper quartile given SBP risk factor (not defined): Childhood (4-17 years): 1.00 (95% CI 0.80-1.25)	Unclear; data from 486 subjects who completed baseline and followup surveys and carotid artery ultrasound (of 3,865 at baseline)	NR (94% [486/516] had data available); data from 13% of original subjects)	Yes	Logistic regression Age, race, sex
Raitakari et al, 2003[53] Cardiovascular Risk in Young Finns Study 21 years	≥80th percentile	≥80th percentile	Relationship between SBP >80th percentile at age 12-18 (mean age 14.9 years) and carotid intima media thickness 21 years later: regression coefficient 0.013 (SE 0.003); p<0.001	Finnish children and adolescents aged 3, 6, 9, 12, and 15 randomly sampled from 5 cities	38% (1,367/3596) lost to follow-up by 21 years	Yes	Logistic regression Age, sex

BMI = body mass index; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; NA = not applicable; NR = not reported; OR = odds ratio; PPV = positive predictive value; SBP = systolic blood pressure; SE = standard error.

Table 4. Drug Interventions for Hypertension in Children and Adolescents

Author, year *Quality rating*	Study design Setting Duration	N	Demographics	Treatment/ Intervention	Proportion of patients achieving ≤95th percentile of BP for age, gender, and height	Blood pressure outcomes (SBP, DBP mmHg)
Batisky et al, 2007[57] *Fair*	RCT Clinical trial from 28 centers U.S. 4 weeks	140	Mean age 13 (SD 2.8) years 70% male 26% black Mean SBP: 132 mmHg Mean DBP: 78 mmHg 74% BMI ≥95% percentile	Group A: Metoprolol extended-release (ER) 0.2 mg/kg Group B: Metoprolol ER 1.0 mg/kg Group C: Metoprolol ER 2.0 mg/kg Group D: placebo	Groups A-C pooled: 46% (95% CI 37 to 55) Group B: 26% (95% CI 8 to 44)	Mean change from baseline, SBP: Group A: -5.2 (95% CI -7.7 to -2.6) Group B: -7.7 (95% CI -11.3 to -4.0) Group C: -6.3 (95% CI -8.7 to -3.8) Group D: -1.9 (95% CI -5.5 to 1.8) Mean change from baseline, DBP: Group A: -3.1 (95% CI -5.7 to -0.5) Group B: -4.9 (95% CI -8.6 to -1.3) Group C: -7.5 (95% CI -10.0 to -5.0) Group D: -2.1 (95% CI -5.7 to 1.5)
Flynn et al, 2004[61] *Fair*	RCT crossover Clinical trial from 49 centers in North and South America 4 weeks	268	Mean age 12 (SD 3.3) years Mean SBP: 137.9 (SD 12.7) mmHg Mean DBP: 74.2 (SD 11.6) mmHg 31.3% (84/268) primary hypertension	Study Phase 2 (included placebo comparison) Group A: Amlodipine 2.5 mg/day Group B: Amlodipine 5.0 mg/day Group C: placebo	SBP ≤95% percentile Group A: 40% Group B: 35% Group C: 30% DBP ≤95% percentile Group A: 42% Group B: 75% Group C: 48%	Phase 2 results Mean change from baseline, SBP: Group A: -6.9 +12.5 (p=0.05 vs. placebo) Group B: -8.7 +13.3 (p=0.01 vs. placebo) Group C: -3.6 +12.7 Mean change from baseline, DBP: Group A: -4.2 (p=NS) Group B: -4.4 (p=NS) Group C: -0.4
Li et al, 2010[65] *Fair*	RCT Clinical trial in 43 centers in the US, India, South Africa, Russia, and Dominican Republic 4 weeks	304	Mean age not reported (53% <12 years) 63% male 35% black 57% white 11% Hispanic 8% Asian 56% primary hypertension	Study Phase B (included placebo comparison) Group A: Eplerenone 25 mg once daily Group B: Eplerenone 25 mg twice daily Group C: Eplerenone 25 mg bid for 2 weeks followed by 50 mg bid for 4 weeks Group D: placebo	NR	Phase B results Least squares mean change from baseline, SBP: Group A: No statistically significant change Group B: 2.76 (95% CI -5.5 to 0; p=0.048 vs. placebo) Group C: No statistically significant change Least squares mean change from baseline, DBP: No statistically significant changes in any group
Sorof et al, 2002[67] *Fair*	RCT Clinical trial from 22 centers in U.S. and Brazil 4 weeks	94	Mean age 14 years 57% male 43% white 41% black 14% Hispanic 1% Asian 1% multiracial Mean BMI 28	Group A: Bisoprolol fumarate (B) 2.5 + hydrochlorothiazide (HT) 6.25 Group B: B 5 mg + HT 6.25 mg Group C: B 10 mg + HT 6.25 mg Group D: placebo	NR	Least squares mean change from baseline, SBP: Groups A-C pooled: -9.3 (p=0.5 vs. placebo) Group D: -4.9 Least squares mean change from baseline, DBP: Groups A-C pooled: -7.2 (p=0.01 vs. placebo) Group D: -2.7

Table 4. Drug Interventions for Hypertension in Children and Adolescents

Author, year *Quality rating*	Study design Setting Duration	N	Demographics	Treatment/ Intervention	Proportion of patients achieving ≤95th percentile of BP for age, gender, and height	Blood pressure outcomes (SBP, DBP mmHg)
Trachtman et al, 2003[68] *Fair*	RCT Clinical trial at 30 sites in the U.S. 3 weeks	133	Mean age 12 years (SD 3) 60% male 39% black	Group A: 2.5 mg felodipine extended-release (ER) Group B: 5 mg felodipine ER Group C: 10 mg felodipine ER, titrated to target dose Group D: placebo	BP ≤90th percentile Group A: 15% Group B: 18% Group C: 19% Group D: 11%	Mean difference SBP at follow-up, vs. placebo (95% CI): Group A: -0.71 (-4.8 to 3.38; p=NS) Group B: -0.06 (-4.6 to 3.3; p=NS) Group C: -1.73 (-6.58 to 3.13; p=NS) Mean difference DBP at follow-up, vs. placebo (95% CI): Group A: -2.07 (-6.82 to 2.69; p=NS) Group B: -4.64 (-9.18 to 0.09; p<0.05) Group C: 1.31 (-3.56 to 6.11; p=NS)
Trachtman et al, 2008[69] *Fair*	RCT Clinical trial at 42 sites in U.S. and Europe 4 weeks	240	Mean age not reported (29% <12 years; 71% >12 years) 71% male 69% BMI ≥95th percentile 47% black 45% white	Group A: Candesartan 2/4 mg Group B: Candesartan 8/16 mg Group C: Candesartan 16/32 mg Group D: placebo	Group A: 54% Group B: 62% Group C: 65% Group D: 31%	Least squares mean change from baseline, SBP: Groups A-C: -10.22 (p<0.0001 vs. placebo) Group D: -3.66 Least squares mean change from baseline, DBP: Groups A-C: -6.56 (p=0.0029 vs. placebo) Group D: -1.8
Wells et al, 2010[70] *Fair*	RCT Clinical trial at 16 centers in U.S., Brazil, and Mexico 4 weeks	77	Mean age: 14 years (SD 3 years) 57% male 51% white 37% black	Group A: Telmisartan 1 mg/kg/day (low-dose group) Group B: Telmisartan 1 mg/kg/day, titrated up to 2 mg/k/day after 1 week (high-dose group) Group C: placebo	Group A: 50% (6 to <12 years); 68% (12 to <18 years) Group B: 86% (6 to <12 years); 79% (12 to <18 years) Group C: 33% (6 to <12 years); 27% (12 to <18 years)	Adjusted mean difference SBP at follow-up, versus placebo (95% CI): Group A: -3.6 (CI -9.2 to 1.9, p=NS) Group B -8.5 (-14 to -3.0, p=0.0027) Adjusted mean difference DBP at follow-up, versus placebo: Group A: -4.5 (-9.5, 0.4, p=NS) Group B: -4.8 (-9.7 to 0, p=0.051)

BMI = body mass index; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; SE = standard error.

Table 5. Drug Combined With Lifestyle Interventions for Hypertension in Children and Adolescents

Author, year *Quality rating*	Study design Setting Duration	N	Demo-graphics	Treatment/Intervention	Blood pressure outcomes (SBP, DBP mmHg)
Berenson et al, 1983[58] *Fair* Other publication: Frank et al, 1982[71]	RCT School-based 6 months	150	NR	ADAPT Program Group A: Propranolol 20-40 mg + chlorthalidone 6.25-12.5 mg + nutrition education and promotion of dietary modification Group B: Hypertensive control group	Mean change from baseline, SBP: Group A: -7.6 Group B: -3.0 Mean change from baseline, DBP: Group A: -6.9 Group B: -3.9
Berenson et al, 1990[59] *Fair* Continuation of Berenson et al, 1983[58]	RCT School-based 30 months	150	Mean age 12 years 55% male 47% white Mean SBP 117.7 Mean DBP 78.1	Same as above	Adjusted mean difference, SBP: Group A vs. Group B: -3.6 (SD 1.12; p<0.01) Adjusted mean difference DBP: Group A vs. Group B: -1.7 (SD 0.82; p<0.05)

ADAPT = A Dietary/Exercise Alteration Program Trial; BMI = body mass index; BP = blood pressure; CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation.

Table 6. Lifestyle Interventions for Hypertension in Children and Adolescents

Author, year *Quality rating*	Study design Setting Duration	N	Demographics	Treatment/ Intervention	Blood pressure outcomes (SBP, DBP mmHg)
Diet					
Couch et al, 2008[60] *Fair*	RCT Cincinnati Children's Hospital Medical Center, U.S. 6 months	57	Mean age 14 years 63% male Mean SBP 128.7 Mean DBP 80.5	Group A: DASH-type diet modified for adolescent population + counseling Group B: Counseling alone	Mean difference at follow-up, SBP: Group A vs. Group B: 0.1 Mean difference at follow-up, DBP: Group A vs. Group B: -1.2 Proportion achieving normotensive status: Group A 61% vs. Group B 44%; p=0.36
Howe et al, 1991[64] *Fair*	RCT crossover School-based Adelaide, Australia 2 phases of 4 weeks each	103	Mean age 13 years (range 11-14) Mean SBP 115.0 Mean DBP 60.1	Group A: Low-sodium diet (<75 mmol/day) + counseling Group B: High-sodium (>150 mmol/day) diet + counseling	No significant differences in SBP or DBP between diets; baseline values not reported
Sinaiko et al, 1993[66] *Fair*	RCT St. Paul and Minneapolis public schools, U.S. 3 years	210	Mean age 13 years 50% male Mean SBP 113.8 Mean DBP 65.1	Group A: Low sodium diet (<70 mmol/day) Group B: Potassium chloride supplementation Group C: Participant's normal diet + placebo	Changes in SBP: Boys: No significant differences in rates of increase in SBP between low sodium, potassium supplement, and placebo groups Girls: Significant difference in SBP between low sodium group (slight overall decrease) and the placebo group (significant increase from baseline). No other differences between groups. Changes in DBP: Boys: No significant differences in rates of increase in BP between low sodium, potassium supplement, and placebo groups Girls: The low sodium group was the only group that had rates of increase in DBP compared to placebo that were significantly greater than zero.
Exercise					
Hansen et al, 1991[63] *Fair*	RCT Odense, Denmark School-based 8 months	137	Mean age not reported (range 9-11); other demographic characteristics not reported	Group A: Three extra lessons per week of an ordinary school physical education (PE) program Group B: No extra PE lessons	Mean difference at follow-up, SBP: Group A vs. Group B: -6.5 Mean difference at follow-up, DBP: Group A vs. Group B: -3.6
Meditation					
Gregoski et al, 2011[62] *Fair*	RCT School-based 3 months	166	Mean age 15 years 59% female 100% Black Mean SBP 118.9 Mean DBP 63.6	Group A. Breathing awareness meditation (BAM) Group B. LifeSkills training: Group C. Health education control	Mean 24-hour SBP at 3-month follow-up: Group A vs. Group B vs. Group C: 116.6 vs. 119.8 vs. 121.0; Group A vs. Group B: p=0.13; Group A vs. Group C: p=0.05 Mean 24-hour DBP at 3-month follow-up: Group A vs. Group B vs. Group C: 66.3 vs. 68.2 vs. 68.7; p>0.05 for all comparisons (not statistically significant)

Table 6. Lifestyle Interventions for Hypertension in Children and Adolescents

Author, year *Quality rating*	Study design Setting Duration	N	Demographics	Treatment/ Intervention	Blood pressure outcomes (SBP, DBP mmHg)
Progressive Muscle Relaxation					
Ewart et al, 1987[35] *Fair*	RCT 2 large Baltimore City public high schools 9 months	159	BMI range: 19.0-31.2 kg/m2 Mean age 15 years (range 13-17 years) 60% male 55% black	Group A: Progressive muscle relaxation (12 weeks, 15-20 minutes, 4 days per week) provided in school Group B: Control (no intervention)	No significant differences between SBP and DBP between treatment and control groups

BP = blood pressure; DBP = diastolic blood pressure; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation.

Table 7. Effect of Interventions on Blood Pressure: Mean Difference From Baseline and/or Placebo, as Reported

Author, Year Duration	Interventions	Baseline SBP and DBP (mmHg)		Followup SBP and DBP (mmHg)		Mean difference, baseline versus followup (mmHg)		Mean difference at followup, intervention versus placebo (mmHg)	
		SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Drug									
Batisky et al, 2007[72] 4 weeks	Metoprolol 0.2 mg/kg	131.4	76.3	126.2	73.2	-5.2	-3.1	-4.6	-6.1
	Metoprolol 1.0 mg/kg	135	81	127.3	76.1	-7.7	-4.9	-3.5	-3.2
	Metoprolol 2.0 mg/kg	130.60	76.7	124.3	69.2	-6.3	-7.5	-0.2	-10.1
	placebo	132.7	81.4	130.8	79.3	-1.9	-2.1		
Flynn et al, 2004[61] 4 weeks	Amlodipine 2.5 mg	137.9*	74.2*	Not reported		-6.9	-4.2	Not reported	
	Amlodipine 5 mg					-8.7	-4.4		
	placebo					-3.6	-0.4		
Li et al, 2010[65] 4 weeks	Eplerenone 25 mg	125.0	71.3	124.1	70.7	-0.9	-0.6	-5.4	0.8
	Eplerenone 50 mg	125.7	70.9	126.2	70.9	0.5	0.0	-3.3	1.0
	Eplerenone 100 mg	128.1	70.3	127.0	69.4	-1.1	-0.9	-2.5	-0.5
	placebo (mean, all arms)	128.7	70.4	129.5	69.9	0.8	-0.5		
Sorof et al, 2002[67] 4 weeks	Bisoprolol + hydrochlorothiazide (all doses)	133.8	83.0	124.0	76.0	-9.8	-7.0	-4.5	-3.5
	placebo	133.8	81.8	128.5	79.5	-5.3	-2.3		
Trachtman et al, 2003[68] 3 weeks	Felodipine 2.5 mg	Not reported						-0.7	-2.1
	Felodipine 5 mg							-0.1	-4.6
	Felodipine 10 mg							-1.1	1.3
	placebo	Not reported	83.1	Not reported	81.0	Not reported	-2.1		
Trachtman et al, 2008[69] 4 weeks	Candesartan (all doses)	Not reported				-10.2	-6.6	Not reported	
	placebo					-3.7	-1.8		
Wells et al, 2010[70] 4 weeks	Telmisartan, low-dose	132.0	79.0	123.0	71.3	-9.7	-8.1	-3.6	-4.2
	Telmisartan, high-dose	131.0	78.4	117.0	70.6	-14	-7.8	-8.5	-4.9
	placebo	130.0	78.4	126.0	75.5	-6	-3.5		
Drug Plus Lifestyle									
Berenson et al, 1983[58] 6 months	Intervention	116.6	77.7	109.0	70.8	-7.6	-6.9	-6.5	-3.6
	Control	118.5	78.3	115.5	74.4	-3.0	-3.9		
Berenson et al, 1990[59] 30 months†	Intervention	116.6	77.7	118.0	73.5	1.4	-4.2	-3.6	-1.7
	Control	118.5	78.5	122.0	75.2	3.5	-3.3		
Lifestyle									
Couch et al, 2008[60] 6 months	DASH diet	129.4	80.4	120.1	75.2	-9.3	-5.2	0.1	-1.2
	Routine care	124.3	81.7	120.0	76.4	-4.3	-5.3		

Table 7. Effect of Interventions on Blood Pressure: Mean Difference From Baseline and/or Placebo, as Reported

Author, Year Duration	Interventions	Baseline SBP and DBP (mmHg)		Followup SBP and DBP (mmHg)		Mean difference, baseline versus followup (mmHg)		Mean difference at followup, intervention versus placebo (mmHg)	
		SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Ewart et al, 1987[35] 9 months	Relaxation training	127.0	79.1	118.6	72.9	-8.4	-6.2	-2.3	-3.1
	Control (no intervention)	126.5	80.4	120.9	76.0	-5.6	-4.4		
Gregoski et al, 2011[62] 3 months	Meditation	119.4	68.1	116.6	66.3	-2.8	-1.8	-4.4	-2.4
	LifeSkills training	119.6	68.0	119.8	68.2	0.2	0.2	-1.2	-0.5
	Regular health education	121.4	69.3	121.0	68.7	-0.4	-0.6		
Hansen et al, 1991[63] 3 months	Extra PE classes	Not reported						-4.9	-3.8
	No extra classes								
Howe et al, 1991[64] 4 weeks	Low sodium diet	115.0*	60.1*	112.6	59.1	Not reported		-1.2	-0.9
	High sodium diet			113.8	60				

*Values for total cohort; data not stratified according to treatment group.
†Continuation of Berenson 1983 study.

Table 8. Harms of Interventions for Hypertension in Children and Adolescents

Author, Year *Quality rating*	Relevancy (best information reported)	Type of study Setting Duration	Mean age (SD)	# randomized or analyzed	Intervention	Adverse events (AEs)
Drug						
Batisky et al, 2007[57] *Fair*	Inclusion criteria of primary hypertension only	RCT Clinical trial from 28 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 dose-ranging study: 1 withdrawal due to AEs Heart rate decreased by 6.5 beats/min in 1.0 mg/kg group (compared to increase of 5.4 bpm in placebo group), fatigue noted by 1 patient each in the 0.2, 1.0 and 2.0 mg/kg groups) 52-week safety study: 5 withdrawals due to AEs (1 each of fatigue, nightmares, anxiety, dizziness, asthma) Serious AEs: 2/100 (2%; 1 pneumonia and 1 menometrorrhagia) Other AEs: Headache: 30% Upper respiratory tract infection: 20% Cough: 19% Nasopharyngitis: 13% Pharyngolaryngeal pain: 12% Fatigue: 9% Diarrhea: 7% Dizziness: 6%
Flynn et al, 2004[61] *Fair*	31% primary hypertension	RCT crossover Clinical trial from 49 centers in North and South America 2 4-week phases	12.1 (3.3)	268 randomized; 84 with primary hypertension	Amlodipine 2.5 to 5.0 mg/day Placebo	Withdrawals due to AEs: 12/268, of which 6 considered by study investigators to be study drug-related (3 worsening hypertension, 1 facial edema, 1 finger edema and rash, 1 premature ventricular contractions) Serious AEs: 5/268 (2%; 1 each: urinary tract infection, gastroenteritis and hypovolemia, pulmonary edema, bilateral pneumonia, pancreatitis)
Hazan et al, 2010[73] *Good*	Hypertensive primary hypertension in 128+97/302; Patients with clinically significant medical condition or chronic disease, malignant hypertension or severe hypertension excluded	RCT clinical trial at 61 sites; 2 cohorts based on race, 2 week washout period Phase 1: 3 week dosing study Phase 2: 2 week withdrawal study	12.2 (2.97)	422 screened 302 randomized to 2 cohorts	Olmesartan medoxomil	Any adverse event: olmesartan 33/93 (36%) vs. placebo 27/89 (30) Incidence of specific AEs not reported; headache reported “most common”

Table 8. Harms of Interventions for Hypertension in Children and Adolescents

Author, Year *Quality rating*	Relevancy (best information reported)	Type of study Setting Duration	Mean age (SD)	# randomized or analyzed	Intervention	Adverse events (AEs)
Li et al, 2004[74] *Fair*	Hypertensive (20.9% with renal etiology, otherwise not reported), or high-normal blood pressure 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	Overall study withdrawals across all 4 phases of study due to AEs: 5/253 (2%) Phase C: Incidence of AEs similar between placebo (33.9%) and combined fosinopril treatment groups (34.3%) Phase D: Specific AEs: Headache: 51/253 (20%) Nasopharyngitis: 24/253 (10%) Cough: 23/253 (9%) Pharyngitis: 22/253 (9%) Abdominal pain: 16/253 (6%)
Li et al, 2010[65] *Fair*	56% primary hypertension 22% obesity-related hypertension 17% renal-related hypertension	RCT clinical trial in 43 centers in the U.S., India, South Africa, Russia, and Dominican Republic Phase A: 6 week dosing study (no placebo) Phase B: 4 week placebo-controlled study	Age <12 years: 52.6%	304 randomized	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	Phase A: Any AE: low-dose 38% vs. middle-dose 31% vs. high-dose 40% 274 reports of mild AEs, mainly headache and upper respiratory tract infections 106 reports of moderate AEs 18 reports of severe AEs (4 possibly or definitely related to treatment: migraine, fatigue, bronchitis, headache) 4 permanent discontinuations, 3 of which were considered treatment-related: hypotension, hypertension, fatigue Phase B: No significant differences in AE frequencies between active therapy and placebo; 8 patients had worsening hypertension during this phase, including 2 in the high dose group that were withdrawn from the study
Shahinfar et al, 2005[75] *Fair*	Hypertension; "more than 50% had underlying kidney disease" (secondary hypertension) but no further details reported	Dose-ranging RCT: Phase 1 randomized to 3 different doses, Phase 2 randomized washout; 43 clinical centers in North and South America (including U.S.), Europe, Africa 36 days	12 (3.1)	175 randomized	Losartan	Withdrawals due to AEs: 1/175 (<1%) Drug-related AEs: 14/175 (8%), of which headache (5) was most common event Comparison of AE in Phase 2 between active drug and control not reported

Table 8. Harms of Interventions for Hypertension in Children and Adolescents

Author, Year *Quality rating*	Relevancy (best information reported)	Type of study Setting Duration	Mean age (SD)	# randomized or analyzed	Intervention	Adverse events (AEs)
Soffer et al, 2003[76] *Fair*	Hypertension; unclear severity of underlying kidney disease (study entry required glomerural filtration rate ≥30 ml/min/1.73 m^2)	Dose-ranging RCT Phase 1 randomized to 3 different doses, Phase 2 randomized washout Multisite (number and location not reported); 29 days	Mean not reported 47% <6 to 12 years, 53% 13 to 16 years	115 randomized	Lisinopril	Withdrawals due to AEs: 1/115 (<1%) Drug-related AEs: 14/115 (12%) Headache: 4/115 (4%) Gastrointestinal (abdominal pain, diarrhea, nausea and/or vomiting): 2/115 (2%) Dizziness: 2/115 (2%) Cough: 1/115 (<1%)
Sorof et al, 2002[67] *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)	Bisoprolol fumarate/ hydrochlorothiazide combination (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) B/HT group: Most common AE was headache (26%) 1 patient had severe hypertension, and discontinued the study. Placebo group: Most common AE was headache (31%) 2 patients had severe hypertension, and discontinued the study
Trachtman et al, 2003[68] *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"; heart rate was 96 bpm and ECG normal; and 1 withdrawal due to vomiting the first dose (5 mg) % reporting AEs: placebo 66% and 64%, 56%, and 77% in the felodine ER 2.5 mg, 5.0 mg, and 10 mg groups, respectively Most common AEs were headaches (33%), respiratory infections (12%), and nausea (10%) Pedal edema was noted in 2 (2%) of patients
Trachtman et al, 2008[69] *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 blood pressure	3/240 patients in the 4 week trial and 5/233 patients in the 52 week study discontinued due to AEs, specifically hypotension, arm fracture, dizziness, headache, low white blood cell count, and progression of underlying renal disease (2 patients) Most common AEs: headache, upper respiratory infection, dizziness, cough, and sore throat

Table 8. Harms of Interventions for Hypertension in Children and Adolescents

Author, Year *Quality rating*	Relevancy (best information reported)	Type of study Setting Duration	Mean age (SD)	# randomized or analyzed	Intervention	Adverse events (AEs)
Wells et al, 2002[77] *Fair*	Severe or symptomatic hypertension excluded	Dose-ranging RCT 2 week dose ranging phase and 2 week placebo controlled washout phase	Median 12 years	110 enrolled	Enalapril	Drug-related AEs: 12/110 (11%) Dizziness: 4/110 (4%) Headache: 2/110 (2%) Cough: 3/110 (3%) No incidence of renal failure, angioedema or hyperkalemia 5 laboratory AEs possibly, probably or definitely related to study drug
Wells et al, 2010[70] *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
Drug Plus Lifestyle						
Berenson et al, 1983[58] *Fair*	BP >90th percentile for height, Control group with blood pressure <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 blood pressure treatment group, 50 high blood pressure comparison group, 50 medium blood pressure 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 <40kg, 12.5 mg/day for those >40 kg + nutrition education and promotion of dietary modification to children and parents Group B (high blood pressure elevation at baseline): No treatment Group C (medium BP elevation at baseline): No treatment	AEs reported as very low incidence with no major complications 1 temporary withdrawal from active treatment due to nightmares

Table 8. Harms of Interventions for Hypertension in Children and Adolescents

Author, Year *Quality rating*	Relevancy (best information reported)	Type of study Setting Duration	Mean age (SD)	# randomized or analyzed	Intervention	Adverse events (AEs)
Other Clinical Studies (FDA Analyses)						
Baker-Smith et al, 2010[79] *Not rated for quality*	Mild to moderate hypertension	Non-systematic review and meta-analysis of data from 8 trials submitted to FDA between 1998 and 2005 (original studies not cited) 2 weeks (median)	13	1,299 analyzed (42% placebo + 58% active drug)	ACEs [6 datasets] and ARBs [2 datasets], including benazepril (n=85), enalapril (n=101), fosinopril (n=222), lisinopril (n=104), quinapril (n=112), ramipril (n=217), irbesartan (n=293), losartan (n=165) Dosages not reported	Subjects who reported cough in the cohort receiving active drugs (21/748, 2.8%) vs. placebo (14/551, 2.5%), p=0.86 Subjects who reported cough in the ACE group: (17/524, 3.2%); ARB group (4/224, 1.8%), p=0.34
Smith et al, 2008[78] *Not rated for quality*	Unclear; severe hypertension and significant renal disease excluded	Non-systematic review and meta-analysis of data from 10 RCTs submitted to FDA between 1998 and 2005 (original studies not cited) 2 to 4 weeks (varied by trial)	12.1	1,707 analyzed (685 placebo, 1,022 active treatments)	Active treatments (n=1,022; mean doses not reported): Amlodipine (n=258), Benazepril (n=85), Enalapril (n=101), Felodipine (n=133), Fosinopril (n=235), Irbesartan (n=295), Lisinopril (n=104), Losartan (n=165), Quinapril (n=112), Ramilpril (n=219) Placebo (n=685)	Placebo vs. active treatment : No significant difference between groups for any AEs Any AE: 235/685 (34%) vs. 382/1,022 (37%) Hypertension: 3/685 (4%) vs. 1/1,022 (>1%) Hypotension: 0/235 (0%) vs. 3/1,022 (>1%) Cardiac: 8/685 (1%) vs. 16/1,022 (2%) Neuropsychological: 13/685 (2%) vs. 26/1,022 (3%) Headache: 113/685 (17%) vs. 179/1,022 (18%) Syncope: 15/685 (2%) vs. 31/1,022 (3%) Gastrointestinal: 54/685 (8%) vs. 90/1,022 (9%) Asthma: 11/685 (2%) vs. 12/1,022 (1%) Elevated LFT: 7/685 (1%) vs. 7/1,022 (>1%) Muscle aches: 11/685 (2%) vs. 17/1,022 (2%)

ACE = angiotensin-converting enzyme inhibitors; AE = adverse events; ARB = angiotensin receptor blockers; bpm = beats per minute; B/HT = bisoprolol fumarate/hydrochlorothiazide; ECG = electrocardiograph; ER = extended release; FDA = United States Food and Drug Administration; LFT = liver function test; RCT = randomized controlled trial; SD = standard deviation.

Table 9. Summary of Evidence

No. of Studies *Overall quality rating*	Limitations	Consistency	Primary care applicability	Summary of findings
Key Question 1. Is screening for hypertension in children/adolescents effective in delaying the onset of or reducing adverse health outcomes related to hypertension?				
No studies	NA	NA	NA	NA
Key Question 2. What is the diagnostic accuracy of screening tests for elevated blood pressure in children/adolescents?				
2 trials *Quality of evidence: Poor*	Studies were flawed or not directly applicable to an asymptomatic U.S. population; Only one included a comparison to a gold standard of ambulatory monitoring	Consistent	Low	Sensitivity and specificity of office-based screening for hypertension was 0.65 and 0.75 (positive predictive value 0.37) compared to ambulatory screening in one study of a referred population A second, school-based study comparing an initial positive screen to subsequent diagnosis of hypertension had similar sensitivity (0.72) and specificity (0.92) but the positive predictive value was lower (0.17)
Key Question 3. What is the association between hypertension in children/adolescents and hypertension and other intermediate outcomes in adults?				
10 cohort studies *Quality of evidence: Poor*	Studies used different thresholds for defining elevated blood pressure and hence hypertension in childhood, and different definitions of hypertension in adulthood; Studies had methodologic shortcomings	Inconsistent	Moderate	Sensitivities and specificities of elevated blood pressure or hypertension from childhood to adult hypertension ranged from 0 to 0.66 and specificities of 0.77 to 1. PPVs ranged from 0.19 to 0.65. Five studies reported significant associations between elevated blood pressure in childhood and hypertension in adults, with ORs ranging from 1.1 to 4.5, and RRs of 1.5 to 9. The two studies which reported associations between childhood hypertension and carotid intima media thickness in young adults provided conflicting findings, while the single study which reported associations between childhood hypertension and microalbuminuria found a significant association only in black individuals
Key Question 4. What are the adverse effects of screening for hypertension in children/adolescents, including labeling and anxiety?				
1 study *Quality of evidence: Poor*	Evidence limited to results from one, good-quality study	Not applicable (one study)	High	Children labeled as hypertensive did not miss more days of school in the year following diagnosis compared to pre-labeling or compared to non-hypertensive children. Other harms associated with screening were not reported
Key Question 5. What is the effectiveness of drug, nondrug, and combination therapies for treating primary hypertension in children/adolescents?				
14 RCTs *Quality of evidence: Poor*	No drug study lasted more than 4 weeks For many studies, the proportion of children with secondary hypertension at baseline was high or unclear	Consistent	Moderate	Children achieving normotensive status (based on varying definitions) ranged from 15% to 86% in patients taking drug treatments and 11% to 48% in patients taking placebo Results showed significant reductions with some doses of some drugs in mean SBP, ranging from 2 to 10 mmHg, and mean DBP, ranging from 0.4 to 8 mmHg from baseline to followup; similarly, SBP reductions were 0 to 9 mmHg and DBP reductions were 0.5 to 10 mmHg between intervention and placebo groups. However reductions were often only at higher doses of active treatments, and studies only lasted for 4 weeks One study of a school-based drug plus lifestyle intervention reported a sustained reduction in blood pressure in the combination group that was significantly better than the control group Studies of non-drug therapies were limited and only one study of additional physical education classes in school compared to no extra classes reported a sustained mean reduction

Table 9. Summary of Evidence

No. of Studies *Overall quality rating*	Limitations	Consistency	Primary care applicability	Summary of findings
Key Question 6. What is the effectiveness of drug, nondrug, and combination therapies initiated for the treatment of primary hypertension in children/adolescents for reducing blood pressure and other intermediate outcomes in adults?				
No studies	NA	NA	NA	NA
Key Question 7. What is the effectiveness of drug, nondrug, and combination therapies initiated for the treatment of primary hypertension in children/adolescents for reducing adverse health outcomes in adults related to primary hypertension?				
No studies	NA	NA	NA	NA
Key Question 8. What are the adverse effects of drug, nondrug, and combination therapies for treating primary hypertension in children/adolescents?				
15 studies (13 RCTs, 2 FDA analyses) *Quality of evidence: Fair*	Numerous trials from Key Question 5 did not report comparative events rates between active treatment and placebo arms, and adverse event rates in general were not well-reported in most studies	Consistent	Moderate	Studies of drug treatments used to treat hypertension in children and adolescents mostly reported no differences between active treatments and placebo in adverse event rates or in withdrawals due to adverse events, except for one study where a combination of bisoprolol and hydrochlorothiazide was associated with lower adverse event rates than placebo Four studies reported serious adverse events, though with the exception of one case of syncope due to a dosing error, serious adverse events were generally not deemed treatment-related. Pooled FDA data found no significant difference between drug treatments and placebo in incidence of specific adverse events, including headache (the most commonly reported adverse event), cardiac events, gastrointestinal events and cough No studies reported on harms associated with non-drug treatments

DBP = diastolic blood pressure; FDA = U.S. Food and Drug Administration; NA = not applicable; OR = odds ratio; PPV = positive predictive value; RCT = randomized controlled trials; RR = relative risk; SBP = systolic blood pressure.

Appendix A1. Search Strategies

Screening

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

1 Hypertension/ or hypertension.mp.
2 prehypertension.mp.
3 pre-hypertension.mp.
4 2 or 3
5 high blood pressure.mp.
6 or/1-5
7 Mass Screening/
8 6 and 7
9 limit 8 to (english language and humans)
10 limit 9 to "all child (0 to 18 years)"
11 9 and (child$ or pediatri$ or adolescen$ or school-age).mp.
12 10 or 11

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 Hypertension/ or hypertension.mp.
2 prehypertension.mp.
3 pre-hypertension.mp.
4 2 or 3
5 high blood pressure.mp.
6 or/1-5
7 Mass Screening/
8 6 and 7
9 8 and (child$ or pediatri$ or school or adolescen$ or teen$).mp.

Diagnostic Accuracy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

1 Hypertension/
2 prehypertension.mp. or Prehypertension/
3 1 or 2
4 Blood Pressure Determination/
5 sensitivity.mp.
6 specificity.mp.
7 5 and 6
8 "Sensitivity and Specificity"/
9 7 or 8
10 3 and 9
11 4 and 9
12 10 or 11
13 limit 12 to "all child (0 to 18 years)"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 Hypertension/
2 prehypertension.mp. or Prehypertension/
3 1 or 2

4 Blood Pressure Determination/
5 sensitivity.mp.
6 specificity.mp.
7 5 and 6
8 "Sensitivity and Specificity"/
9 7 or 8
10 3 and 9
11 4 and 9
12 10 or 11
13 12 and (child$ or pediatr$ or school or adolescen$ or teen$).mp.

Tracking

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE
1 "cardiovascular risk in young finns".mp.
2 "bogalusa heart".mp.
3 muscatine.mp.
4 ("childhood determinants of adult health" or cdah).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5 or/1-4
6 5 and (child$ or pediatric$ or adolescen$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7 blood pressure.mp. or Blood Pressure/
8 Hypertension/ or hypertension.mp.
9 7 or 8
10 9 and (child$ or pediatric$ or adolescen$).mp.
11 10 and adult$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12 Longitudinal Studies/
13 11 and 12
14 6 or 13
15 "Amsterdam Growth and Health Longitudinal Study".mp.
16 15 and (child$ or pediatric$ or adolescen$).mp.
17 14 or 16
18 17 not pregnancy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19 17 not infan$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20 18 or 19
21 limit 20 to (english language and humans)
22 Atherosclerosis/
23 Vascular Diseases/
24 Albuminuria/

25 Cerebrovascular Disorders/
26 Hypertrophy, Left Ventricular/
27 Hypertension/
28 or/22-27
29 21 and 28

Interventions

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

1 Hypertension/dh, de, dt, pc, rt, rh, su, th [Diet Therapy, Drug Effects, Drug Therapy, Prevention & Control, Radiotherapy, Rehabilitation, Surgery, Therapy]
2 Weight Loss/
3 Exercise/
4 dietary modification.mp. or Food Habits/
5 Diet, Sodium-Restricted/
6 Angiotensin-Converting Enzyme Inhibitors/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
7 Angiotensin II Type 1 Receptor Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
8 Labetalol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
9 Adrenergic beta-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
10 Atenolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
11 Bisoprolol/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use]
12 Metoprolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
13 Propranolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
14 Calcium Channel Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
15 Amlodipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
16 Felodipine/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
17 Isradipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
18 Nifedipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
19 Clonidine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
20 Diuretics/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
21 Hydrochlorothiazide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]

22 Chlorthalidone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
23 Furosemide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
24 Spironolactone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
25 Triamterene/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity] (
26 Amiloride/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
27 Adrenergic alpha-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
28 Doxazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
29 Prazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
30 Vasodilator Agents/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
31 Hydralazine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
32 Minoxidil/ad, ae, po, tu [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use]
33 Captopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
34 Enalapril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
35 Fosinopril/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
36 Lisinopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
37 Losartan/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
38 (benazepril or quinapril or irbesartan or terazosin).mp.
39 or/2-38
40 Hypertension/
41 39 and 40
42 1 or 41
43 limit 42 to (english language and humans)
44 limit 43 to "all child (0 to 18 years)"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Weight Loss/
2 Exercise/
3 dietary modification.mp. or Food Habits/
4 Diet, Sodium-Restricted/

5 Angiotensin-Converting Enzyme Inhibitors/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
6 Angiotensin II Type 1 Receptor Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
7 Labetalol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
8 Adrenergic beta-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
9 Atenolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
10 Bisoprolol/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use]
11 Metoprolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
12 Propranolol/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
13 Calcium Channel Blockers/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
14 Amlodipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
15 Felodipine/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
16 Isradipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
17 Nifedipine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
18 Clonidine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
19 Diuretics/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
20 Hydrochlorothiazide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
21 Chlorthalidone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
22 Furosemide/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
23 Spironolactone/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
24 Triamterene/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
25 Amiloride/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
26 Adrenergic alpha-Antagonists/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
27 Doxazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]

28 Prazosin/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
29 Vasodilator Agents/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
30 Hydralazine/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
31 Minoxidil/ad, ae, po, tu [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use]
32 Captopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
33 Enalapril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
34 Fosinopril/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
35 Lisinopril/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
36 Losartan/ad, ae, po, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Toxicity]
37 (benazepril or quinapril or irbesartan or terazosin).mp.
38 or/1-37
39 Blood Pressure/
40 38 and 39

Systematic Reviews
Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 hypertension.ti.
2 blood pressure.ti.
3 1 or 2
4 3 and (child$ or pediatri$ or school or adolescen$ or teen$).mp.
5 4 not (neonat$ or newborn or infan$).ti.
6 5 not (pregnan$ or postpartum).ti.

Appendix A2. Inclusion and Exclusion Criteria

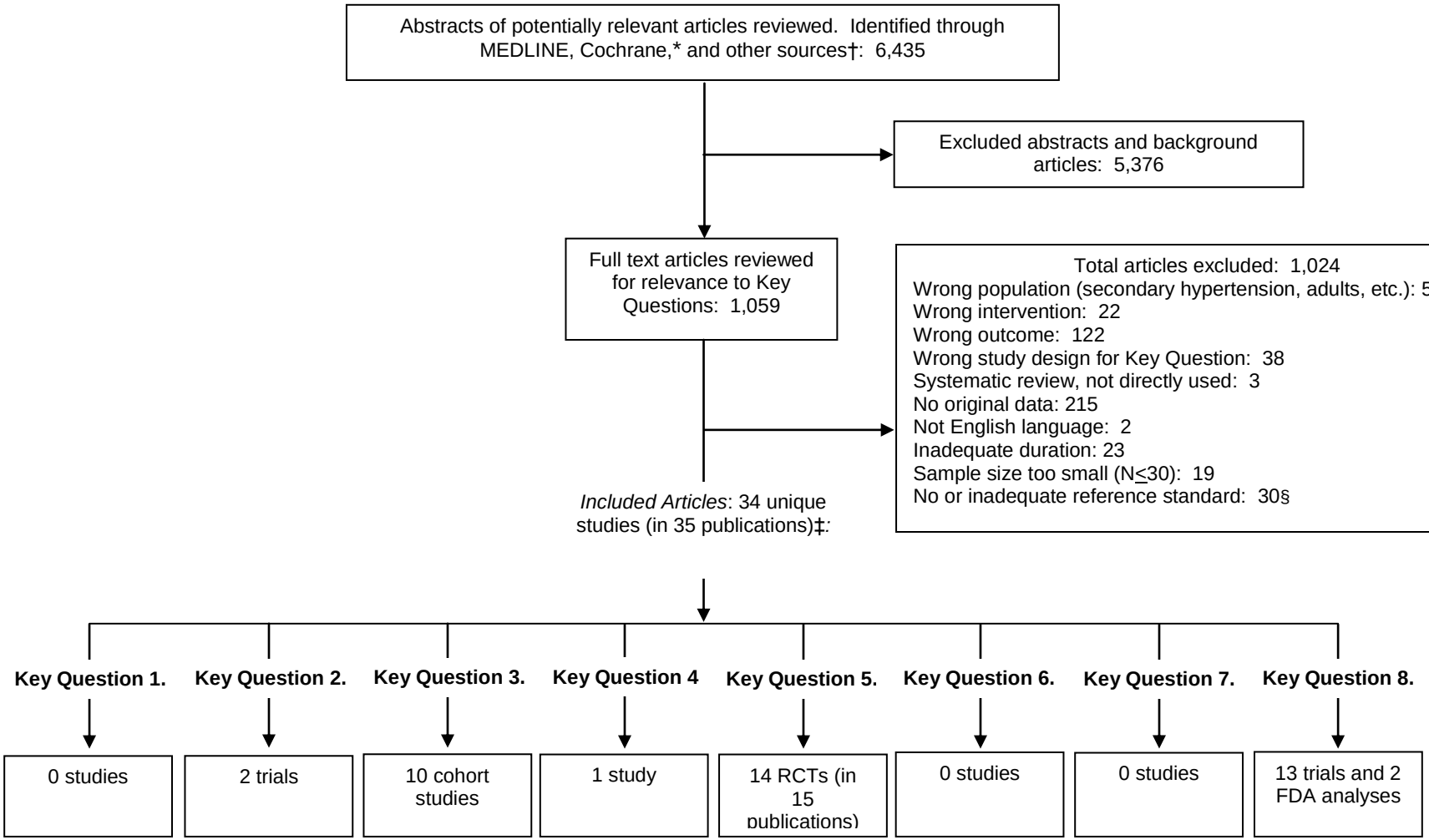
	Key Questions	Inclusion Criteria	Exclusion Criteria
Settings	All KQs	Primary care clinics, well-child/adolescent visits, school or community-based screening	Pediatric specialty/subspecialty clinics, inpatient or long-term care settings, emergency or urgent care facilities
Populations	KQs 1, 2 & 4:	Asymptomatic, otherwise healthy children and adolescents, ages 0-18, with no known diagnosis of hypertension	Pregnant adolescents Majority of study population includes secondary hypertension
	KQs 3, 5-8:	Primary hypertension defined as average blood pressure between 95th centile and 5mmHg above the 99th percentile	
Interventions	KQs 1-4:	Blood pressure measurements using auscultatory or oscillometric devices that can be performed in a primary care clinic	24 hour or ambulatory blood pressure measurements, home-based blood pressure measurements; Diagnostic tests or investigations used to identify or confirm possible causes of secondary hypertension
	KQs 5-8:	*Drug:* Antihypertensive medications which are currently FDA-approved for use in children/adolescents *Lifestyle:* Diet, exercise, etc.	Interventions for treatment of secondary hypertension Interventions where hypertension was not a primary objective of the study (e.g., weight loss studies)
Outcomes	KQs 4, 5 & 6:	Blood pressure Left ventricular hypertrophy (defined using left ventricular mass index and/or measures of left ventricular geometry) Urinary albumin excretion (microalbuminuria) Intima-medial thickness (measured at carotid and/or femoral arteries) Retinal vascular changes	Measures of cognitive function Blood pressure variability, such as diurnal variations, or nocturnal blood pressure dipping Arterial wall dysfunction, including measures of arterial stiffness, pulse wave velocity, augmentation index Metabolic measures, namely glucose tolerance or other measures of impaired glucose tolerance, insulin levels, lipid profiles, homocysteine levels Uric acid levels Inflammatory markers including C-reactive protein Changes in weight or body mass index
	KQs 1 & 7:	Severe visual impairment Stage IV or V chronic kidney disease Cardiovascular events, including ischemic heart disease, heart failure Cerebrovascular events, including haemorrhagic and thrombotic stroke, hypertensive encephalopathy Mortality (all-cause and disease-specific)	-
	KQ 2	Measures of predictive validity of screening studies (e.g., predictive value, likelihood ratios, sensitivity, specificity)	Studies that do not provide enough data to recreate 2 x 2 tables or calculate sensitivity and specificity Studies that do not employ a true reference standard for comparison
	KQ 3	Measures of association (e.g., odds, odds ratio; risk ratio, sensitivity, specificity, correlation or regression coefficients)	-
	KQ 8	Side effects of hypertension treatments for interventions	-

Appendix A2. Inclusion and Exclusion Criteria

	Key Questions	Inclusion Criteria	Exclusion Criteria
Study Designs	KQ 1	RCTs, controlled clinical trials, observational studies with a comparison group (e.g., comparative cohort and case-control studies), and systematic reviews	-
	KQ 2	Studies of predictive validity that compare to a reference standard (i.e., ambulatory monitoring)	-
	KQ 3	Longitudinal cohort and epidemiology studies	-
	KQs 4 & 8	RCTs, controlled clinical trials, observational studies with a comparison group (e.g., large cohort and case-control studies), and systematic reviews. If none, uncontrolled before-after studies	-
	KQs 5, 6, 7	RCTs, controlled clinical trials, observational studies with a comparison group (e.g., large cohort and case-control studies), and systematic reviews	-

KQ = key question.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Other sources include reference lists, suggested by peer reviewers, etc.
‡ Some articles are included for more than one Key Question.
§ Twelve of these studies did not provide enough data to recreate 2 x 2 tables or calculate sensitivity and specificity.

FDA = United States Food and Drug Administration; RCT = randomized controlled trial.

Wrong Population

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Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test
- Random or consecutive selection of patients
- Screening cutoff pre-determined
- All patients undergo the reference standard

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; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients (i.e. applicable to most screening settings).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) 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, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- 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 (follow-up at least 80 percent); 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 to confounders in analysis.

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 whether some (although not major) differences occurred in follow-up; 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.

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

Reference: Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: A review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID: 11306229

Appendix A6. Expert Reviewers of the Draft Report

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Appendix B1. Diagnostic Accuracy of Screening Tests for Elevated Blood Pressure

Study, year	Screening test	Reference standard	Type of study	Country Setting Screener	Population	Proportion with condition	Definition of a positive screening exam	Proportion unexaminable by screening test
Fixler and Laird, 1983[33]	Three measures with mercury manometer measured at least 4 weeks apart	Initial screening results compared to subsequent measures	Prospective cohort	U.S. Middle and high school Trained school health personnel and nurses	8th graders with follow up at 10th grade n=9,017 Mean age not reported; all were in 8th grade at time of initial screening 53% male 44% Black 42% White 14% Hispanic	10th grade: 153/9017 (2%)	Systolic or diastolic blood pressure ≥95th percentile based on normative levels for the study population	NR
Stergiou et al, 2008[31]	Three averaged measurements with mercury sphygmomanometer, measured in nondominant arm in sitting position after 5 minutes at rest	24-hour ambulatory measurements at 20-minute intervals	Prospective cohort	Greece Specialty hypertension clinic Physicians	n=102; 100% referred for screening Mean age 12.8 years (SD 2.9; range 6-18) 63% male Race NR Mean BMI 23.8 kg/m^2	Clinic: 38/102 (37%) Ambulatory: 31/102 (30%) Home: 23/102 (22%)	Systolic or diastolic blood pressure ≥95th percentile based on U.S. normative blood pressure tables	NR

Study, year	Analysis of screening failures	Proportion who underwent reference standard and included in analysis	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Quality rating
Fixler and Laird, 1983[33]	NR	100%	Initial positive screen vs subsequent screens: 0.72 (0.65 to 0.78)	Initial positive screen vs subsequent screens: 0.92 (0.91 to 0.92)	Initial positive screen vs subsequent screens: 8.5 (7.6 to 9.5)	Initial positive screen vs subsequent screens: 0.31 (0.24 to 0.38)	Initial positive screen vs subsequent screens: 0.17 (0.15 to 0.2)	Initial positive screen vs subsequent screens: 0.993 (0.991 to 0.994)	Fair
Stergiou et al, 2008[31]	NR	100%	Positive ambulatory result vs positive clinic result: 0.65 (0.45 to 0.80)	Positive ambulatory result vs positive clinic result: 0.75 (0.63 to 0.84)	Positive ambulatory result vs positive clinic result: 1.11 (0.71 to 1.74)	Positive ambulatory result vs positive clinic result: 0.48 (0.29 to 0.77)	Positive ambulatory result vs positive clinic result: 0.37 (0.28 to 0.47)	Positive ambulatory result vs positive clinic result: 0.63 (0.53 to 0.72)	Fair

BMI = body mass index; CI = confidence interval; NR = not reported; SD = standard deviation; U.S. = United States.

Appendix B2. Quality Assessment of Diagnostic Accuracy Studies

Study, year	Representative spectrum	Random or consecutive sample	Screening test adequately described	Screening cutoffs predefined	Credible reference standard	Reference standard applied to all screened patients	Same reference standard applied to all patients	Reference standard and screening examination interpreted independently	High rate of uninterpretable results or noncompliance with screening test	Analysis includes patients with uninterpretable results or noncompliance	Quality rating
Fixler and Laird, 1983[33]	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	No	No	Fair
Stergiou et al, 2008[31]	No	No	Yes	Yes	Yes	Yes	Yes	Unclear	No	No	Fair

Appendix B3. Other Studies of Diagnostic Accuracy

Study, year	Screening test	Reference standard	Type of study	Setting; Screener	Subjects	Age, sex, and race of enrollees
Berenson et al, 1993[34]	Mercury sphygmomanometer or physiometrics automatic recording device	Three additional measurements at three week intervals	Cohort	School-based screening; Nurses	Children in third grade through high school in Franklinton, LA	Mean age NR (range 8-18 years) 50% White 50% Black
Ewart et al, 1987[35]	Hawksley mercury column sphygmomanometer, using either adult or pediatric cuff, after 10 minutes at rest	Two additional measurements over six-week screening period	RCT	School-based screening; Certified technicians	Children in 9th and 10th grade at two large public high schools in Baltimore, Maryland	Mean age 15 years 55% Black (of 110 participants)
Fixler et al, 1979[36]	Random-zero mercury sphygmomanometer with appropriate cuff, on right arm, in sitting position after four minutes rest	Two subsequent measurements with at least four weeks between second and third measurements	Cohort	Dallas Independent School District; Public health, vocational, and school nurses and nurses' aides	Eighth-grade students	Mean age 14 years 46% Black 40% White 14% Latin-Americans
Kelsall & Watson, 1990[37]	Standard mercury sphygmomanometer with appropriate cuff, at end of health appraisal with child in sitting position	Three measurements; ≥95th percentile referred for further testing	Cohort	18 junior schools: Nottingham, England; School nurses	School children aged 10 or 11	Mean age NR (range 10-11 years) Race not reported
Michaud et al, 1989[38]	Random-zero mercury sphygmomanometer with adult cuff, on right arm, in sitting position after a few minutes rest	Two additional measurements, one after 10 minutes followed by a third measurement after one month or Confirmation by a physician	Cohort	High schools and vocational schools; the Canton of Vaud, Switzerland; Public health nurses	White adolescents aged 16 through 19 years	Mean age NR (range 16-19 years) 100% White
Miller and Shekelle, 1976[39]	Mercury sphygmomanometer on right arm after 5 to 10 minutes lying flat quietly on a cot	Elevated BP on screening, recalled for repeat BP by pediatric cardiologist. If BP at this visit remained high, then had up to four subsequent measurements over 20 to 30 minutes	Cohort	High school;Greater Chicago, IL region;Trained technicians	Black or White 10th graders	Mean age 15 years 52% Male 94% White 6% Black
Moore et al, 2009[40]	Average of two measurements one minute apart using digital BP monitor, with appropriate cuff on right arm, in seated position, after resting for 3-5 minutes	Two additional measurements on separate occasions	Cohort	Anadarko, OK public school district; School nurses	Elementary, middle or high-schoolers	Mean age 11 years (range 5-17 years) 50% Male 61% American Indian 28% White 6% Hispanic 5% Black

Appendix B3. Other Studies of Diagnostic Accuracy

Study, year	Screening test	Reference standard	Type of study	Setting; Screener	Subjects	Age, sex, and race of enrollees
Rames et al, 1978[41]	Mercury sphygmomanometer on right arm, in seated position, after a short explanation of the procedure	Second measurement, followed by three more measurements after lying quietly for 30 minutes	Cohort	Schools; Muscatine, IA; Nurses	Students aged 5 to 18 years	Mean age NR (range 5 to 18 years) 50% Male 96% White other races not reported
Reichman et al, 1975[42]	Mercury sphygmomanometer, in seated position, with left arm resting on a table; positive screens immediately confirmed by a blinded observer	Rescreening at least one week after initial positive	Cohort	High School of Fashion Industries, New York, NY; Trained community workers	Students aged 12 to 20 years	Mean age NR (90% aged 14-17 years; total range 12 to 20 years) 10% Male 78% Black 21% White 1% Other
Sailors et al, 1983[43]	Mercury sphygmomanometer	Subsequent mercury sphygmomanometer readings (up to three measurements)	Cohort	Elementary, middle, and high schools Yonkers, NY; Trained health aid	Children in grades 3, 7, and 10	Mean age NR; 36% 3rd graders, 39% 7th graders, 25% high school (primarily 10th grade) 69% White 19% Black 11% Hispanic 1% Arabic 1% Asian
Sinaiko et al, 1988[44]	Mercury sphygmomanometer on right arm, in seated position, average of 2 readings	Children with BP $\geq$70th centile of age specific distribution had a single further visit for a 2 further BP measurements which were averaged, within three weeks of the initial screen	Cohort	Public schools; St. Paul and Minneapolis, MN; Trained personnel	Children aged 10 to 16 years old	Mean age NR (range 10 to 16 years) 74% White 26% Black
Stern et al, 1980[45]	Two averaged measurements with a mercury sphygmomanometer, on the right arm, with students in sitting position	Rescreening four months after index test	Baseline sampling for trial recruit-ment	High schools; Kannapolis, Concord, and Cabarrus Counties, North Carolina; Nurses	High school students	Mean age NR (range 15-19 years) Race NR

Appendix B3. Other Studies of Diagnostic Accuracy

Study, year	Number screened	Definition of a positive screening exam	Proportion with positive screening exam	Definition of a case	Proportion with positive reference standard and recreened	True positive rate
Berenson et al, 1993[34]	1,604	BP ≥90th percentile	255/1,604 (15.9%)	Four consecutive measurements ≥90th percentile	255/1,604 (16%)	89/255 (35%)
Ewart et al, 1987[35]	1,400	Blood pressure >85th percentile of the screening distribution	299/1,400 (21.4%)	Initial screening between 85th and 95th percentile: second measurement at the end of the semester Initial screening above the 95th percentile: three measurements above 95th percentile during six-week screening period	299/1,400 (21%)	159/299 (53%)
Fixler et al, 1979[36]	10,641	SBP or DBP ≥95th percentile	Single measurement 947/10,641 (8.9%)	Three positive screens	947/10,641 (9%)	167/947 (18%)
Kelsall & Watson, 1990[37]	677	SBP or DBP >90th or 95th percentile	Single measurement 90th percentile: 35/677 (5.2%) 95th percentile: 19/677 (2.8%)	Positive screen on three measurements	35/677 (5%)	9/35 (26%)
Michaud et al, 1989[38]	3,386	DBP ≥90 or above and/or SBP ≥140	113/3,386 (3.3%)	Positive screen on three measurements	338/3,386 (10%)	113/338 (33%)
Miller and Shekelle, 1976[39]	13,231	SBP ≥145 and/or DBP ≥85	602/13,231 (4.5%) initial positive screen	Positive screen upon second examination	403/13,231 (3%)	191/403 (47%)
Moore et al, 2009[40]	1,829	≥95th percentile according to NHBPEP standards	252/1,829 (13.8%)	BP >95th percentile upon 2 or more occasions of rescreening	252/1,829* (13.8%) *Assuming all initially positive screens rescreened; unclear from text if this is the case	42/252 (17%)
Rames et al, 1978[41]	6,622	BP >95th percentile or greater than 140/90	1,179/6,622 (17.8%)	Up to 4 positive rescreens	931/6,622 (14%; not all positive screens rescreened)	41/931 (4%)
Reichman et al, 1975[42]	1,863	BP ≥140/90	110/1,863 (5.9%)	Positive screen on two measurements (includes initial screening measurement)	110/1,862 (5.9%)	46/110 (42%)
Sailors et al, 1983[43]	5,399	SBP 130 mmHg systolic and/or DBP 85 mmHg or higher	140/5,399 (2.6%)	Followup BP at or above 130/85	140/5,399 (3%)	36/140 (26%)

Appendix B3. Other Studies of Diagnostic Accuracy

Study, year	Number screened	Definition of a positive screening exam	Proportion with positive screening exam	Definition of a case	Proportion with positive reference standard and recreened	True positive rate
Sinaiko et al, 1988[44]	10,446	DBP ≥82 mmHg in children 10 to 12 years old, or ≥85 mmHg in children 13 years or older or SBP ≥130 mmHg	SBP: 223/10,446 DBP: 475/10,446	Elevated BP on 2 separate occasions.	2,808/10,446 (27%)	SBP: 50/223 (22%) DBP: 81/475 (17%)
Stern et al, 1980[45]	5,000	SBP ≥140 mmHg, and/or DBP >90 mmHg	172/5,000 (3.4%), of which only 118 available for confirmation by reference standard, of whom 50 had elevated BP at 2nd measure	Elevated BP on 2 occasions (initial screen, and repeat test 4 months later)	118/5,000 (2%)	50/118 (42%)

BP = blood pressure; DBP=diastolic blood pressure; NHBPEP = National High Blood Pressure Education Program; NR = not reported; RCT = randomized controlled trial; SBP=systolic blood pressure.

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name	Study design	Country	Number screened/ eligible/enrolled	Eligibility/ exclusion criteria	Length(s) of followup	BP measurement method in children	Defintion of hypertension in children
Bao et al, 1995[46] Bogalusa Heart Study	Longitudinal cohort	United States	NR/1,505/1,505	Bogalusa Heart Study participants with data in 1973-74 and 1988-91; age 5-14 at baseline and 20-31 at follow-up	15 years	Seated measure repeated 6 times by two nurses; mean of measures used for BP value	>80th percentile
Beckett et al, 1992[47] Fels Longitudinal Study	Longitudinal cohort	United States	976/523/501	Fels Longitudinal Study participants with at least 10 serial BP readings	20 years	Mean of 2 of 3 repeat measures	Not defined; DBP >80 mm Hg described as >90th percentile
Gillman et al, 1993[48]	Prospective cohort	United States	317 (316 with adult followup data)	Schoolchildren aged 8 to 15 years at a single school in East Boston, MA	12 years	Six measurements on right arm, seated with 5-minute rest; 3 with Hawksley random-zero sphygmomanometers and three with standard mercury sphygmomanometers, without removing cuff. Four visits, one week apart.	Above the 90th percentile (SBP: 113 mm Hg, within study)
Hoq et al, 2002[49] Bogalusa Heart Study	Longitudinal cohort	United States	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 years	Mean of six measures by two nurses using mercury sphygmomanometer with age/size appropriate BP cuff at 1st, 4th and 5th Korotkoff phases	≥90th percentile for age, ethnicity and sex
Juhola et al, 2011[50] Cardiovascular Risk in Young Finns Study Other publication: Juonala et al, 2004[55]	Prospective cohort	Finland	3,596 randomized in 1980 61.3% (2,204/3596) at 2007 followup	Finnish children ages 3, 6, 9, 12, 15, and 18	27 years	Three averaged measurements on right arm, in seated position, after 5 minutes rest, with a standard mercury sphygmomanometer	BP ≥95th percentile

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name	Study design	Country	Number screened/ eligible/enrolled	Eligibility/ exclusion criteria	Length(s) of followup	BP measurement method in children	Defintion of hypertension in children
Lauer et al, 1993[51] Muscatine Study	Longitudinal cohort	United States	NR/NR/2,445	Adult Muscatine Study participants who had BP measurements during childhood	Unclear; range 13 to 23 years based on study intiation at age 7 and followup at age 20-30; few participants had measure at age 7	Second of two measures using seated, right arm cuff mercury sphygmomamometers at 1st, 4th and 5th phase	Unclear; results reported for >90th percentile
Li et al, 2003[52] Bogalusa Heart Study	Prospective cohort	United States	486	Children aged 4 to 17 years in September 1973	Median followup: 22.2 years	Six averaged replicate blood pressure measurements, by two randomly assigned trained observers, using a mercury sphygmomanometer on right arm in seated position	NR
Raitakari et al, 2003[53] Cardiovascular Risk in Young Finns Study	Prospective cohort	Finland	3,596 randomized in 1980 61.9% (2,229/3596) at 2001 followup	Finnish children ages 3, 6, 9, 12, 15, and 18	21 years	Three averaged measurements on right arm, in seated position, after 5 minutes rest, with a standard mercury sphygmomanometer	BP $\geq$80th percentile
Shear et al, 1987[54] Bogalusa Heart Study	Longitudinal cohort	United States	4,238/1,501/1,501	Bogalusa Heart Study participants with data from 1976-77, 1978-79 and 1988-91; age 2-14 at baseline	8 years	Mean of six measures by two nurses using mercury sphygmomanometer with age/size appropriate BP cuff	NR
Sun et al, 2007[24] Fels Longitudinal Study	Cohortl analyzed retrospectively	United States	493	Participants in Fels Longitudinal Study who had been monitored since birth and had serial blood pressure readings from age 2 to adulthood	NR (compares childhood BP at ages 5-18 to adult BP at mean age of 38.4 years)	Three averaged measurements by trained technicians using a standard mercury sphygmomanometer on participants in seated position	Least-squares means determined according to age and gender (absolute values NR)

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name	BP measurement method in adults	Defintion of hypertension in adults	Baseline population (Mean age, race, sex)	Baseline population characteristics	% Treated; treatment duration	% Attrition/ loss to followup
Bao et al, 1995[46] Bogalusa Heart Study	Seated measure repeated 6 times by two nurses; mean of measures used for BP value	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 35% black 65% white 56% female	Mean SBP (mm Hg) - Black males: 95 Black females: 94 White males: 97 White females: 95 Mean DBP (mm Hg) - Black males: 60 Black females: 59 White males: 58 White females: 59	99% of hypertensive patients at follow up had previously received treatment for hypertension	No loss (cohort selected based on availability of data)
Beckett et al, 1992[47] Fels Longitudinal Study	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 99% white 1% other 50% female	NR	NR	No loss (cohort selected based on availability of data)
Gillman et al, 1993[48]	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 (SBP: 139 mmHg, within study)	Mean age: NR (range 8-18 years)Sex: 56% (177/316) femaleRace: NR	Mean SBP: 107 (males), 102 (females) Mean DBP: 64 (males), 62.5 (females)	NR	6% (20/337) attrition
Hoq et al, 2002[49] Bogalusa Heart Study	Mean of six measures by two nurses using mercury sphygmomanometer with age/size appropriate BP cuff at 1st, 4th and 5th Korotkoff phases	≥90th percentile for age, ethnicity and sex	Mean age 10 years68% white32% black57% female	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 (mm Hg) - 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)	Unclear; currently treated patients excluded, but study reports inclusion of data from hypertensive subjects (defined as those currently taking antihypertensives) did not alter results	Cohort selected based on availability of data

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

Author, year Study name	BP measurement method in adults	Defintion of hypertension in adults	Baseline population (Mean age, race, sex)	Baseline population characteristics	% Treated; treatment duration	% Attrition/ loss to followup
				White females: 17.6 (SD 3.4)		
Juhola et al, 2011[50] Cardiovascular Risk in Young Finns Study Other publication: Juonala et al, 2004[55]	Similar to child measurements, but with a random zero sphygmomanometer	Unclear	Mean age: NR (range 3-18 years) Sex: 51% (1832/3596) female Race: NR	Mean SBP: 112 (female), 114 (male) Mean DBP: 68 (female), 69 (male) BMI: 17.9 (female), 18.0 (male)	2.7% (61/2283) subjects on anti-hypertensive medications in 2001	38.7% (1,392/3596) lost to follow-up by 27 years
Lauer et al, 1993[51] Muscatine Study	Mean of three 1st phase and three 5th phase measures	SBP or DBP >90th percentile (cohort specific)	Baseline characteristics NR	NR	NR	No loss (cohort selected based on availability of data)
Li et al, 2003[52] Bogalusa Heart Study	Six averaged replicate blood pressure measurements, by two randomly assigned trained observers, using a mercury sphygmomanometer on right arm in seated position	NR	Mean age: NR (range 4-17 years) Sex: NR Race: 65% White, 35% Black	NR	NR	NR (94% [486/516] had data available)
Raitakari et al, 2003[53] Cardiovascular Risk in Young Finns Study	Similar to child measurements, but with a random zero sphygmomanometer	≥80th percentile	Mean age: NR (range 3-18 years) Sex: 51% (1832/3596) female Race: NR	Mean SBP: 112 (female), 114 (male) Mean DBP: 68 (female), 69 (male) BMI: 17.9 (female), 18.0 (male)	3.1% taking anti-hypertensive medication	38% (1,367/3596) lost to follow-up by 21 years
Shear et al, 1987[54] Bogalusa Heart Study	Mean of six measures by two nurses using mercury sphygmomanometer with age/size appropriate BP cuff	≥140/90 mmHg	Mean age NR; 37% (557/1,501) age 2 to 5 years, 37% (548/1,501) age 6 to 9 years, 26% (396/1,501) age 10 to 14 years 41% (622/1,501) black 59% (879/1,501) white 51% (764/1,501) female	Mean BP 99/92	NR	No loss (cohort selected based on availability of data)
Sun et al, 2007[24] Fels Longitudinal Study	Three averaged measurements by trained technicians using a standard mercury sphygmomanometer on participants in seated position	SBP >130 mm Hg and/or DBP >85 mm Hg	Mean age: NR Sex: 51% (253/493) female Race: NR	Reported in figures of least-squares means and standard deviations	NR	8% loss to follow-up in Fels Longitudinal Study overall

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

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.)
Bao et al, 1995[46] Bogalusa Heart Study	Logistic regression Age, race, sex, SBP, DBP, BMI, change in BMI	Hypertension at follow-up, baseline highest SBP quintile vs other SBP quintiles: 18% (54/301) vs 5% (60/1204); RR 3.6 (2.5-5.1) Hypertension at follow-up, baseline highest DBP quintile vs other DBP quintiles: 15% (45/301) vs 6% (72/1204); RR 2.5 (1.8-3.6) Baseline SBP at baseline, highest quintile (mean 107 mm Hg) vs lowest quintile (mean 93 mm Hg) and hypertension at follow-up: OR 2.0 (CI NR; p≤0.001) Subgroups - Black males: OR 1.3 (CI NR; p≤0.05) Black females: OR 2.3 (CI NR p≤0.05) White males: OR 2.6 (CI NR; p≤0.05) White females: OR 1.7 (CI NR; p=NS) Baseline DBP at baseline, highest quintile (mean 68 mm Hg) vs lowest quintile (mean 57 mm Hg) and hypertension at follow-up: OR 1.5 (CI NR; p≤0.05) Subgroups - (only reported for white males) White males: OR 2.1 (CI NR; p=NS)	NR
Beckett et al, 1992[47] Fels Longitudinal Study	NA	DBP 80 mm Hg vs 60 mm Hg at age 15 and presence of hypertension at age 35 - Males: Risk ratio 3.0 Females: Risk ratio 4.5 DBP 85 mm Hg vs 60 mm Hg at age 15 and presence of hypertension at age 35 - Males: Risk ratio 3.9 Females: Risk ratio 6.6 DBP 90 mm Hg vs 60 mm Hg at age 15 and presence of hypertension at age 35 - Males: Risk ratio 4.9 Females: Risk ratio 9.0	NR
Gillman et al, 1993[48]	NA	PPV, sensitivity, and specificity of BP at age 10 predicting BP>90th percentile at age 20 (SBP males: 139 mm Hg, SBP females: 124 mm Hg, DBP males: 84 mm Hg, DBP females: 78 mm Hg) -SBP, males, >75th percentile (108 mm Hg): 0.26, 0.59, 0.80 SBP, males, >90th percentile (113 mm Hg): 0.35, 0.33, 0.93 SBP, males, >95th percentile (117 mm Hg): 0.44, 0.17, 0.97 SBP, males, >99th percentile (123 mm Hg): 0.58, 0.04, >0.99 SBP, females, >75th percentile (108 mm Hg): 0.27, 0.66, 0.79 SBP, females, >90th percentile (114 mm Hg): 0.39, 0.36, 0.94 SBP, females, >95th percentile (118 mm Hg): 0.48, 0.20, 0.98 SBP, females, >99th percentile (125 mm Hg): 0.65, 0.04, >0.99 DBP, males, >75th percentile (68 mm Hg): 0.21, 0.34, 0.82 DBP, males, >90th percentile (71 mm Hg): 0.24, 0.16, 0.93 DBP, males, >95th percentile (73 mm Hg): 0.27, 0.08, 0.97 DBP, males, >99th percentile (77 mm Hg): 0.34, 0.01, >0.99 DBP, females, >75th percentile (67 mm Hg): 0.19, 0.49, 0.77 DBP, females, >90th percentile (71 mm Hg): 0.24, 0.23, 0.92 DBP, females, >95th percentile (74 mm Hg): 0.30, 0.10, 0.98 DBP, females, >99th percentile (78 mm Hg): 0.38, 0.02, >0.99	NR

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

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[49] Bogalusa Heart Study	Logistic regression Sex, childhood age, BMI, BP, annual change in BP	NR	Microalbuminuria Childhood SBP African Americans: regression coefficient 0.016 (p=0.05) Whites: regression coefficient 0.002 (p=0.78) Annual change in SBP from childhood to adulthood African Americans: regression coefficient 0.315 (p=0.002) Whites: regression coefficient 0.045 (p=0.55) Childhood DBP African Americans: regression coefficient 0.026 (p=0.012) Whites: regression coefficient 0.002 (p=0.761) Annual change in DBP from childhood to adulthood African Americans: regression coefficient 0.292 (p=0.016) Whites: regression coefficient 0.063 (p=0.5)
Juhola et al, 2011[50] Cardiovascular Risk in Young Finns Study Other publication: Juonala et al, 2004[55]	Linear regression Age, sex, race, study year	Odds of prehypertension or hypertension in adulthood given BP ≥95th percentile as child - Female, ages 6 and 9: OR 2.4 (95% CI 1.1-5.2) Female, ages 12, 15, and 18: OR 2.3 (95% CI 1.6-3.5) Males, ages 6 and 9: OR 2.8 (95% CI 1.5-5.1) Males, ages 12, 15, and 18: OR 2.1 (955 CI 1.5-3.1) 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 6-18: 0.44; 0.1; 0.97	NR
Lauer et al, 1993[51] Muscatine Study	NA	24% of children with SBP >90th percentile had BP >90th percentile in adulthood; risk ratio 2.4 (p<0.001)39% of children with SBP >90th percentile had SBP >80th percentile in adulthood; risk ratio 1.9 (p<0.001)17% of children with DBP >90th percentile had DBP >90th percentile in adulthood; risk ratio 1.7 (p<0.001)32% of children with DBP >90th percentile had DBP >80th percentile in adulthood; risk ratio 1.5 (p<0.001)	NR

Appendix B4. Studies Tracking Hypertension and Other Outcomes From Childhood to Adulthood

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.)
Li et al, 2003[52] Bogalusa Heart Study	Logisitc regression Age, race, sex	NR	Carotid IMT in upper quartile given SBP risk factor* - Childhood (14-17 years): OR 1.00 (95% CI 0.80-1.25); Correlation coefficient 0.103; p=0.02 * SBP risk factor not defined
Raitakari et al, 2003[53] Cardiovascular Risk in Young Finns Study	Logistic regression Age, sex	NR	Relationship between SBP >80th percentile at age 12-18 (mean age 14.9 years) and carotid IMT 21 years later: regression coefficient 0.013 (SE 0.003); p<0.001
Shear et al, 1987[54] Bogalusa Heart Study	NA	SBP ≥80th percentile at years 1,4 and 6 and hypertensive at follow-up: Sensitivity: 0.27 Specificity: 0.95 DBP ≥80th percentile at years 1,4 and 6 and hypertensive at follow-up: Sensitivity: 0.33 Specificity: 0.96 SBP ≥90th percentile at years 1,4 and 6 and hypertensive at follow-up: Sensitivity: 0.13 Specificity: 0.99 DBP ≥90th percentile at years 1,4 and 6 and hypertensive at follow-up: Sensitivity: 0.07 Specificity: 0.99 SBP ≥95th percentile at years 1,4 and 6 and hypertensive at follow-up: Sensitivity: 0.07 Specificity: 1.0 DBP ≥95th percentile at years 1,4 and 6 and hypertensive at follow-up: Sensitivity: 0.0 Specificity: 1.0	NR
Sun et al, 2007[24] Fels Longitudinal Study	NA	Odds of hypertension at >30 years of age given SBP exceeding criterion values at single examination in childhood - 5-7 year old males: 3.8 (95% CI 1.5-9.7) 5-7 year old females: 4.5 (95% CI 1.1-17.7) 8-13 year old males: 3.5 (95% CI 1.5-8.3) 8-13 year old females: 2.7 (95% CI 1.0-7.1) 14-18 year old males: 1.1 (95% CI 0.5-2.4) 14-18 year old females:3.8 (95% CI 1.2-12.7)	NR

BMI = body mass index; BP = blood pressure; DBP = dialstolic blood pressure; NA = not applicable; NR = not reported; SBP = systolic blood pressure.

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Type of study Setting	Study duration	Eligibility criteria	# Screened/# Eligible/# Enrolled
Drugs				
Batisky et al, 2007[57]	RCT Clinical trial from 28 centers U.S.	4-week dose-ranging study; 52-week safety study	Children ages 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 <10mmHg DBP above the 95th perecentile. Excluded if secondary hypertension, type 1 DM, impaired liver function, asthma, contraindication to B blockers	204 enrolled (60 patients [29%] due to not completing eligibility criteria) 144 randomized 140 analyzed in dosing study 100 analyzed in safety study
Flynn et al, 2004[61] *Pediatric use of Amlodipine in the Treatment of Hypertension (PATH) 1 Study*	RCT 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 $\geq$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 chronice 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)
Li et al, 2010[65]	RCT Clinical trial in 43 centers in the U.S., India, South Africa, Russia, and Dominican Republic	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 $\geq$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
Sorof et al, 2002[67] *Ziac Pediatric Hypertension Study*	RCT Clinical trial from 22 centers in U.S. and Brazil	2 week run in, 8 week titration period, 4 week dose maintainence 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 arhythmia, renal impairment, and concomitant medication that might induce BP elevation.	140 enrolled 94 randomized (62 treatment + 32 placebo)
Trachtman et al, 2003[68] *Plendil Pediatric Clinical Trial*	RCT Clinical trial at 30 sites in the U.S.	1-3 week screening period, 2-3 week dose titration period, 3 week maintainence study	Children ages 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 screened133 randomized128 completed treatment

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Type of study Setting	Study duration	Eligibility criteria	# Screened/# Eligible/# Enrolled
Trachtman et al, 2008[69] *Candesartan in Children with Hypertension (CINCH) program*	RCT Clinical trial at 42 sites in U.S. and Europe	4 week trial and 1 year open-label study	Children ages 6 to 17 years with newly diagnosed and previously diagnosed hyppertension, 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 et al, 2010[70]	RCT Clinical trial at 16 centers in U.S., Brazil, and Mexico	4 weeks, after 2 week washout period	Children ages 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 $\geq$ 20 mmHg or DBP $\geq$ 10 mmHg above 99th percentile, congestive heart failure, vavular 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
Drug Plus Lifestyle				
Berenson et al, 1983[58] *Franklinton Blood Pressure Intervention Study, ADAPT* Same study as Berenson et al, 1990[59]; Other publication: Frank et al, 1982[71]	RCT of complex intervention with additional comparison group School-based, U.S.	6 months	Children ages 8 to 18 years with BP $\geq$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	1804 eligible 1604 screened 443 assessed and 150 selected in phase 2; received informed consent from 150 (100 with BP >90th percentile randomized to treatment group) (50, or whom 47 included) and comparision group (50, or whom 47 included), a further 50 (of whom 47 included) children with midrange BP (<80th percentile) provided further comparision group)
Berenson et al, 1990[59] *Franklinton Blood Pressure Intervention Study, ADAPT* Same study as Berenson et al, 1983[58]; Other publication: Frank et al, 1982[71]	Same as above	30 months	Same as above	Same as above

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Type of study Setting	Study duration	Eligibility criteria	# Screened/# Eligible/# Enrolled
Lifestyle				
Couch et al, 2008[60]	RCT Cincinnati Children's Hospital Medical Center, U.S.	3 month-long intervention; 6 month follow-up	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[35]	RCT2 large Baltimore City public high schools, U.S.	9 months	SBP or DBP between 85th and 95th percentiles, after 2 screeningsStudents in grade 9 and 10SBP $\geq$121 mmHgDBP $\geq$ 74 mmHgExclude BP above 95th percentile	1654 eligible 1400 screened 299 met criteria on 1st screen 159 met criteria on 2nd screen and were randomized (79 treatment, 80 control)
Gregoski et al, 2011[62]	RCT School-based, U.S.	3 months	Resting SBP between the 50th and 95th percentile for age, height and sex on 3 consecutive occasions at school; parental report of no history of congenital heart defect, diabetes, sickle cell anemia, asthma or any chronic illness of health problem that required regular pharmacological treatment; no formal exercise program including organized individual or team sport (current as of study or planned); willingness to accept randomization; parental report of being African American or Black; not pregnant	1968/175/166
Hansen et al, 1991[63] *Odense Schoolchild Study*	RCTOdense, DenmarkSchool-based	8 months	Children in the Odense, Denmark school system aged 9-11 years with a mean BP $\geq$95th centile (hypertensive group) or <95th centile (normotensive group)	1369 screened 137 randomized (69 hypertensive vs. 68 normotensive)
Howe et al, 1991[64]	RCT crossover School-based Adelaide, Australia	2 phases of 4 weeks each	Children aged 11-14 years representing top (>90th), middle (45-55th), and bottom (<10%) deciles of the BP range attending 2 schools in Adelaide, Australia	692 (432 boys and 260 girls) screened 103 enrolled
Sinaiko et al, 1993[66]	RCT St. Paul and Minneapolis public schools, U.S.	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)

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Withdrawals or Loss to Follow-up; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Drugs			
Batisky et al, 2007[57]	2 patients randomized incorrectly and 2 patients had no postbaseline BP measures	Mean age (SD): 12.5 ± 2.8 years Mean baseline BP: 132/78 ± 9/9 mgHg % Male: 70% % Black: 25.7% % Previously treated for hypertension: 22.9% % BMI ≥95% percentile: 74.3%	4 week dosing trial of extended release (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
Flynn et al, 2004[61] *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)
Li et al, 2010[65]	27 not re-randomized 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
Sorof et al, 2002[67] *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)
Trachtman et al, 2003[68] *Plendil Pediatric Clinical Trial*	5 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	Extended release (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 doseage Placebo (n=35)

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Withdrawals or Loss to Follow-up; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Trachtman et al, 2008[69] *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 et al, 2010[70]	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
Drug Plus Lifestyle			
Berenson et al, 1983[58] *Franklinton Blood Pressure Intervention Study, ADAPT* Same study as Berenson et al, 1990[59]; Other publication: Frank et al, 1982[71]	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 (A Dietary/Exercise Alteration Program Trial) 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 comparision 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

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Withdrawals or Loss to Follow-up; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Berenson et al, 1990[59] *Franklinton Blood Pressure Intervention Study, ADAPT* Same study as Berenson et al, 1983[58]; Other publication: Frank et al, 1982[71]	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
Lifestyle			
Couch et al, 2008[60]	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[35]	Participated treatment: 51/79 (65%) Control: 59/80 (74%) Withdrawls 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) occuring supine on mats for first 6 weeks then while sitting, including assuming relaxed posture, muscle relaxation, slow diaphragmatic breathing, & handwarming, 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 School 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 B5. Interventions for Hypertension in Children and Adolescents

Author, year *Study name (if applicable)*	Withdrawals or Loss to Follow-up; % Analyzed	Demographics/Baseline Disease	Treatment/Intervention
Gregoski et al, 2011[62]	2/166 (for stress outcome measure only); 166/166 included in analysis of other outcomes	Mean age 15 years 59% female 100% black Mean SBP 118.9 Mean DBP 63.6	A. Breathing awareness meditation (BAM): Daily 10 minute sessions during the week, 2 times/day on the weekends. BAM focuses on paying attention to the breathing process. B. LifeSkills training: Weekly 50-minute sessions focusing on training in problem-solving skills, reflective listening, conflict resolution and anger management to enhance social skills, assertiveness, personal and social competence C. Health education control: Weekly health education classes based on NIH guidelines for youth (usual practice)
Hansen et al, 1991[63] *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[64]	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[66]	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 supportB: Potassium chloride supplementation: participants's normal diet +1 mmol/kg body weight per day, not to exceed 80 mmol/dayC: Placebo: participant's normal diet + placeboMeasured every 3 months for 3 years

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *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	Quality Rating
Drugs						
Batisky et al, 2007[57]	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 A: SBP -5.2, 95% CI -7.7 to -2.6 (p=0.145) DBP -3.1, 95% CI -5.7 to -0.5 (p=0.655) B: SBP -7.7, 95% CI -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, 95% CI -8.7 to -3.8 (p=0.049) DBP -7.5, 95% CI -10.0 to -5.0 (p=0.017) D: SBP -1.9, 95% CI -5.5 to 1.8 DBP -2.1, 95% CI -5.7 to 1.5 All Metoprolol ER groups pooled: SBP -6.1, 95% CI -7.7 to -4.5 (p=0.035) DBP -5.3, 95% CI -6.9 to -3.7 (p=0.119)	NR	NR	Fair
Flynn et al, 2004[61] *Pediatric use of Amlodipine in the Treatment of Hypertension (PATH) 1 Study*	Oscillometric device, cuff Seated BP 4 BP measurements taken 24 hours after lst 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 redution for 5.0 mg group: -4.4 + 8.3 mmHg Phase 2 (compared to placebo): Mean SBP reduction for 2.5 mg group: -6.9 $\pm$12.5 mmHg; significantly greater than placebo group (values not NR), p=0.045 Mean SBP reduction for 5.0 mg group: -8.7 $\pm$13.3 mmHg vs placebo group -3.6$\pm$12.7 mmHg, p=0.005 Mean DBP reduction for 2.5 mg group: NR Mean DBP redution for 5.0 mg group: NR	NR	NR	Fair

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *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	Quality Rating
Li et al, 2010[65]	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 mm Hg (95% CI -5.5 to 0), p=0.048 No other doses or DBP received statistical significance. No other doses or DBP received statistical significance.	NR	NR	Fair
Sorof et al, 2002[67] *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: 6-12 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). 13-17 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). 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	NR	Fair

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *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	Quality Rating
Trachtman et al, 2003[68] *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.	Felodine ER 5 mg reduced trough sitting, supine, and standing DBP compared to placebo, -4.64 mmHg (95% CI -9.18 to 0.09), -5.05 (95% CI -9.68 to -0.45), and -5.09 (95% CI, -9.53 to -0.63), respectively, p<0.05 Felodine ER 2.5 mg vs placebo, p=ns Felodine ER 10 mg vs placebo, p=ns	NR	NR	Fair
Trachtman et al, 2008[69] *Candesartan in Children with Hypertension (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, p<0.0001 Adjusted mean DBP reduction for all active doses combined vs placebo: -6.56, 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	Fair
Wells et al, 2010[70]	NR	Achivement of <95th percentile for both SBP and DBP: High dose vs placebo: ages 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: ages 6 to <12 years, 50.0% vs 33.3%, ages 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: -4.5mmHg (SE 2.5, 95% CI -9.5, 0.4, p=ns)	NR	NR	Fair

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *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	Quality Rating
Drug Plus Lifestyle						
Berenson et al, 1983[58] *Franklinton Blood Pressure Intervention Study, ADAPT* Same study as Berenson et al, 1990[59]; Other publication: Frank et al, 1982[71]	Mercury manometer or automatic recording device 3 resting, seated BP measurements averaged and recorded	NR	Mean SBP mmHg (SD), baseline, 6 month follow-up 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, follow-up 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	Fair
Berenson et al, 1990[59] *Franklinton Blood Pressure Intervention Study, ADAPT* Same study as Berenson et al, 1983[58]; Other publication: Frank et al, 1982[71]	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	Fair

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *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	Quality Rating
Lifestyle						
Couch et al, 2008[60]	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: 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 to routine care, relative change -6.8 vs -2.8, p<0.05	NR	NR	Fair
Ewart et al, 1987[35]	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 post baseline: Change in SBP from baseline to 4 month follow up: 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 follow up 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	Fair
Gregoski et al, 2011[62]	Ambulatory BP measured for 24 hours	NR	Mean 24-hour SBP at 3-month follow-up, Group A vs Group B vs Group C: 116.6 vs 119.4 vs 121.0; Group A vs Group B: p=0.13; Group A vs Group C: p=0.05 Mean 24-hour DBP at 3-month follow-up, Group A vs Group B vs Group C: 62.4 vs 67.8 vs 68.7; p>0.05 for all comparisons	NR	NR	Fair

Appendix B5. Interventions for Hypertension in Children and Adolescents

Author, year *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	Quality Rating
			(not statistically significant)			
Hansen et al, 1991[63] *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	Fair
Howe et al, 1991[64]	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	Fair
Sinaiko et al, 1993[66]	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 to placebo that were significantly greater than zero 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 differenes in rates of increase in BP over 36 months were found between or within the groups	NR	NR	Fair

Appendix B5. Interventions for Hypertension in Children and Adolescents

ADAPT = Dietary/Exercise Alteration Program Trial; BAM = breathing awareness meditation; BP = blood pressure; BMI = body mass index; B/HT = bisoprolol fumarate/hydrochlorothiazide; CI = confidence interval; CKD = chronic kidney disease; DASH = dietary approaches to stop hypertension; DBP = dialstolic blood pressure; DM = diabetes mellitus; ER = extended releas; ITT = intention to treat; NR = not reported; PMR = progressive muscle relaxation; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; U.S. = United States.

Appendix B6. Quality Assessment of Intervention and Harms 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	Funding source
Batisky et al, 2007[57]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	No	Fair	AstraZeneca
Berenson et al, 1983[58], 1990[59]	Unclear	Unclear	No	Yes	Unclear	No	No	Yes	Differential: no High overall: no	Yes	Fair	NHLBI
Couch et al, 2008[60]	Unclear	Unclear	No	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: no	Yes	Fair	AHA, Ohio Valley Affiliate
Ewart et al, 1987[35]	Unclear	Unclear	Yes	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: yes	No	Fair	NHLBI
Flynn et al, 2004[61]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	No	Fair	Pfizer
Gregoski et al, 2010[62]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Yes	Differential: unclear High overall: no	Yes	Fair	Not reported
Hansen et al, 1991[63]	Yes	Unclear	Yes	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: no	Yes	Fair	Danish Health Insurance Foundation; Danish Health Services Development Foundation; Danish Heart Foundation; Health Insurance Foundation of Denmark; Danish Medical Research Council; Funen Prevention Council; Danish Sports Research Council; Rosalie Petersen Foundation
Hazan et al, 2010[73]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Differential: no High overall: no	Unclear	Good	Daiichi Sankyo
Howe et al, 1991[64]	Yes	Unclear	Yes	Yes	Unclear	Not applicable	Not applicable	Yes	Differential: no High overall: no	No	Fair	Channel 7 Children's Research Foundation of South Australia
Li et al, 2004[74]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: yes	Unclear	Fair	Bristol Myers Squibb
Li et al, 2010[65]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	Differential: no High overall: no	Yes	Fair	Pfizer
Shahinfar et al, 2005[75]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Fair	Merck
Sinaiko et al, 1993[66]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	Differential: unclear High overall: unclear	No	Fair	NIH
Soffer et al, 2003[76]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Fair	Merck
Sorof et al, 2002[67]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: yes	No	Fair	Not reported

Appendix B6. Quality Assessment of Intervention and Harms 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	Funding source
Trachtman et al, 2003[68]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	Unclear	Fair	Not reported
Trachtman et al, 2008[69]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: no	Yes	Fair	AstraZeneca
Wells et al, 2002[77]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Fair	Merck
Wells et al, 2010[70]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Differential: no High overall: yes	Yes	Fair	Boehringer Ingelheim

AHA=American Heart Association; NHLBI=National Heart, Lung, and Blood Institute; NIH=National Institutes of Health.