Screening for Hypertension in Children and Adolescents to Prevent Cardiovascular Disease

abstract

BACKGROUND AND OBJECTIVE: The prevalence of hypertension is increasing in children, and may persist into adulthood. This systematic review was conducted for the US Preventive Services Task Force recommendation on the effectiveness of screening asymptomatic children and adolescents for hypertension in order to prevent cardiovascular disease.

METHODS: Eligible studies were identified from Medline and the Cochrane Library (through July 2012). We included trials and controlled observational studies in asymptomatic children and adolescents on the effectiveness and harms of screening and treatment, as well as accuracy of blood pressure measurement. One author extracted study characteristics and results, which were checked for accuracy by a second author.

RESULTS: No studies evaluated the effects of screening for hypertension on health outcomes. Two studies of screening tests for elevated blood pressure reported moderate sensitivities (0.65, 0.72) and specificities (0.75, 0.92). Sensitivities and specificities of child hypertension for the later presence of adult hypertension (7 studies) were wide ranging (0–0.63 and 0.77–1.0, respectively), and associations between child hypertension and carotid intima media thickening and proteinuria in young adults (3 studies) were inconsistent. Seven studies reported that drug interventions effectively lowered blood pressure in adolescents over short follow-up periods. No serious treatment-related adverse effects were reported.

CONCLUSIONS: There is no direct evidence that screening for hypertension in children and adolescents reduces adverse cardiovascular outcomes in adults. Additional studies are needed to improve diagnosis and risk stratification of children with elevated blood pressure and to quantify risks and benefits of interventions. *Pediatrics* 2013;131:490–525

AUTHORS: Matthew Thompson, MD, MPH, DPhil,[a,b] Tracy Dana, MLS,[a] Christina Bougatsos, MPH,[a] Ian Blazina, MPH,[a] and Susan L. Norris, MD, MPH, MSc[a]

[a]Oregon Evidence-Based Practice Center, Oregon Health and Science University, Portland, Oregon; and [b]Department of Primary Care Health Sciences, Oxford University, Oxford, United Kingdom

KEY WORDS

hypertension, children, adolescents, screening, treatment, drug, lifestyle

ABBREVIATIONS

ADAPT—Dietary/Exercise Alteration Program Trial
CI—confidence interval
DBP—diastolic blood pressure
OR—odds ratio
RCT—randomized controlled trial
SBP—systolic blood pressure
USPSTF—US Preventive Services Task Force

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Address correspondence to Matthew Thompson, MD, MPH, DPhil, Department of Primary Care Health Sciences, Oxford University, New Radcliffe House, Woodstock Road, Oxford OX2 6GG, UK. E-mail: matthew.thompson@phc.ox.ac.uk

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Between 1% and 5% of children and adolescents have hypertension, and its prevalence has risen in the United States by 1% to 2% over recent decades.[1–4] Hypertension is usually asymptomatic, and a significant proportion of children with hypertension are undiagnosed.[5,6] Screening children and adolescents for elevated blood pressure could identify hypertension at an early stage where interventions could be initiated, potentially decreasing the rate of progression of hypertension from childhood to adulthood and reducing the clinical consequences of hypertension in adulthood.[7]

The strongest risk factor for primary hypertension in children of all ages and both genders is elevated BMI[8–14]; children who are overweight or obese have a two- to threefold increased risk of hypertension.[8–10] This increased risk is particularly concerning given that ~17% of children and adolescents in the United States are now obese[15] and have higher risk of other cardiovascular risk factors such as an adverse lipid profile and insulin resistance.[16] Other risk factors for primary hypertension include low birth weight, gender, ethnicity, and a positive family history.[2,3,9,10,17–19]

Secondary hypertension is most commonly related to underlying renal parenchymal or renovascular disease; less common causes include aortic coarctation and endocrine disorders.[20,21] Elevated blood pressure is usually only 1 clinical manifestation of the underlying disorder, and treatment is typically directed at correcting the underlying cause.

For the majority of children and adolescents, the rationale for identifying elevated blood pressure lies in the potential to stratify risk of future cardiovascular disease. There is convincing evidence that structural and functional changes in the cardiovascular system, which indicate early atherosclerosis, can be detected in adolescents and young adults. What is less clear are the nature and magnitude of the relationship between elevated blood pressure and other cardiovascular risk factors in children or adolescents and cardiovascular risk in adults. Cohort studies that have followed children to young adulthood suggest that adiposity, insulin resistance, and an adverse lipid profile progress at an increased rate in prehypertensive and hypertensive children and adolescents compared with normotensive children.[7,22,23]

AIMS OF THIS REVIEW

The purpose of this systematic review is to provide the US Preventive Services Task Force (USPSTF) with evidence to update their 2003 recommendation on screening for high blood pressure in children and adolescents.[24] The larger review is available at www.uspreventiveservicestaskforce.org.[25] With the input of members of the USPSTF, we developed an analytic framework (Fig 1) and key questions to guide our literature search and review.

1. Is screening for hypertension in children/adolescents effective in delaying the onset 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

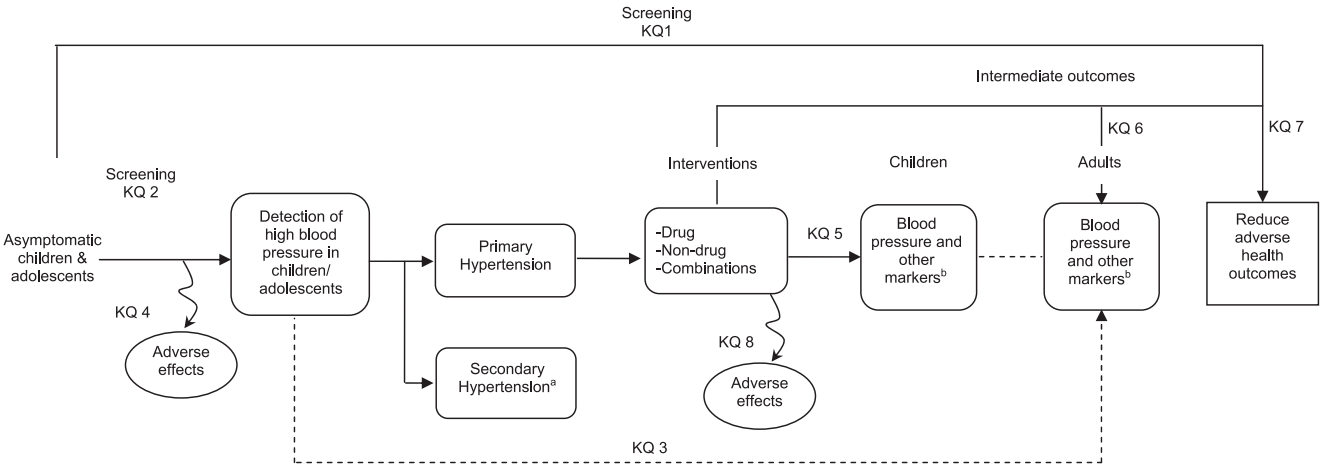

FIGURE 1

Analytic framework and key questions. [a]The assessment and treatment of secondary hypertension is beyond the scope of this review. [b]Includes left ventricular hypertrophy, urinary albumin excretion (microalbuminuria), intima media thickness (measured at carotid and/or femoral arteries), and retinal vascular changes. KQ, key question.

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?

METHODS

This review was developed by the Oregon Evidence-Based Practice Center under contract with the Agency for Healthcare Research Quality (contract 290-2007-10057-I) and follows the systematic review methods of the USPSTF.[26,27]

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews (through July 2012) and Medline (1946 to July 9, 2012) for relevant studies and systematic reviews, and manually reviewed reference lists for relevant citations (Appendix 1).

Study Selection and Processes

Papers were selected for full review if they met predefined inclusion criteria (Appendix 2). Controlled studies of screening for hypertension in asymptomatic children and adolescents were included. For studies of diagnostic accuracy, eligible studies included a reference standard comparison and provided adequate data to reproduce contingency tables. Evidence from randomized placebo-controlled trials was used to assess the efficacy of treatments on multiple outcomes, including blood pressure, other intermediate health outcomes, and final health outcomes, in childhood, adolescence, and adulthood. Studies with <30 participants and studies of interventions for the treatment of obesity and lipid disorders in children were excluded, because these populations are considered in other USPSTF recommendations.[28,29] To assess harms of treatment, studies without a comparison or a placebo group were included. Studies of secondary hypertension were excluded, although some studies included proportions of participants with secondary hypertension.

All citations identified through searches and other sources were independently reviewed by 2 authors for inclusion and exclusion. Discrepancies at the full-text level were resolved through consensus. One author extracted data on the patient population, study design, testing methods, analysis, follow-up, and results, and a second author checked data extraction for accuracy.

Quality Assessment and Synthesis

By using predefined criteria developed by the USPSTF,[26] 2 authors rated the quality of studies (good, fair, poor) and resolved discrepancies by consensus. Authors assessed the overall strength of the body of evidence for each key question as good, fair, or poor by using methods developed by the USPSTF on the basis of the number, quality, and sample size of studies, as well as the consistency of results among studies and directness of the evidence.[26] The limited number of studies and the heterogeneity of study designs, interventions, and diagnostic tests precluded meta-analyses; results are therefore summarized qualitatively as means or as ranges, as appropriate.

RESULTS

Our literature search identified a total of 6435 citations, of which we reviewed 1059 full-text publications and included 34 studies (Fig 2).

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

No randomized trials compared health outcomes related to hypertension in screened versus nonscreened child or adolescent populations.

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

We identified 2 fair-quality studies that provided data on the diagnostic accuracy of screening tests (Appendix 3).[30,31] Compared with a reference standard of 24-hour ambulatory measurement, office-based blood pressure measurement (3 measurements at each of 2 clinic visits) had a sensitivity of 0.65 (95% confidence interval [CI], 0.45–0.80) and a specificity of 0.75 (95% CI, 0.63–0.84).[31] The positive predictive value was 0.37 (95% CI, 0.28–0.47) and the negative predictive value was 0.63 (95% CI, 0.53–0.72). All 105 participants (mean age, 13 years) had been referred for evaluation at a specialty clinic, so they may not have been representative of screened populations of asymptomatic children. In addition, ambulatory measurement is not yet an internationally accepted reference standard in children and adolescents. A second study examined a random sample of 9017 eighth graders, of whom about 10% (900/9017) had blood pressure >95th percentile on initial screening, whereas the remainder (8117/9017) were normotensive.[30] At follow-up in 10th grade, the sensitivity

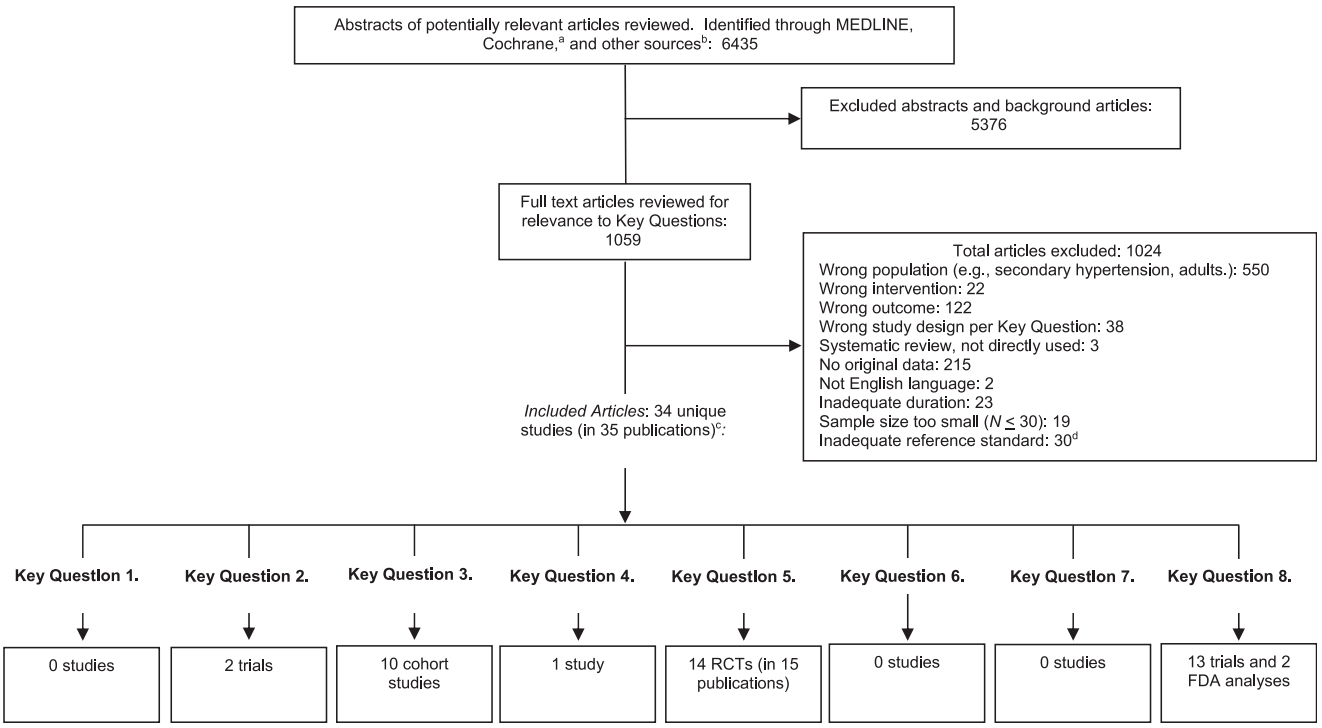

FIGURE 2

Literature search flow diagram. [a]Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. [b]Other sources include reference lists, suggested by peer reviewers, etc. [c]Some articles are included for >1 key question. [d]Twelve of these studies did not provide enough data to recreate 2 × 2 tables or calculate sensitivity and specificity.

and specificity of initial elevated blood pressure for persistent elevation of blood pressure were 0.72 (95% CI, 0.65–0.78) and 0.92 (95% CI, 0.91–0.92), respectively; however, the positive predictive value was low (0.17 [95% CI, 0.15–0.20]). This study primarily followed only the sample of children whose initial screening test was positive rather than the entire population, which may have biased the diagnostic accuracy in this study.

In addition, 12 studies compared ≥1 measurement of blood pressure with subsequent reference measurements but did not meet our inclusion criteria because either they failed to apply the reference tests to participants who initially screened negative or they did not use an acceptable reference standard.[11,32–42] Positive predictive values among these studies ranged from 0.04 to 0.53. The reasons for this heterogeneity were unclear but did not appear to be related to varying prevalence of hypertension, method or device used for testing, or thresholds used to define positive tests.

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

Ten longitudinal studies provided evidence on the association between elevated blood pressure or hypertension in childhood and elevated blood pressure, hypertension, or intermediate outcomes in adults (Appendix 4).[7,43–51] These studies used different thresholds for defining elevated blood pressure and hypertension in childhood and different definitions of hypertension in adults. The sensitivities and specificities of elevated blood pressure or hypertension in childhood for predicting adult hypertension ranged from 0 to 0.63 and 0.77 to 1, respectively, depending on thresholds.[45,47,51] Positive predictive values (ie, the probability of adult hypertension given the presence of elevated blood pressure or hypertension in childhood) ranged from 0.19 to 0.65.[45,47] Five 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[7,47] and relative risks ranging from 1.5 to 9.[43,44,48] Two studies reported conflicting findings on the association between childhood hypertension and carotid intima media thickness in young adults. Systolic blood pressure (SBP) >80th percentile in adolescence was mildly associated with carotid intima media thickness in adulthood in 1 study (regression coefficient, 0.013; $P < .001$).[50] A second study, however, found no increased risk of carotid intima media thickness in adulthood related to

elevated systolic blood pressure in childhood (highest quartile versus lower 3 quartiles: OR, 1; 95% CI, 0.80–1.25), although the level of SBP elevation is not defined in this study.[49] Childhood hypertension was significantly associated with microalbuminuria in black but not white adults in a single study.[46] We found no evidence for associations between diagnosed hypertension in childhood and other intermediate or final health outcomes.

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

One small good-quality study compared 85 children (10–18 years of age) with elevated blood pressure identified by screening to children matched by age and gender from the same community.[52] The only outcome reported was rates of school absenteeism, which did not differ significantly between the 2 groups.

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

Fourteen fair-quality randomized controlled trials (RCTs)[33,53–66] (in 15 publications) of treatment of hypertension in children and adolescents met inclusion criteria (Table 1; Appendix 5). The proportion of children with primary hypertension ranged from 31%[54] to 56%[55]; however, most studies did not report the proportion of participants with secondary hypertension.[53,57–60,62,64–66]

Drug Interventions

All seven included trials of drug interventions examined different drugs.[53–59] Most compared active drug (in different doses) to placebo, with follow-up of only 4 weeks. The magnitude of effects on SBP and diastolic blood pressure (DBP) varied and were not consistently different from changes in blood pressure in the placebo group (or these differences were not reported).

Five studies[53,54,57–59] reported the percentage of participants achieving target blood pressure at the end of the follow-up period, and all noted an increase in those who achieved target levels with the active drug (range 15–86% of subjects). However, 26% to 47% of children in the placebo groups also achieved normal blood pressure at the end of the study period.[53–59] Most studies reported significant reductions in mean SBP (range, 1.9–10.2 mm Hg) and DBP (range, 0.4–8.1 mm Hg). Eplerenone (50 mg/day) produced a small increase in mean SBP and no change in DBP.[55] Most studies had limitations, most notably the failure to report the statistical significance of differences between treatment groups in addition to within-group treatment differences. Also, comparison among studies was difficult because of varying drug dosages.

Drug Plus Lifestyle Interventions

The school-based A Dietary/Exercise Alteration Program Trial (ADAPT) examined the effectiveness of a multicomponent, school-based intervention, including nutrition education for and promotion of diet modification to children and parents; expanded community availability of low-sodium foods in grocery stores, restaurants, and school lunches; a school-based exercise program; and propranolol and chlorthalidone compared with a no intervention group.[60,61] This complex intervention resulted in a significant decrease in both SBP and DBP at the 6-month follow-up (mean SBP change: −7.6 mm Hg [$P < .0001$]; mean DBP change: −6.9 mm Hg [$P < .01$]) compared with the control group. At 30 months, however, SBP increased from baseline in both the intervention (1.4 mm Hg) and control groups (3.5 mm Hg), although DBP remained below baseline levels (mean change: −4.2 mm Hg in the intervention group and −3.3 mm Hg in the control group).

Lifestyle Interventions

Most of the six trials examining lifestyle interventions included support related to the interventions (eg, regular check-ins) in addition to diet, exercise, or meditation.[33,62–66] Only 1 study demonstrated statistically significant reductions in blood pressure compared with untreated controls.[64] This small, school-based RCT compared the effects of 5 versus 3 weekly physical education classes in hypertensive children and reported that blood pressure decreased significantly more in participants receiving 5 weekly classes over the 8-month follow-up period (mean between-group difference in SBP = −4.9 mm Hg and DBP = −3.8 mm Hg; $P < .05$ for both outcomes).[64] In another trial, a low-sodium diet combined with personalized support from a nutritionist and/or potassium chloride supplementation was effective in reducing blood pressure compared with usual care plus placebo at 36 months among girls but not among boys.[66] Other studies of meditation,[63] relaxation,[33] and dietary changes[62,65] reported no significant differences 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?

No RCTs examined the effectiveness of interventions for hypertension in children or adolescents for reducing blood pressure or other intermediate outcomes in adults.

TABLE 1 Effect of Interventions on Blood Pressure: Reported Mean Differences From Baseline and/or Placebo

Author, Year, Duration	Interventions	Baseline (mm Hg)		Follow-up (mm Hg)		Mean Difference: Follow-up Versus Baseline (mm Hg)		Mean Difference at Follow-up: Intervention Versus Placebo (mm Hg)	
		SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Drug interventions									
Batisky et al 2007[76] (4 wk)	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	135.0	81.0	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[54] (4 wk)	Amlodipine 2.5 mg	137.9[a]	74.2[a]	Not reported		−6.9	−4.2	Not reported	
	Amlodipine 5 mg					−8.7	−4.4		
	Placebo					−3.6	−0.4	—	—
Li et al 2010[55] (4 wk)	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[56] (4 wk)	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[57] (3 wk)	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[58] (4 wk)	Candesartan (all doses)	Not reported				−10.2	−6.6	Not reported	
	Placebo					−3.7	−1.8	—	—
Wells et al 2010[59] (4 wk)	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 interventions									
Berenson et al 1983[60] (6 mo)	ADAPT program	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[61] (30 mo)[b]	ADAPT program	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 interventions									
Couch et al 2008[62] (6 mo)	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	—	—
Ewart et al 1987[33] (9 mo)	Relaxation training	127.0	79.1	118.6	72.9	−8.4	−6.2	−2.3	−3.1
	No intervention	126.5	80.4	120.9	76.0	−5.6	−4.4	—	—
Gregoski et al 2011[63] (3 mo)	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[64] (3 mo)	Extra physical education classes			Not reported				−4.9	−3.8
	No extra classes							—	—
Howe et al 1991[65] (4 wk)	Low sodium diet	115.0[a]	60.1[a]	112.6	59.1	Not reported		−1.2	−0.9
	High sodium diet			113.8	60			—	—

DASH, Dietary Approaches to Stop Hypertension; —, indicates that data is not available.

[a] Values for total cohort; data not stratified according to treatment group.

[b] Continuation of Berenson et al 1983 study.

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?

No RCTs examined the effectiveness of interventions for hypertension in children or adolescents for reducing clinical outcomes in adults.

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

Drug Interventions

Twelve trials reported adverse events with drug therapy (Appendix 6).[53–59,67–71] One study was rated good quality[67]; the remainder were of fair quality.[53–55,57–59,68–71] Four of the studies included children with primary hypertension,[53,57–59] whereas the remainder included children with primary or secondary hypertension.[54,55,67–71] The number of children enrolled in the studies ranged from 76 to 304, the mean age ranged from 12 to 14 years, and the duration of follow-up for reporting adverse events ranged from 4 weeks to 1 year.

Serious adverse events were rarely reported, and there were no deaths in any of the studies. One study of metoprolol reported 1 case each of pneumonia and metometrorrhagia.[53] Another study reported a case of near syncope and an elevated creatinine in a patient who received an incorrect dose of telmisartan. A third study reported 8 serious adverse events among 304 patients, although none were considered to be treatment related.[55]

Adverse event data were often poorly reported, and most studies reported noncomparative data from open-label extensions of RCTs. Five studies of monotherapy reported similar rates of adverse events in the intervention (range, 27–77%) and placebo groups (range, 25–66%).[55,57,59,67,68] Children taking a combination of bisoprolol plus hydrochlorothiazide had lower overall rates of adverse events compared with placebo (53–75%, $P = .05$) after 12 weeks of follow-up.[56] Withdrawals caused by adverse events ranged from 0% to 7% in children receiving active treatments[53,54,56–59,67–71] and 0% to 6.2% in placebo groups.[53,56,58,59,67,68] Headache was the most common specific adverse event in most studies: rates ranged from 2% to 33% in children receiving active treatments,[53,56,57,59,68,71] but only 2 studies reported rates for the placebo group. One study reported that no headaches occurred in the placebo group compared with 11% of active treatment patients,[59] whereas in a second study, headache was reported in 31% versus 26% (placebo versus combination treatment, significance not reported).[56] Other commonly reported adverse events associated with active treatments were cough, upper respiratory infections, and gastrointestinal events, including nausea and diarrhea, although specific rates were not always reported.[53,54,56–59,68–71]

Two studies pooled adverse event data from selected drug trials submitted to the Food and Drug Administration over a 7-year period; however, neither study used standard systematic review methods.[72,73] Pooled patient-level data from 1707 children from 10 placebo-controlled RCTs of 10 different active agents[72] revealed similar rates of adverse events between active treatment (0.83 events per patient) and placebo groups (0.76 per patient) after 2 to 4 weeks of follow-up (between-group $P = .37$). Pooled data from 8 RCTs of hypertensive children revealed no difference in the incidence of cough between active treatment and placebo groups (3% in both groups; $P = .86$).[73]

Other Interventions

The fair-quality ADAPT of a propranolol and chlorthalidone/lifestyle intervention described in key question 54 reported no adverse events.[60,61] No studies of lifestyle modification alone reported adverse events.

DISCUSSION

Direct evidence linking screening of children and adolescents for hypertension and delaying the onset or reducing the risk cardiovascular outcomes in adults is not available, and indirect evidence is sparse and of variable quality. We did not identify evidence for the effectiveness of interventions used to treat primary hypertension in children on lowering blood pressure levels or reducing adverse health outcomes in adults. A summary of the evidence is provided in Table 2.

High-quality data on the diagnostic accuracy of blood pressure measurement to detect hypertension were also sparse and suggest moderate sensitivities (0.65 and 0.72), with somewhat higher specificities (0.75 and 0.92). These data suggest that many children who have elevated blood pressure on screening will not have hypertension. There are also some data to suggest that hypertension in childhood is associated with hypertension in young adults (OR range, 1.1–4.5; relative risk range, 1.5–9) or has low to moderate sensitivities (0 and 0.63) and specificities (0.77 and 1) for predicting adult hypertension. Moreover, the association between childhood hypertension and carotid intima media thickness and microalbuminura in young adults was also inconclusive, and direct evidence on other intermediate or final health outcomes was lacking.

The effectiveness of antihypertensive medications in children and adolescents has been examined in 7 trials, all of which were small and of short duration, and each examined a different

TABLE 2 Summary of Evidence

Number of Studies (Overall Quality)	Limitations	Consistency	Applicability to Primary Care	Summary of Findings
Key question 1: Is screening for hypertension in children/adolescents effective in delaying the onset 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 (poor)	Studies were flawed or not directly applicable to an asymptomatic US population. Only 1 included a comparison with 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 with ambulatory screening in 1 study of a referred population. A second, school-based study comparing an initial positive screen to subsequent diagnosis of hypertension had 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 (poor)	Studies used different thresholds for defining elevated blood pressure and hypertension in children and different definitions of hypertension in adults. 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. Two studies reported associations between childhood hypertension and carotid intima media thickness in young adults, with conflicting findings. One study reported a significant association between childhood hypertension and microalbuminuria 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 (poor)	Evidence limited to results from 1, good-quality study	NA (1 study)	High	Children labeled as hypertensive did not miss more days of school in the year after diagnosis compared with prelabeling or compared with nonhypertensive 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 (poor)	Longest drug study duration was only 4 wk For many studies, the proportion of children with secondary hypertension was unclear	Consistent	Moderate	Children achieving normotensive status (on the basis of varying definitions) ranged from 15% to 86% in patients taking drug treatments and 11% to 48% in patients taking placebo. There were significant reductions of mean SBP (range 2–10 mm Hg), and mean DBP (range 0.4–8 mm Hg) with some drugs and dosages. The difference between intervention and placebo groups ranged from 0 to 9 mm Hg for SBP and 0.5 to 10 mm Hg for DBP. However, reductions were often only at higher doses of active treatments, and studies only lasted for 4 wk. One school-based study of a drug plus lifestyle intervention reported a significant, sustained reduction in blood pressure in the combination group versus the control group. Studies of nondrug therapies were limited, and only 1 study examining the effect of additional physical education classes in school reported a sustained mean reduction in blood pressure in for both boys and girls.

TABLE 2 Continued

Number of Studies (Overall Quality)	Limitations	Consistency	Applicability to Primary Care	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) (fair)	Numerous trials from key question 5 did not report comparative events rates between active treatment and placebo arms, and adverse event rates overall ere not well-reported in most studies.	Consistent	Moderate	Studies of antihypertensive drugs in children and adolescents generally reported no significant difference between active treatments and placebo in adverse event rates or in withdrawals due to adverse events. In one study, a combination of bisoprolol and hydrochlorothiazide was associated with lower adverse event rates than placebo. Four studies reported serious adverse events, although with the exception of 1 case of syncope due to a dosing error, serious adverse events were generally not deemed treatment related. Analysis of FDA data revealed no significant difference between drug treatments and placebo in the 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 nondrug treatments.

FDA, Food and Drug Administration; NA, not applicable; PPV, positive predictive value; RR, relative risk.

agent. Most importantly, their antihypertensive effects varied in magnitude, were not consistently present for a given agent for both SBP and DBP, and were not consistently different from placebo or from baseline. Blood pressures in placebo groups often improved along with those of the intervention group, suggesting regression to the mean. From the limited data we identified, medications appeared to be well tolerated, with no serious adverse effects.

Interventions for treating elevated blood pressure that involve lifestyle interventions alone or in combination with an antihypertensive medication found inconsistent results. Of the 3 studies that had positive results, increased physical education at school was effective at reducing blood pressure in 1 study,[64] whereas in a second longer-term school-based study, the effects of an antihypertensive combined with a complex lifestyle program (the ADAPT program) were not sustained,[60,61] and finally, a low sodium diet combined with personalized support was only effective in girls.[66]

The most important potential limitation of this review was the absence of any evidence to address several of the key questions and the limited quantity and quality of evidence for others. This lack of evidence inevitably limits the conclusions that can be drawn from this review. Second, our search strategy, although rigorous, may have failed to identify relevant studies. We used citation searching of included articles and reviewed all articles identified by the expert reviewers to augment our search strategy. We limited our search to English language publications, which could have limited eligible studies. We cannot exclude the possibility of publication and selective reporting biases, but we were not able to formally test for this. In addition, by including only studies where the interventions were directed against treatment of hypertension (eg, rather than obesity), indirect evidence was excluded. Finally, identified studies had multiple deficiencies in reporting and methodology, which limited the data available for analysis and interpretation. Limitations included the lack of studies that examined 1 intervention in >1 trial or obvious clinical heterogeneity, precluding the use of meta-analyses.

Future research in this area needs to address the following major gaps in the current state of evidence.

- Diagnostic accuracy of blood pressure measurement in primary care and community settings for screening children of varying ages and characteristics. This includes

identifying the number, frequency, and timing of readings needed to confirm or rule out hypertension.[74]

- Adverse effects of screening, including health care utilization, burden on the family, and discomfort and anxiety for the child and family.
- Epidemiologic studies to describe the natural history of elevated blood pressure and hypertension in children and adolescents, identifying factors that predict persistence into adulthood, and regression to normal based on baseline characteristics such as age, BMI, and pattern of blood pressure. Such studies need to use current definitions of hypertension and be of sufficient duration to draw clinically useful conclusions.[74,75]
- Epidemiologic studies to better define thresholds used to define hypertension in children and adolescents and their association with both structural (eg, carotid intima media thickening, left ventricular mass) and functional (eg, arterial stiffening) markers of target end organ damage related to hypertension.
- Longer-term trials of benefits and risks of all antihypertensive agents (as monotherapy and in combination) and evidence for both short- and long-term safety. Given the expected duration of antihypertensive therapy, the absence of long-term safety data is a significant limitation.
- Large, controlled, good-quality trials of feasible nondrug interventions for children and adolescents using more sophisticated approaches to complex interventions to identify components that provide the greatest benefit over prolonged periods.

CONCLUSIONS

The prevalence of hypertension in children and adolescents is increasing in the United States, largely driven by increased BMI. Screening children for elevated blood pressure or hypertension has the potential to shift the management of hypertension to younger age groups and potentially reduce future cardiovascular disease risk in adults. However, at present, the evidence needed to support these practices is limited. Although it would be logistically (and ethically) very challenging to demonstrate the effects of interventions in children and adolescents with elevated blood pressure on cardiovascular outcomes occurring many decades later in adults, there are clearly a number of outstanding research gaps that can be addressed by feasible research designs in a much shorter time frame. Increasingly, blood pressure is being viewed within a paradigm of overall cardiovascular risk stratification, along with other risk factors, such as lipid profiles, insulin resistance, and BMI.[16] We anticipate that addressing these current gaps in the evidence for blood pressure will be critical to add to clinicians' ability to identify children and adolescents with increased cardiovascular risk and also to offer a balanced assessment of the overall benefit of interventions to reduce this risk and prevent future cardiovascular disease.

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APPENDIX 1 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]

APPENDIX 1 Continued

Screening

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 Wt 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 β-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 α-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]

APPENDIX 1 Continued

Screening
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 Wt 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 β-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 α-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 2 Inclusion and Exclusion Criteria

	Key Questions	Inclusion Criteria	Exclusion Criteria
Settings	All	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	1, 2, and 4	Asymptomatic, otherwise healthy children and adolescents, 0–18 y of age, with no known diagnosis of hypertension	Pregnant adolescents
	3 and 5–8:	Primary hypertension defined as average blood pressure between 95th percentile and 5 mm Hg above the 99th percentile	Majority of study population included secondary hypertension
Interventions	1–4:	Blood pressure measurements using auscultatory or oscillometric devices that can be performed in a primary care clinic	24-h, ambulatory, or home-based blood pressure measurements. Diagnostic tests or investigations used to identify or confirm possible causes of secondary hypertension
	5–8:	Drug: Antihypertensive medications which are currently FDA-approved for use in children/adolescents	Interventions for treatment of secondary hypertension
		Lifestyle: Diet, exercise, etc.	Interventions where reduction in blood pressure was not a primary objective of the study (eg, weight loss studies)
Outcomes	4, 5, and 6:	Blood pressure	Measures of cognitive function
		Left ventricular hypertrophy (defined using left ventricular mass index and/or measures of left ventricular geometry)	Blood pressure variability, such as diurnal variations or nocturnal blood pressure dipping
		Urinary albumin excretion (microalbuminuria)	Arterial wall dysfunction, including measures of arterial stiffness, pulse wave velocity, or augmentation index
		Intima-medial thickness (measured at carotid and/or femoral arteries)	Metabolic measures, eg, measures of impaired glucose tolerance, levels of insulin, lipid profiles, homocysteine levels
		Retinal vascular changes	uric acid levels
			Inflammatory markers including C-reactive protein
			Body changes in weight or BMI
	1 and 7:	Severe visual impairment	Studies reporting intermediate outcomes
		Stage IV or V chronic kidney disease	
		Cardiovascular events, including ischemic heart disease, heart failure	
		Cerebrovascular events, including hemorrhagic and thrombotic stroke, Hypertensive encephalopathy	
		Mortality (all-cause and disease-specific)	
	2	Measures of predictive validity of screening tests (eg, predictive value, likelihood ratios, sensitivity, specificity)	Studies that do not provide enough data to recreate 2 × 2 tables or calculate sensitivity and specificity
			Studies that do not use a true reference standard for comparison
	3	Measures of association (eg, odds ratio; risk ratio, sensitivity, specificity, correlation or regression coefficients)	Studies not reporting measures of association
	8	Side effects of hypertension treatments or interventions	—
Study designs	1	Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, comparative cohort and case-control studies), and systematic reviews	Study designs other than those specified
	2	Studies of predictive validity that compare with a reference standard (eg, ambulatory monitoring)	Study designs other than those specified
	3	Longitudinal cohort and epidemiology studies	Study designs other than those specified
	4 and 8	Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, large cohort and case-control studies), and systematic reviews. If none were identified, uncontrolled before-after studies were examined.	Study designs other than those specified
	5–7	Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, large cohort and case-control studies), and systematic reviews	Study designs other than those specified

APPENDIX 3 Diagnostic Accuracy of Screening for Elevated Blood Pressure in Children and Adolescents

Study, Year	Screening Test	Reference Standard	Definition of a Positive Screening Examination	Population	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Quality Rating
Fixler and Laird 1983[30]	Three measures with mercury manometer measured at least 4 wk apart	Initial screening results compared with subsequent measures	SBP or DBP ≥95th percentile based on normative levels for the study population	*n* = 9017; eighth graders with follow-up at 10th grade; mean age not reported; all were in eighth grade at time of initial screening: 53% male, 44% black, 42% white, 14% Hispanic	Initial positive screen versus subsequent screens: 0.72 (95% CI, 0.65–0.78)	Initial positive screen versus subsequent positive screening test: 0.92 (95% CI, 0.91–0.92)	Initial positive screen versus subsequent positive screening test: 0.17 (95% CI, 0.15–0.2)	Initial positive screen versus subsequent positive screening test: 0.993 (95% CI, 0.991–0.994)	Fair
Stergiou et al 2008[31]	Three averaged measurements with mercury sphygmomanometer, measured in nondominant arm in sitting position after 5 min at rest	24-h ambulatory blood pressure measurements	SBP or DBP ≥95th percentile based on US normative blood pressure tables	*N* = 102; 100% referred for screening; mean age 13 y (SD, 3; range, 6–18); 63% male; race not reported	Positive ambulatory result versus positive clinic result: 0.65 (95% CI, 0.45–0.80)	Positive ambulatory result versus positive clinic result: 0.75 (95% CI, 0.63–0.84)	Positive ambulatory result versus positive clinic result: 0.37 (95% CI, 0.28–0.47)	Positive ambulatory result versus positive clinic result: 0.63 (95% CI, 0.53–0.72)	Fair

APPENDIX 4 Studies Tracking Hypertension From Childhood to Adulthood

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Blood pressure outcomes							
Bao et al 1995[43]; Bogalusa Heart Study (15 y)	>80th percentile	SBP >140 mm Hg or DBP >90 mm Hg or ever treated for hypertension	Hypertension at follow-up, baseline highest SBP quintile versus other SBP quintiles: 18% (54/301) vs. 5% (60/1204); risk ratio 3.6; 95% CI, 2.5–5.1 Hypertension at follow-up, baseline highest DBP quintile versus other DBP quintiles: 15% (45/301) vs. 6% (72/1204); risk ratio 2.5; 95% CI, 1.8–3.6	Unclear; data from 1505 subjects who completed baseline and follow-up surveys (of 3865 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[44]; Fels Longitudinal Study (20 y)	SBP not defined	DBP >90 mm Hg	DBP 80 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 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 vs. 60 mm Hg 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 follow-up surveys (of 976 at baseline)	No loss (Cohort selected based on availability of data; 54% of original cohort completed both surveys)	No	not applicable

APPENDIX 4 Continued

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Gillman et al 1993[45]; Study not named (12 y)	>90th percentile (SBP: 113 mm Hg, within study)	>90th percentile (SBP: 139 mm Hg, 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 mm Hg): 0.26, 0.59, 0.80 >90th percentile (113 mm Hg): 0.35, 0.33, 0.93 >95th percentile (117 mm Hg): 0.44, 0.17, 0.97 >99th percentile (123 mm Hg): 0.58, 0.04, >0.99 SBP, females: >75th percentile (108 mm Hg): 0.27, 0.66, 0.79 >90th percentile (114 mm Hg): 0.39, 0.36, 0.94 >95th percentile (118 mm Hg): 0.48, 0.20, 0.98 >99th percentile (125 mm Hg): 0.65, 0.04, >0.99 DBP, males: >75th percentile (68 mm Hg): 0.21, 0.34, 0.82 >90th percentile (71 mm Hg): 0.24, 0.16, 0.93 >95th percentile (73 mm Hg): 0.27, 0.08, 0.97 >99th percentile (77 mm Hg): 0.34, 0.01, >0.99 DBP, females: >75th percentile (67 mm Hg): 0.19, 0.49, 0.77 >90th percentile (71 mm Hg): 0.24, 0.23, 0.92 >95th percentile (74 mm Hg): 0.30, 0.10, 0.98 >99th percentile (78 mm Hg): 0.38, 0.02, >0.99	Children from a single school in East Boston, MA; sampling method unclear	6% (20/337) attrition	Yes	not applicable

APPENDIX 4 Continued

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Juhola et al 2011[47]; Cardiovascular Risk in Young Finns Study (27 y) Other publication: Juonala et al 2004[77]	≥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 (95% 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 y randomly sampled from 5 cities	38.7% (1392/3596) lost to follow-up at 27 y	Yes	Logistic regression; age, sex, race, study year
Lauer et al 1993[48]; Muscatine Study (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 ($P < .001$) 39% of children with SBP >90th percentile had SBP >80th percentile in adulthood; risk ratio 1.9 ($P < .001$) 17% of children with DBP >90th percentile had DBP >90th percentile in adulthood; risk ratio 1.7 ($P < .001$) 32% of children with DBP >90th percentile had DBP >80th percentile in adulthood; risk ratio 1.5 ($P < .001$)	Unclear; data from 2445 subjects who completed baseline and follow-up surveys (number at baseline not reported)	No loss (Cohort selected based on availability of data)	Yes	not applicable

APPENDIX 4 Continued

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Shear et al 1987[51]; Bogalusa Heart Study (8 y)	Not reported	≥140/90 mm Hg	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	Data from 1501 subjects who completed baseline and follow-up surveys (of 4238 subjects at baseline)	No loss (cohort selected based on availability of data; 35% of original subjects completed both surveys)	Yes	not applicable

APPENDIX 4 Continued

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Sun et al 2007[7]; Fels Longitudinal Study (unclear)	Least-squares means determined according to age and gender (absolute values not reported)	SBP >130 mm Hg and/or DBP >85 mm Hg	Odds of hypertension at >30 y of age given SBP exceeding criterion values at single examination in childhood: Males 5–7 y old males: 3.8 (95% CI, 1.5–9.7) 8–13 y old males: 3.5 (95% CI, 1.5–8.3) 14–18 y old males: 1.1 (95% CI, 0.5–2.4) Females 5–7 y old females: 4.5 (95% CI, 1.1–17.7) 8–13 y old females: 2.7 (95% CI, 1.0–7.1) 14–18 y old females:3.8 (95% CI, 1.2–12.7)	Unclear; data from 493 subjects who completed baseline and follow-up surveys (of 976 at baseline)	8% loss to follow-up in Fels Longitudinal Study overall; data from 51% of original subjects	Yes	not applicable
Other outcomes							

APPENDIX 4 Continued

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Hoq et al 2002[46]; Bogalusa Heart Study (16 y)	≥90th percentile for age, ethnicity, and gender	≥90th percentile for age, ethnicity, and gender	Annual change in BP on adulthood urinary albumin/creatinine ratio by ethnicity: Childhood SBP by ethnicity: Blacks: regression coefficient 0.016 (P = .05) Whites: regression coefficient −0.002 (P = .78) Annual change in SBP from childhood to adulthood by ethnicity: Blacks: regression coefficient 0.315 (P = .002) Whites: regression coefficient −0.045 (P = .55) Childhood DBP by ethnicity: Blacks: regression coefficient 0.026 (P = .012) Whites: regression coefficient −0.002 (P = .761) Annual change in DBP from childhood to adulthood by ethnicity: Blacks: regression coefficient 0.292 (P = .016) Whites: regression coefficient 0.063 (P = .5)	Unclear; data from 2122 subjects who completed baseline and follow-up surveys (of 3865 at baseline)	No loss (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[49]; Bogalusa Heart Study (22 y)	Not reported	Not reported	Odds of carotid intima media thickness in upper quartile given SBP risk factor (not defined): childhood (14–17 y): 1.00 (95% CI, 0.80–1.25)	Unclear; data from 486 subjects who completed baseline and follow-up surveys and carotid artery ultrasound (of 3865 at baseline)	NR (94% [486/516] had data available); data from 13% of original subjects)	Yes	Logistic regression; age, race, sex

APPENDIX 4 Continued

Author, Year, and Study Name (Follow-up)	Definition of HTN in Childhood	Definition of HTN in Adulthood	Outcomes	Quality Considerations			
				Recruitment	Attrition: % with complete data, % of original *N* at follow-up	Measurement Method Stated for Both Time Periods?	Statistical Analysis and Adjusted Variables
Raitakari et al 2003[50]; Cardiovascular Risk in Young Finns Study (21 y)	≥80th percentile	≥80th percentile	Relationship between SBP >80th percentile at age 12–18 (mean age 14.9 y) and carotid intima media thickness 21 y later: regression coefficient 0.013 (SE 0.003); $P < .001$	Finnish children and adolescents aged 3, 6, 9, 12, and 15 y randomly sampled from 5 cities	38% (1367/3596) lost to follow-up at 21 y	Yes	Logistic regression; age, sex

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; NR, not reported; PPV, positive predictive value; SBP, systolic blood pressure.

APPENDIX 5 Interventions for Hypertension in Children and Adolescents

Author, Year (Quality Rating)	Study Design and Setting Duration	*N*	Demographic Characteristics	Intervention	Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height	Blood Pressure (mm Hg)
Drug interventions						
Batisky et al 2007[53] (fair)	RCT	140	Mean age 13 (SD 2.8) y	Group A: Metoprolol ER 0.2 mg/kg	Groups A–C pooled: 46% (95% CI, 37–55)	Mean change from baseline, SBP:
	28 sites		70% male	Group B: Metoprolol ER 1.0 mg/kg	Group B: 26% (95% CI, 8–44)	Group A: −5.2 (95% CI, −7.7 to −2.6)
	United States		26% black	Group C: Metoprolol ER 2.0 mg/kg		Group B: −7.7 (95% CI, −11.3 to −4.0)
	4 wk		Mean SBP: 132 mm Hg	Group D: Placebo		Group C: −6.3 (95% CI, −8.7 to −3.8)
			Mean DBP: 78 mm Hg			Group D: −1.9 (95% CI, −5.5 to 1.8)
			74% BMI ≥95% percentile			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[54] (fair)	RCT crossover	268	Mean age 12 (SD 3.3) y	Study Phase 2 (included placebo comparison)	SBP	Phase 2 results
	49 sites in North and South America		Mean SBP: 137.9 (SD 12.7) mm Hg	Group A: Amlodipine 2.5 mg/day	Group A: 40%	Mean change from baseline, SBP:
	4 wk		Mean DBP: 74.2 (SD 11.6) mm Hg	Group B: Amlodipine 5.0 mg/day	Group B: 35%	Group A: −6.9 ± 12.5 (P = NS) (P = .05 versus placebo)
			31.3% (84/268) primary hypertension	Group C: Placebo	Group C: 30%	Group B: −8.7 ± 13.3 (P = NS) (−3.6 ± 12.7, P = .01 versus placebo)
					DBP	Group C: −3.6 ± 12.7 (P = NS)
					Group A: 42%	Mean change from baseline, DBP:
					Group B: 75%	Group A: −4.2 ± 10.7 (P = NS)
					Group C: 48%	Group B: −4.4 ± 10.2 (P = NS)
						Group C: −0.4 ± 11.0 (P = NS)
Li et al 2010[55] (fair)	RCT	304	Mean age not reported (53% <12 y)	Study Phase B (included placebo comparison)	NR	Phase B results
	43 sites in the US, India, South Africa, Russia, and Dominican Republic		63% male	Group A: Eplerenone 25 mg once daily		Least-squares mean change from baseline, SBP:
	4 wk		35% black	Group B: Eplerenone 25 mg twice daily		Group A: P = NS
			57% white	Group C: Eplerenone 25 mg bid for 2 wk followed by 50 mg bid for 4 wk		Group B: 2.76 (95% CI, −5.5 to 0; P = .048 versus placebo)
			11% Hispanic	Group D: Placebo		Group C: P = NS
			8% Asian			Least-squares mean change from baseline (any group), DBP: P = NS
			56% primary hypertension			

APPENDIX 5 Continued

Author, Year (Quality Rating)	Study Design and Setting Duration	*N*	Demographic Characteristics	Intervention	Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height	Blood Pressure (mm Hg)
Sorof et al 2002[56] (fair)	RCT	94	Mean age 14 y	Group A: Bisoprolol fumarate 2.5+ hydrochlorothiazide 6.25	NR	Least squares mean change from baseline, SBP:
	Clinical trial from 22 sites in United States and Brazil		57% male	Group B: Bisoprolol 5 mg + hydrochlorothiazide 6.25 mg		Groups A–C pooled: −9.3 ($P < .05$ versus placebo)
	4 wk		43% white	Group C:: Bisoprolol fumarate 10 mg + hydrochlorothiazide 6.25 mg		Group D: −4.9
			41% black	Group D: Placebo		Least-squares mean change from baseline, DBP:
			14% Hispanic			Groups A–C pooled: −7.2 ($P < .05$ versus placebo)
			1% Asian			Group D: −2.7
			1% multiracial			
			Mean BMI = 28			
Trachtman et al 2003[57] (fair)	RCT	133	Mean age 12 y (SD 3)	Group A: 2.5 mg felodipine ER	BP ≤90th percentile	Mean difference SBP at follow-up versus placebo (95% CI):
	Clinical trial at 30 sites in the United States		60% male	Group B: 5 mg felodipine ER	Group A: 15%	Group A: −0.71 (−4.8 to 3.38; P = NS)
	3 wk		39% black	Group C: 10 mg felodipine ER, titrated to target dose	Group B: 18%	Group B: −0.06 (−4.6 to 3.3; P = NS)
				Group D: Placebo	Group C: 19%	Group C: −1.73 (−6.58 to 3.13; P = NS)
					Group D: 11%	Mean difference DBP at follow-up versus placebo (95% CI):
						Group A: −2.07 (−6.82 to 2.69; P = NS)
						Group B: −4.64 (−9.18 to 0.09; $P < .05$)
						Group C: 1.31 (−3.56 to 6.11; P = NS)
Trachtman et al 2008[58] (fair)	RCT	240	Mean age not reported (29% <12 y; 71% >12 y)	Group A: Candesartan 2/4 mg	Group A: 54%	Least-squares mean change from baseline, SBP:
	Clinical trial at 42 sites in United States and Europe		71% male		Group B: 62%	Groups A–C: -10.22 ($P < .0001$ versus placebo)
	4 wk		69% BMI ≥95th percentile	Group B: Candesartan 8/16 mg	Group C: 65%	Group D: −3.66
			47% black	Group C: Candesartan 16/32 mg	Group D: 31%	Least squares mean change from baseline, DBP:
			45% white	Group D: Placebo		Groups A–C: −6.56 (P = .0029 versus placebo)
						Group D: −1.8

APPENDIX 5 Continued

Author, Year (Quality Rating)	Study Design and Setting Duration	*N*	Demographic Characteristics	Intervention	Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height	Blood Pressure (mm Hg)
Wells et al 2010[59] (fair)	RCT	77	Mean age: 14 y (SD 3 y)	Group A: Telmisartan 1 mg/kg/day (low-dose group)	Group A: 50% (6–<12 y); 68% (12–<18 y)	Adjusted mean difference SBP at follow-up versus placebo (95% CI):
	Clinical trial at 16 sites in United States, Brazil, and Mexico		57% male	Group B: Telmisartan 1 mg/kg/day, titrated up to 2 mg/k/day after 1 wk (high-dose group)	Group B: 86% (6–<12 y); 79% (12–<18 y)	Group A: −3.6 (−9.2 to 1.9, *P* = NS)
	4 wk		51% white 37% black	Group C: Placebo	Group C: 33% (6–<12 y); 27% (12–<18 y)	Group B −8.5 (−14 to −3.0, *P* = .0027) Adjusted mean difference DBP at follow-up versus placebo: Group A: −4.5 (−9.5 to 0.4, *P* = NS) Group B: −4.8 (−9.7 to 0, *P* = .051)
Drug plus lifestyle interventions						
Berenson et al 1983[60] (fair)	RCT	150	NR	ADAPT Program	NR	Mean change from baseline, SBP:
	School-based in United Sates			Group A: Propranolol 20–40 mg + chlorthalidone 6.25–12.5 mg + nutrition education and promotion of dietary modification		Group A: −7.6
Other publication: Frank et al 1982[78]	6 mo			Group B: Hypertensive control group with no treatment		Group B: −3.0 Mean change from baseline, DBP: Group A: −6.9 Group B: −3.9
Berenson et al 1990[61] (fair)	RCT	150	Mean age 12 y	Same as above	NR	Adjusted mean difference, SBP:
	School-based in United States		55% male			Group A versus Group B: −3.6 (SD 1.12; *P* < .01)
Continuation of Berenson et al 1983[60]	30 mo		47% white Mean SBP 117.7 mm Hg Mean DBP 78.1 mm Hg			Adjusted mean difference DBP: Group A versus Group B: −1.7 (SD 0.82; *P* < .05)
Lifestyle interventions						
Diet						
Couch et al 2008[62] (fair)	RCT	57	Mean age 14 y	Group A: DASH-type diet modified for adolescent population + counseling	NR	Mean difference at follow-up, SBP:
	Cincinnati Children's Hospital Medical Center, United States		63% male	Group B: Counseling alone		Group A versus Group B: 0.1
	6 mo		Mean SBP 128.7 mm Hg Mean DBP 80.5 mm Hg			Mean difference at follow-up, DBP: Group A versus Group B: −1.2 Proportion achieving normotensive status: Group A 61% versus Group B 44%; *P* = NS
Howe et al 1991[65] (fair)	RCT crossover	103	Mean age 13 y (range 11–14 y)	Group A: Low-sodium diet (<75 mmol/day) + counseling	NR	No significant differences in SBP or DBP between diets; baseline values not reported
	School-based Adelaide, Australia 2 phases of 4 wk each		Mean SBP 115.0 mm Hg Mean DBP 60.1 mm Hg	Group B: High-sodium diet (>150 mmol/day) diet + counseling		

APPENDIX 5 Continued

Author, Year (Quality Rating)	Study Design and Setting Duration	*N*	Demographic Characteristics	Intervention	Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height	Blood Pressure (mm Hg)
Sinaiko et al 1993[66] (fair)	RCT	210	Mean age 13 y	Group A: Low sodium diet (<70 mmol/day)	NR	Changes in SBP:
	St. Paul and Minneapolis public schools, United States		50% male	Group B: Potassium chloride supplementation		Boys: No significant differences in rates of increase in SBP between low sodium, potassium supplement, and placebo groups.
	3 y		Mean SBP 113.8 mm Hg	Group C: Participant's usual diet + placebo		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.
			Mean DBP 65.1 mm Hg			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 with placebo that were significantly greater than zero
Exercise						
Hansen et al 1991[64] (fair)	RCT	137	Age range 9–11 y	Group A: 3 extra lessons per week of an ordinary school physical education program	NR	Mean difference at follow-up, SBP:
	Odense, Denmark		Other demographic characteristics: NR	Group B: No extra physical education lessons		Group A versus Group B: −4.9; $P < .05$
	School-based					Mean difference at follow-up, DBP:
	8 mo					Group A versus Group B: −3.8; $P < .05$;
Meditation						

APPENDIX 5 Continued

Author, Year (Quality Rating)	Study Design and Setting Duration	*N*	Demographic Characteristics	Intervention	Proportion of Patients Achieving ≤95th Percentile of Blood Pressure for Age, Gender, and Height	Blood Pressure (mm Hg)
Gregoski et al 2011[63] (fair)	RCT	166	Mean age 15 y	Group A: Breathing awareness meditation	NR	Mean 24-h SBP at 3-mo follow-up:
	School-based in United States		59% female	Group B: LifeSkills training (weekly 50-min sessions focusing on training in problem-solving skills, reflective listening, conflict resolution, anger management to enhance social skills and assertiveness)		Group A versus Group B versus Group C:
	3 mo		100% black Mean SBP 118.9 mm Hg Mean DBP 63.6 mm Hg	Group C: Health education control		116.6 vs 119.8 vs 121.0 Group A versus Group B: P = NS Group A versus Group C: P = .05 Mean 24-h DBP at 3-mo follow-up: Group A versus Group B versus Group C: 66.3 vs 68.2 vs 68.7; P = NS for all comparisons
Progressive muscle relaxation						
Ewart et al 1987[33] (fair)	RCT	159	BMI range: 19.0–31.2 Mean age 15 y (range 13–17 y)	Group A: Progressive muscle relaxation (12 wk, 15–20 min, 4 d/wk) provided in school	NR	No significant differences between SBP and DBP between treatment and control groups
	2 large US Baltimore City public high schools					
	9 mo		60% male 55% black			

BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; ER, extended release; NR, not reported; NS, not significant.

APPENDIX 6 Harms of Interventions for Hypertension in Children and Adolecents

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Drug interventions						
Batisky et al 2007[53] (fair)	All participants had primary hypertension	RCT 28 centers Unites States 4-wk dose-ranging study 52-wk safety study	12.5 (2.8)	144 randomized in dosing study 100 analyzed in safety study	4-wk dose ranging study: ER metoprolol succinate 0.2–2.0 mg/kg Placebo 52-wk open-label study: 25 mg or 12.5 mg once daily at investigator discretion; increase every 2 wk until maximum of 200 mg once daily	4-wk dose-ranging study: 1 withdrawal due to AEs Heart rate decreased by 6.5 bpm in 1.0 mg/kg group (compared with 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-wk 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[54] (fair)	31% with primary hypertension	RCT crossover Clinical trial from 49 centers in North and South America 2 4-wk phases	12.1 (3.3)	268 randomized; 84 with primary hypertension	Amlodipine 2.5–5.0 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, pneumonia, pancreatitis)

APPENDIX 6 Continued

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Hazan et al 2010[67] (good)	Primary hypertension 75% (225/302); Patients with clinically significant medical condition or chronic disease, malignant or severe hypertension excluded	RCT Clinical trial at 61 sites; 2 cohorts stratified by race 2-wk washout period Phase 1: 3-wk dosing study Phase 2: 2-wk withdrawal study	12.2 (2.97)	422 screened 302 randomized	Olmesartan medoxomil	Any adverse event: olmesartan 33/93 (36%) versus placebo 27/89 (30) Incidence of specific AEs not reported; headache most common
Li et al 2004[68] (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 United States, Russia, Israel Phase A: 10-day run-in Phase B: 4-wk dose-ranging Phase C: 2-wk withdrawal versus placebo Phase D: 1-y 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%)

APPENDIX 6 Continued

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Li et al 2010[55] (fair)	56% primary hypertension 22% obesity-related hypertension 17% renal-related hypertension	RCT Clinical trial in 43 centers in the United States, India, South Africa, Russia, and Dominican Republic Phase A: 6-wk dosing study (no placebo) Phase B: 4-wk placebo-controlled study	Age <12 y: 52.6%	304 randomized	Eplerenone 25 mg once daily, 25 mg twice daily, or 25 mg twice daily for 2 wk then 50 mg twice daily for 4 wk Placebo	Phase A: Any AE: low dose 38% versus middle dose 31% versus 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[69] (fair)	Hypertension; "more than 50% had underlying kidney disease" (secondary hypertension) but no additional 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 United States), 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

APPENDIX 6 Continued

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Soffer et al 2003[70] (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% <6–12 y, 53% 13–16 y	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[56] (fair)	Excluded severe hypertension and correctable secondary hypertension	RCT Clinical trial from 22 centers in United States and Brazil 2-wk run-in, 8-wk titration period, - wk dose maintenance period, 2-wk tapering period	13.8 (3.1)	94 randomized (62 treatment + 32 placebo)	B/HT (*n* = 62): B 2.5 mg/HT 6.25 mg B 5 mg/HT 6.25 mg B 10 mg/HT 6.25 mg Placebo (*n* = 32)	B/HT group had fewer overall AEs than placebo group, 33/62 (53%) vs 24/32 (75%) (*P* = .047) and fewer serious AEs, 1/62 (2%) vs 5/32 (16%) (*P* = .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[57] (fair)	Excluded secondary hypertension	RCT Clinical trial at 30 sites in the United States 1- to 3-wk screening period, 2- to 3-wk dose titration period, 3-wk 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 wk, 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

APPENDIX 6 Continued

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Trachtman et al 2008[58] (fair)	Excluded secondary hypertension	RCT	% Age >12 y: 70.8%	240 randomized	4 wk trial:	3/240 patients in the 4 wk trial and 5/233 patients in the 52 wk study discontinued due to AEs, specifically hypotension, arm fracture, dizziness, headache, low white blood cell count, and progression of underlying renal disease (2 patients)
	Other hypertensives, except for other angiotension receptor blockers, were permitted	Clinical trial at 42 sites in United States and Europe			Candesartan doses 2, 8, and 16 mg/day for those <50 kg, and 4, 16, and 32 mg/day for those ≥50 kg	Most common AEs: headache, upper respiratory infection, dizziness, cough, and sore throat
		4-wk trial and 1-y open-label study			Placebo Open label study: Candesartan at 4 or 8 mg/day to start, but later adjusted to control BP	
Wells et al 2002[71] (fair)	Severe or symptomatic hypertension excluded	Dose-ranging RCT 2-wk dose ranging phase and 2-wk placebo controlled washout phase	Median 12 y	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

APPENDIX 6 Continued

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Wells et al 2010[59] (fair)	Excluded secondary hypertension	RCT	14 (2.5)	115 enrolled	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 wk) (n = 31)	Any AE:
		Clinical trial at 16 centers in United States, Brazil, and Mexico		77 randomized	Placebo (n = 16)	High-dose patients: 41.9%
		4 wk, after 2-wk washout period				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 interventions						
Berenson et al 1983[60] (fair)	BP >90th percentile for height, control group with blood pressure <80th percentiles and the 50–60th percentile for comparison (based on centiles derived from study)	"Close to clinical trial"	12	150 (50 high blood pressure treatment group, 50 high blood pressure comparison group, 50 medium blood pressure comparison group)	Group A:	AEs reported as very low incidence with no major complications
	Excluded children with evidence of secondary hypertension	School-based 6 mo			Propranolol 20 mg/day for children n < 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 BP elevation at baseline): No treatment Group C (medium BP elevation at baseline): No treatment	1 temporary withdrawal from active treatment due to nightmares

APPENDIX 6 Continued

Author, Year (Quality Rating)	Relevance	Type of Study Setting and Duration	Mean Age (SD) (y)	Number Randomized or Analyzed	Intervention	AEs
Other clinical studies (FDA analyses)						
Baker-Smith et al 2010[73] (not rated)	Mild to moderate hypertension	Nonsystematic review and meta-analysis of data from 8 trials submitted to FDA between 1998 and 2005 (original studies not cited)	13	1299 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)	Subjects who reported cough in the cohort receiving active drugs (21/748, 2.8%) vs placebo (14/551, 2.5%), *P* = .86
		2 wk (median)			Dosages not reported	Subjects who reported cough in the ACE group: (17/524, 3.2%); ARB group (4/224, 1.8%), *P* = .34
Smith et al 2008[72] (not rated)	Unclear; severe hypertension and significant renal disease excluded	Nonsystematic review and meta-analysis of data from 10 RCTs submitted to FDA between 1998 and 2005 (original studies not cited)	12.1	1707 analyzed (685 placebo, 1022 active treatments)	Active treatments (*n* = 1022; mean doses not reported): amlodipine (*n* = 258), benazepril (*n* = 85), enalapril (*n* = 101), felodipine (*n* = 133),	Placebo versus active treatment:
		2 to 4 wk (varied by trial)			fosinopril (*n* = 235), irbesartan (*n* = 295), lisinopril (*n* = 104), losartan (*n* = 165), quinapril (*n* = 112), ramilpril (*n* =219) placebo (*n* = 685)	No significant difference between groups for any AEs Any AE: 235/685 (34%) vs 382/1022 (37%) Hypertension: 3/685 (4%) vs 1/1022 (>1%) Hypotension: 0/235 (0%) vs 3/1022 (>1%) Cardiac: 8/685 (1%) vs 16/1022 (2%) Neuropsychological: 13/685 (2%) vs 26/1022 (3%) Headache: 113/685 (17%) vs 179/1022 (18%) Syncope: 15/685 (2%) vs 31/1022 (3%) Gastrointestinal: 54/685 (8%) vs 90/1022 (9%) Asthma: 11/685 (2%) vs 12/1022 (1%) Elevated LFT: 7/685 (1%) vs 7/1022 (>1%) Muscle aches: 11/685 (2%) vs 17/1022 (2%)

ACE, angiotensin-converting enzyme inhibitors; AE, adverse event; ARB, angiotensin receptor blockers; bpm, beats per minute; B/HT, bisoprolol fumarate/hydrochlorothiazide; ECG, electrocardiograph; ER, extended release; FDA, Food and Drug Administration; LFT, liver function test.