UK National Screening Committee

Screening to prevent adverse outcomes from primary hypertension in children and young people

External review against programme appraisal criteria for the UK National Screening Committee

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Author: Solutions for Public Health

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

UK NSC, Floor 2, Zone B, Skipton House, 80 London Road, London SE1 6LH
www.gov.uk/uknsc
Twitter: @PHE_Screening Blog: phescreening.blog.gov.uk

For queries relating to this document, please contact: phe.screeninghelpdesk@nhs.net

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Plain English summary

Hypertension is when a child's blood pressure is higher than the normal level for children of the same age and sex.

This is usually caused by another health problem. This is called secondary hypertension. For example kidney problems and heart defects can cause secondary hypertension.

Primary hypertension is when high blood pressure is not caused by another problem.

Children with high blood pressure are also likely to have hypertension as adults. This can cause problems such as heart disease and stroke in later life.

More children are developing high blood pressure without having another condition. The reasons for this are not clear. There may be a link with being overweight or obese. There may also be a link to having a parent with high blood pressure.

Screening may help identify children with primary hypertension. They could then be helped to reduce their blood pressure. The aim of this would be to prevent health problems in later life.

This review looks at whether there is evidence that screening children can achieve this.

The UK National Screening Committee last considered hypertension in children in 2010. It recommended that the NHS should not screen children for high blood pressure.

This was because:

- the causes and effects of primary hypertension were unclear
- it was not clear how to define high blood pressure in children and young people
- there was not a simple, accurate screening test

This review examines evidence produced over the past 8 years to see if this has changed.

The review found:

- some evidence which suggests that high blood pressure in children may result in early signs of ill health. But it is not known how big a problem this is in the UK

- an accurate screening test for high blood pressure in children and young people is still not available
- the best way to avoid the early signs of ill health and longer term disease in adults is not known.

For these reasons, this review does not recommend screening for hypertension in children.

Executive summary

Purpose of the review

This document reviews the evidence on screening for primary hypertension in children and young people aged 3 to 18.

Background

The development of primary or essential hypertension in children and young people has been linked with numerous factors, including elevated Body Mass Index (BMI), parental history of hypertension, nutrition, physical activity, ethnicity and gender. The clinical sequelae of elevated blood pressure are due to its effect on the vascular system over a long period of time. In children, early changes to the vascular system (eg early atherosclerosis), the heart (eg increase in left ventricle mass) and end organ damage are some of the conditions reported as resulting from high blood pressure. Sustained elevation of blood pressure in children and young people continues into adulthood where it is an established risk factor for multiple conditions, including cardiovascular and cerebrovascular disorders and renal impairment.

Focus of the review

The function of a national screening programme in this area would be to reduce morbidity from early vascular changes in children with primary hypertension and reverse or stop the rate of progression to cardiovascular disease in adulthood.

This evidence summary includes studies published between 2010 and October 2017. It considers the following key questions relating to the natural history, test, the intervention and the screening programme:

- what is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?
- what is the association between primary hypertension in children and young people and the risk of adverse outcomes?
- what is the diagnostic accuracy of the screening tests for primary hypertension in children and young people?
- what is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young people?

- what is the effectiveness of pharmacological and non pharmacological and /or combination interventions in children and young people for preventing hypertension in adulthood?
- is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?
- what are the optimal ages to initiate screening?
- what are the optimal time intervals at which to repeat screening?
- who should do the screening?

Recommendation under review

The current UK NSC policy is that systematic population screening for hypertension in children and young people is not recommended. The previous UK NSC external review was published in 2010 and concluded that there were challenges around understanding the natural history of hypertension in children and young people, the accuracy of the test, the effectiveness of the interventions and an effective screening strategy for a population-wide screening programme.

Findings and gaps in the evidence of this review

The current review found that the volume, quality and direction of new evidence published since 2010 does not indicate that there have been significant changes in some areas of the evidence base concerning the accuracy of the screening test and the effectiveness of the intervention since the previous review.

What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?

There is reasonable evidence to suggest that there is likely to be increasing prevalence of elevated blood pressure in children and adolescents in the UK, however it is uncertain what this prevalence is.

What is the association between primary hypertension in children and young people and the risk of adverse outcomes?

There is good quality evidence from Europe, the US and Australia that high blood pressure is an independent factor associated with target organ damage in children and adolescents.

What is the diagnostic accuracy of the screening tests for primary hypertension in children and young people?

Hypertension may be identified in individuals using current standard techniques in a clinical setting; however, from the perspective of population screening these methods would result in many children being identified with elevated blood pressure who did not have hypertension.

What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young people?

Some types of non pharmacological interventions showed some reduction in BP, but it was not clear if this would result in any clinically meaningful change and could be maintained over the long term.

Evidence for effectiveness of use of pharmacological interventions alone for children with primary hypertension was limited in that the trials included in the key systematic review:

- included children with symptomatic primary or secondary hypertension
- were typically of a short duration with a mean of 7 weeks
- showed a modest short term effect of two drugs that were evaluated.

The trials were graded by the authors of the systematic review as low quality using the GRADE working group grades of evidence. This infers that further research is very likely to have an important impact on confidence in the estimate effect and is likely to change that estimate.

The evidence for effectiveness of combined pharmacological and non pharmacological interventions in lowering blood pressure was limited to one RCT reported in a systematic review and a small promising observational study that reported regression of target organ damage.

Overall there was not the volume or quality of evidence available for interventions that could be implemented to effectively manage children with hypertension detected from a population based screening programme

What is the effectiveness of pharmacological and non pharmacological and /or combination interventions in children and young people for preventing hypertension in adulthood?

There was no evidence that pharmacological, non pharmacological or a combination of both interventions begun in childhood were effective in reducing hypertension in adulthood.

Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?

No studies demonstrating effective BP screening strategies in children and adolescents were identified.

What are the optimal ages to initiate screening?
What are the optimal time intervals at which to repeat screening?
Who should do the screening; general paediatricians, renal physicians, other?

No evidence was identified that addressed the questions of optimal ages to initiate a population based screening programme, optimum time intervals between tests or who should carry out the screening test.

Recommendations on screening

The volume, quality and direction of new evidence published since 2010 does not indicate that there have been significant changes in the evidence base. This particularly relates to the accurate identification of children and young people with hypertension and an effective intervention which would reverse or stop the progression of adverse outcomes such as target organ damage and decrease the rate of progression of hypertension from children to adults.

The current recommendation not to introduce a UK systematic population screening programme for hypertension in children and young people should be retained.

Limitations

This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by one information scientist, and further appraisal and study selection by one reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Evidence uncertainties

The aim of this review was to evaluate the evidence about the likely number of children with hypertension in the UK, the adverse impact of hypertension in children, how a

population based screening programme could test for hypertension in children and what would be an effective intervention to reduce the adverse effects.

The evidence is not entirely clear about the prevalence of children with hypertension in the UK. Using an agreed definition it would be useful to estimate as accurately as possible the current prevalence of hypertension in the UK and how that is expected to increase year on year given recent trends.

There was little evidence from the UK about blood pressure testing in children; when, where and how it is undertaken. It would be helpful to explore the current approach to blood pressure testing and how testing in different settings (school, health clinic, home) vary and ways to reduce that variation.

The volume and quality of evidence about pharmacological interventions to reduce the adverse effects of hypertension in children that could be generalised to those detected via a screening programme was limited as it mostly came from studies of children with primary and secondary hypertension identified in clinical settings and treated for short periods of time. Similarly the evidence about non pharmacological interventions and combined interventions was sparse. Understanding how to effectively manage children identified with hypertension through a population based screening programme would be helpful.

Introduction and approach

This paper reviews screening to prevent adverse outcomes from primary hypertension in the UK childhood population (3 to 18 years) against selected UK National Screening Committee (NSC) Criteria. The previous UK NSC external review was published in 2010 and concluded that there was insufficient evidence to recommend a population screening programme for hypertension for children and young people.

The current review explores the volume, quality and direction of the literature published since 2010 and focuses on key questions relating to the conclusions of the previous review. The aim of the review is to inform discussion on the impact of the most recent evidence on the current policy of the UK NSC not to recommend the introduction of a population screening programme for primary hypertension in children and young people in the UK.

Background

The development of primary or essential hypertension in children and young people has been linked with numerous factors, including elevated Body Mass Index (BMI), parental history of hypertension, nutrition, physical activity, ethnicity and gender (Lurbe et al 2016)[1]. Secondary hypertension in children and young people is caused by a large number of underlying conditions in children, most commonly renal parenchymal disease (eg glomerulonephritis, polycystic kidney disease, and chronic renal failure) or renovascular disease. Therefore, hypertension in childhood is not a disease entity but a measurement identifying potential future morbidity (essential or primary hypertension) or existing underlying disease (secondary hypertension)[4]. This review considers the clinical impact of screening for primary (also known as essential) hypertension only.

The clinical sequelae of elevated blood pressure are due to its effect on the vascular system over a long period of time. In children, early changes to the vascular system (eg early atherosclerosis), the heart (eg increase in left ventricle mass) and end organ damage are some of the conditions reported as resulting from high blood pressure[1]. These would be the target outcomes for any population based screening programme for hypertension in children and young people. The aim would be to reduce blood pressure with anti hypertensive interventions thus reversing or stopping the progression of these changes and decreasing the rate of progression of hypertension from children to adults. Sustained elevation of blood pressure in adults is an established risk factor for multiple conditions, including cardiovascular and cerebrovascular disorders and renal impairment (Flynn et al

2017)[2]. Hypertension is often asymptomatic so screening might help to identify children with elevated blood pressure who may not otherwise have been diagnosed.

Definition of hypertension in children and young people

The diagnosis of hypertension in children and young people is based on blood pressure (BP) values that are at the highest end of the normal distribution in a healthy cohort and not determined by risk of cardiovascular morbidity and mortality associated with a certain level of BP. There is no standard definition of hypertension but European and US guidelines describe the same methodology to determine hypertension in children and young people[1,2].

In children BP naturally increases with age and body size making it impossible to use one cut off level to define hypertension. The European Society of Hypertension guidelines[1] define hypertension in children as systolic blood pressure (SBP) (maximum arterial pressure when left ventricle is contracted) and/or diastolic blood pressure (DBP) (minimum arterial pressure during relaxation of the heart ventricles) measuring at least the 95th percentile for sex, age and height, on at least 3 separate occasions. Those children with blood pressure between the 95-99th percentile are classified as grade 1 and those >99th percentiles have grade 2 hypertension.

Children with SBP or DBP measuring at least the 90th percentile but less than the 95th percentile are classified as having high-normal BP (also known as pre hypertension).

In order to align with adult definitions, the European guidelines report a pragmatic consensus that for males and females aged 16 years and over hypertension would no longer be based on percentiles but would be based on the same absolute cut off levels used for adults[1].

Current policy context and previous review

Data from the Global Burden of Disease, 2015[3] reports that, despite some success bringing down the premature cardiovascular diseases (CVDs) death rate, England still ranks lower than 9 other EU nations in terms of years of life lost and that England's premature CVD death rate is 29% higher than France, which has the lowest rate among EU countries.

The 2010 UK NSC[4] review reported that the prevalence of hypertension in children is reported to be rising due in part to increasing childhood obesity and that a proportion of these children will continue to experience elevated blood pressure in adulthood along with all the attendant risks of premature CVD. In this context it is important to consider whether

screening children and young people would be an effective disease prevention measure during childhood that may have ongoing benefits in adulthood.

In order to screen children for hypertension there should be good quality evidence about each element of a potential screening programme covered by UK NSC criteria 1-14. This includes:

- understanding the natural history and impact of the condition in the UK (Criteria 1-3)
- having a valid, accurate, acceptable test and cut off levels (Criteria 4-8)
- having well evidenced further diagnostic tests and treatment for those people with a positive screen(Criteria 9-11)
- understanding the clinical and cost effectiveness of the full screening programme in the form of trials ie that it will reduce mortality or morbidity and is value for money in the medium to long term (Criteria 12 – 14)
- where evidence is robust around these 4 elements of a screening programme there are a further set of criteria (15-20) which consider the potential feasibility of implementing the screening programme.

The previous evidence review in 2010[4] found that there were criteria within each of the 4 elements of a potential screening programme that were not met:

- the prevalence of childhood hypertension in the UK was unknown and it was not clear what the significance of this condition was in terms of childhood morbidity and mortality
- there was not a simple, agreed validated test for identifying childhood hypertension
- there was a paucity of evidence about the long term consequences of not treating childhood hypertension or the long term effects of pharmacological interventions on growth and development
- there were no UK or international clinical trials or cost effectiveness studies of the full screening programme that showed a reduction in morbidity or mortality or that screening was value for money.

As there were a significant number of criteria (1-14) not met, evidence for criteria 15-20 was not reviewed.

Based on the evidence presented in the 2010 review, the UK NSC concluded that screening for hypertension should not be offered to children and young people (3 to 18 years).

The 2010 review drew heavily on 2 publications:

- The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents in the US[5]
- Management of High Blood Pressure Guidelines by the European Society of Hypertension (Lurbe et al 2009)[1]

This evidence update is focussed on questions about selected criteria arising from the previous evidence review in 2010.

Objectives

The aim of a screening programme in this area would be to reduce morbidity from early vascular changes and reverse or stop the rate of progression to cardiovascular disease in adulthood in those children with primary hypertension.

This review assessed key questions to determine if new evidence published since 2010 suggests that reconsideration of the current recommendation for screening for hypertension in children and young people in the UK is required.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
			Condition
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK? What is the association between primary hypertension in children and young people and the risk of adverse outcomes?	15
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	What is the diagnostic accuracy of the screening tests for primary hypertension in children and young people?	4
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example	What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young	4

	Criterion	Key questions	Studies Included Condition
	those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldnot be further considered.	people? What is the effectiveness of pharmacological and non pharmacological and /or combination interventions in children and young people for preventing hypertension in adulthood?	
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (eg. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?	1
12	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	What are the optimal ages to initiate screening? What are the optimal time intervals at which to repeat screening? Who should do the screening; general paediatricians, renal physicians, other?	1

Methods

The current review was conducted by Solutions for Public Health, in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 24th October 2017 by a librarian at the Bodleian Health Care Library, University of Oxford, to identify studies relevant to the questions detailed in Table 1.

Eligibility for inclusion in the review

A total of 223 references were sent to SPH from the Bodleian Health Care Library for further appraisal and possible inclusion in the final review. Selection and appraisal of studies was undertaken by one reviewer taking into account the inclusion and exclusion criteria in the PICOs table below (Table 2). Information from each abstract was logged including type of study, relevant question number, topic area and whether they were included or excluded at this stage. Any queries were resolved through discussion with a second reviewer.

Of the 223 abstracts 65 articles were acquired for the full-text review stage.

Each full-text article was reviewed against the inclusion/exclusion criteria by one reviewer, who determined whether the article was relevant to one or more of the review questions. A second independent reviewer provided input in cases of uncertainty, and any queries were resolved through discussion with the second reviewer.

Table 2. Defining the population, intervention, comparators and outcomes of the key questions

Question 1: What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?

Population: Children and young people (3 to 18 years of age)
Target condition: Hypertension and prehypertension in children and young people
Intervention: NA
Comparator: NA
Outcome: Prevalence rates of primary hypertension in children and young people (3 to18)
Study type: Observational studies with comparison group, systematic reviews

Question 2: What is the association between primary hypertension in children and young people and the risk of adverse outcomes?

Population: Children and young people (3 to 18 years of age) with primary hypertension
Target condition: Hypertension and pre hypertension in children and young people
Intervention: NA
Comparator: Young people (3 to 18 years of age) with normal BP or NA for non-comparative studies
Outcome: • End organ damage (such as ventricular hypertrophy, thickening of the carotid vessel wall and retinal vascular changes) • Cognitive changes • Retinal vascular changes • Cardiovascular disease • Measures of association (eg, odds ratio; risk ratio, sensitivity, specificity etc
Study type: Longitudinal cohort epidemiology and case control studies

Question 3: What is the diagnostic accuracy of screening tests for primary hypertension in children and young people?

Population: Children and young people (3 to 18 years of age)

Target condition: Primary hypertension in children and young people

Intervention: BP measurements using auscultatory or oscillometric devices performed by a health care professional

Comparator: Ambulatory monitoring

Outcome: Measures of predictive validity of screening tests (eg, PPV, NPV, PLR, NLR, sensitivity, specificity)

Study type: Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, comparative cohort, cross-sectional and case-control studies), and systematic reviews Exclusion: Case reports, case series, reviews, non-peer reviewed literature

Question 4: What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in a) children and young people b) adulthood?

Population: Children and young people (3 to 18 years of age) with primary hypertension

Target condition: Hypertension and prehypertension in children and young people

Intervention:

- Pharmacological interventions
- Non-pharmacological interventions (Diet, exercise, etc.)
- Combination of the above

Comparator: No screening and treatment or screening and placebo if comparative

Outcome:

- BP
- Retinal vascular changes
- End organ damage (such as ventricular hypertrophy, thickening of the carotid vessel wall and retinal vascular changes)
- Cognitive changes
- Cardiovascular disease

Study type: Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, comparative cohort and case-control studies), and systematic reviews Exclusions: Case reports, case series, reviews, non-peer reviewed literature

Question 5: Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life including:

- **Optimal age to initiate screening**
- **Optimal time intervals if any to repeat screening**

- **Who should do the screening – general paediatricians, renal physicians, others**

Population: Children and young people (3 to 18 years of age) with primary hypertension

Target condition: Hypertension and prehypertension in children and young people

Intervention:

- Pharmacological interventions
- Non-pharmacological interventions (Diet, exercise, etc.)
- Combination of the above

Comparator: No screening and treatment or screening and placebo if comparative

Outcome:

- BP normalisation
- Retinal vascular changes
- Reduced end organ damage (such as ventricular hypertrophy, thickening of the carotid vessel wall and retinal vascular changes)
- Cognitive changes
- Cardiovascular disease

Study type: Randomized controlled trials, controlled clinical trials, observational studies with a comparison group (eg, comparative cohort and case-control studies), and systematic reviews. Exclusions: Case reports, case series, reviews, non-peer reviewed literature

Appraisal for quality/risk of bias tool

Where appropriate 1 of the following tools was used to assess the quality and risk of bias of each study included in the review:

- epidemiology studies: JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data
- systematic reviews: Critical Appraisal Skills Programme(CASP) systematic review checklist
- diagnostic accuracy studies: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool
- interventional non-RCTs: Downs and Black checklist
- cohort studies: Critical Appraisal Skills Programme (CASP) Cohort Study Checklist
- case control studies: Critical Appraisal Skills Programme (CASP) Case Control Checklist.

Databases/sources searched

Database searches on Embase, Medline & Cochrane Library, limiting to English from 2010 onwards were conducted on 24th October 2017 to identify studies relevant to the questions detailed in Table 1. The search strategies for each question are in Appendix 1. Appendix 2 contains a full PRISMA flow diagram along with a table of the review questions and the included publications relevant to each one.

Question level synthesis

Criterion 1

The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Question 1: What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?

The previous NSC review (2010) looked at the prevalence of hypertension in children and young people 3 to 18 years of age, however, the data were reported separately for primary and secondary hypertension. There was 1 UK study quoted based on 3 UK health surveys carried out between 1995 and 1998 that reported high/normal blood pressure prevalence of 6.9% and hypertension of 2.6%. The cut offs defining elevated blood pressure in a healthy cohort of children was the 91st to 98th percentile and hypertension was defined as any readings above the 98th percentile[4].

The review stated that the prevalence for secondary hypertension is usually quoted to be around 0.1%, with one study reporting that it is usually considered to be more common in children than in adults.

The challenges with determining hypertension prevalence in children are:

- blood pressure rises with age and weight
- different methods of taking blood pressure in children report different results
- the definition of hypertension varies between studies
- there is a lack of evidence about what constitutes hypertension in children.

The aim of addressing this question in this review update is to evaluate if more recent evidence has been published to more accurately determine prevalence of hypertension in UK children and young people.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- the target population is children and young people aged 3-18 years

- the condition is hypertension and pre-hypertension in children and young people aged 3-18 years
- the outcome of interest is prevalence of primary (essential) hypertension in children and young people
- the search should prioritise systematic reviews and observational studies.

Description of the evidence

Database searches yielded 7 results and 3 were determined to be relevant from the abstracts. On receiving the full papers 1 was excluded as it was a poster from a conference and a second excluded because it focussed on the increase in blood pressure in children over time but did not address the question of the prevalence of hypertension in the population.

Summary of findings

A study-level summary of data extracted from each included publication is presented in the summary and appraisal of individual studies in Appendix 3 listed by question.

Table 3. Study included following search for criteria 1 question 1

Study	N	Age group	Outcome
De Moraes et al (2014) Prospective epidemiological cohort study Europe	5221	2-9	Prehypertension: Males 12%, females 13% Hypertension males: 9% females11%

De Moraes et al (2015)[6] analysed a sample of the IDEFICS study (identification and prevention of dietary and lifestyle induced health effects in children and infants) and the effects of physical activity and sedentary behaviours on blood pressure in children. This study analysed data from 5221children aged 2-9 years sampled from 8 countries across the European Union (not the UK) between September 2007 and May 2008. An arm BP oscillometric monitor device that was previously validated for the age group was used. At each appointment after 10 minutes rest BP was taken then again after a further 5 minutes rest. The lowest BP measurement of the 2 was used. Pre hypertension was defined as SBP or DBP between 90th-95th percentile and hypertension was SBP or DBP >95th percentile for age and height.

Table 4. Prevalence of elevated blood pressure and hypertension in children aged 2-9 years

	Males % (95% CI) n=2638	Females %(95% CI) n=2583

Normal BP≤90th percentile	78.8 (77.2-80.4)	75.5 (73.8-77.2)
Elevated blood pressure ≥90th and < 95th percentile	12.1 (10.9-13.4)	13.2 (11.8-14.5)
Hypertension ≥95th percentile	9.1 (7.9-10.2)	11.3 (10.0-12.5)

The table shows the findings of the study and indicates that around 10% of males and females aged 2-9 years were identified as having high blood pressure and a further 12-13% had elevated blood pressure.

It is difficult to compare prevalence reported in De Moraes with the paper described in the previous NSC review (Jackson et al 2007)[7] as the cut off levels used were different (91st to ≤ 98th percentile for elevated blood pressure and >98th percentile for hypertension). However by combining both categories the percentage of people tested who had either elevated blood pressure or hypertension in Jackson (2007) was 9.2% (all those ≥91st percentile) and in De Mores was 22.9% (all those ≥ 90th percentile). Neither paper separates out children whose elevated blood pressure was subsequently diagnosed as secondary hypertension.

A further publication that didnot report overall prevalence of hypertension (so is included for information only) found from comparison of studies between 1980 and 2008 that blood pressure in children is rising year on year in the UK (Peters et al, 2012)[8.] The authors reported a year on year increase in systolic blood pressure in 9-11 year olds of 0.45mHg (95% CI 0.43-0.48) for boys and 0.51mmHg (95% CI 0.49--0.53) for girls. This suggests that historical prevalence estimates are unlikely to reflect current rates.

Question 2: What is the association between primary hypertension in children and young people and the risk of adverse outcomes?

The 2010 NSC review reported that there was strong evidence that blood pressure measured in childhood predicted adult BP and therefore adverse outcomes in adults (tracking). There was very limited evidence reported about adverse outcomes of hypertension in children and young people but what there was focused on hypertensive end-organ-damage including the thickening and stiffening of large arteries and left ventricle hypertrophy. This is typically seen in children with conditions such as chronic kidney disease who have developed secondary hypertension[9].

The aim of addressing this question in this review update is to evaluate if more recent evidence has been published to more fully understand the early vascular changes due to hypertension in children and young people.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- the target population is children and young people aged 3-18 years
- the condition is primary hypertension and pre-hypertension in children and young people aged 3-18 years.
- if a comparator is part of the study it should be young people (3-18 years) with normal blood pressure
- the outcomes of interest are:
- end organ damage of the cardio vascular system(LVMI, CIMT)
- cognitive changes
- retinal blood vessel changes
- measures of association (eg; odds ratio, risk ratio, sensitivity, specificity)
- the search should prioritise systematic reviews, longitudinal cohort and case control studies.

Description of the evidence

Of the 78 results identified for this question from the database search 28 were determined to be relevant from the abstracts. On receiving the full papers:

- 9 were excluded as they focussed on tracking BP from childhood to adulthood and did not report childhood adverse outcomes listed in the PICO
- 1 paper was excluded because it combined children with both primary and secondary hypertension and did not report the results separately
- 1 paper was excluded because study groups varied in size (range of n=14-n=57), it wasnot clear how the control group was recruited and a similar much larger study was available
- 1 paper was excluded as the focus was on children with type 2 diabetes
- 1 paper about retinal vascular calibre in Singaporeans aged 4 to 5 years was excluded as four more recent publications with a similar number of participants covering the same age range were included based on populations from Switzerland, Australia(2 papers) and Germany.

Fourteen papers were included (Table 5) and the adverse outcomes reported in the included papers were:

- Changes to the left ventricle of the heart (left ventricle mass (LVM,) left ventricle hypertrophy (LVH) and left ventricle mass index(LVMI)
- Changes to the thickness of the middle two layers of the carotid artery both left and right sides(CIMT)
- Changes to the diameter of the blood vessels in the retina including central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE) and the ratio of the two, the arterial/vein ratio(AVR)

- Changes in neurocognitive performance.

The papers reported associations with elevated blood pressure (hypertension), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MADP).

Summary of findings

A study-level summary of data extracted from each included publication is critically appraised and presented in the summary and appraisal of individual studies (Appendix 3) where publications are stratified by question.

Table 5. Studies included in evidence summary following search and selection; Criterion 1 question 2

	Target end organ damage measure	Number	Age group	Outcome
Kollias et al (2014) Systematic review	LVMI,CIMT	860 from11 studies from (1998 to 2011)	Mean age 14.4	Pooled difference in LVMI 6.53 $gm^{2.7}$(4.73-8.33) (I^2=51%, p=0.03)
Stelcar et al (2017) Prospective case control Germany	LVM, CIMT	150	5 to 20	Those with hypertension had greater LVM and CIMT(left sided) than control p<0.001 (for each comparison)
Gupta-Malhotra et al (2016) USA	LVH, CIMT	89	9 to 18	32 of 89 children had LVH. Those who had LVH were more likely to have higher: BMI, (p=0.001), higher weight (p=0.0004) and thicker CIMT (p=0.002)
Mir et al (2016) Case control study Turkey	LVMI,CIMT	110	5 to 17	Those with hypertension had higher LVMI and thicker CIMT than controls p<0.01(both comparisons)
Meng et al (2015) Case control study China	LVMI,CIMT	238	9 to 15	LVMI higher in hypertensives vs controls (p<0.01). Change of elevated LVMI prevalence over 2 years higher in hypertensives vs controls. CIMT thicker in hypertensives vs controls (p=0.007)
Pieruzzi et al (2015) Case control study Italy	LVH	526	6 to 15	SBP associated with LVH and prevalence of LVH (both p<0.001)
Day et al (2017) Systematic review	CIMT	8 studies 2004 to 2013	0 to 19	CIMT associated with SBP in 5/8 studies CIMT associated boys but not girls 2/8 case studies CIMT associated with DBP in 1/8 studies All associations p<0.05
White et al (2017) Prospective cohort study	CIMT	119	10 to 11	SBP associated with left and right mean CIMT p<0.05

USA				
Hao et al (2017) Longitudinal observational study USA	LVH, CIMT	683	5 to 16 (in 1989)	23 year follow up of blood pressure. Those with the highest BP aged 5 to 16 had strongest associations with thicker CIMT and higher LVMI and BP after 23 years (p=0.012 and p<0.001 respectively).
Imhof et al (2016) Prospective cohort study Switzerland	Retinal blood vessels diameter	391	4 to 5	SBP and DBP were associated with increased retinal vessel diameters (CRAE and AVR) p<0.001 (all comparisons).
Gopinath et al (2016) Propective cohort study Australia	Retinal blood vessels diameter	379	3 to 6	SBP associated with retinal arteriolar diameter (p=0.02). DBP and MABP not associated with retinal vessel diameter
Gopinath et al (2010) Prospective cohort study Australia	Retinal blood vessels diameter	2272	12	SBP, DBP and MABP in boys and girls associated with retinal arteriole diameter (p values from p=0.005 to p<0.0001) but associations (SBP, DBP and MADP only seen in boys for retinal venular diameter (p=0.003, p<0.001 and p<0.0003 respectively).
Murgan et al (2013) Prospective cohort study Munich	Retinal blood vessels diameter	121	13 to 19	Hypertension associated with CRAE(p<0.05) but not CRVE or AVR
Lande et al (2017) Case control study USA	Neurocognitive measures	75	10 to 18	Hypertension associated with worse performance for verbal and visual reasoning, recall and verbal reasoning (all p<0.05)

Left Ventricular Mass Index

Primary hypertension can lead to cardiovascular changes in childhood and left ventricular hypertrophy (LVH) as demonstrated by an increase in the left ventricular mass(LVM) on an echocardiogram, is a common surrogate marker of end organ damage[10]. Left ventricular mass index (LVMI) can be calculated by the measurement of the left ventricle mass thickness divided by height in meters to the 2.7th power to minimise the effect of age, gender, ethnicity and weight status. There are other methods used to calculate LVMI which means it is difficult to compare studies directly.

The systematic review by Kollias et al (2014)[11] identified and carried out a meta-analysis on 93 studies of blood pressure measurements in children taken using ambulatory monitoring or other home blood pressure methods. A sub set of 11 studies published between 1978 and 2011 provided data on the differences in left ventricular mass index (LVMI) between normotensive (n=428) and hypertensive children (n=432) which included children with primary hypertension. The hypertensive group was found to have a higher LVMI by 6.53g/m2.7 (95% CI 4.73-8.33).

Stelcar et al (2017)[12] measured a range of early markers of target organ damage including LVMI in 100 children aged 5-20 with primary hypertension and 50 who were normotensive (control group). Of the 100 children with hypertension (study group 1) a sub-group (study group 2) was defined as children with normal (≤90th percentile) basal metabolic indices (BMI). LVMI was significantly greater in thickness in both study group 1 and study group 2 compared to the control group ($p<0.001$ and $p=0.003$ respectively, no confidence intervals reported).

Gupta –Malhotra et al (2016)[10] recruited 89 newly diagnosed but untreated children with pre-hypertension or primary hypertension aged 9-18. Of those with hypertension 23 (26%) had stage I hypertension[a], 58 (65%) had stage II hypertension and 8 (9%) had pre-hypertension. A range of observations were made including BMI, LVH, weight, height, gender, age and ethnicity. BMI in children who were pre-hypertensive or hypertensive was significantly associated with LVH (OR:5.69; 95% CI 2.10-15.44 p=0.001). Among non-obese children the mean 24 hour ambulatory systolic BP was significantly higher in children with LVH compared to those without LVH (mean 132mm/Hg SD10 vs mean

[a] For Children Aged 1–13 y[2]
Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg,or 130/80 to 139/89 mm Hg (whichever is lower)
Stage 2 HTN: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg(whichever is lower)
For Children Aged ≥13 y
Stage 1 HTN: 130/80 to 139/89 mm Hg, Stage 2 HTN: ≥140/90 mm Hg

123mm/HG SD7 p=0.003). Amongst obese children with and without LVH there was no difference in mean systolic BP (mean 122mm/Hg SD 9 vs 120mm/Hg SD 9 p=0.659).

Mir et al (2016)[13] enrolled 75 children (consecutively) newly diagnosed with prehypertension or hypertension and 35 normotensive controls. A range of variables including systolic and diastolic blood pressure, BMI and LVH were measured. Hypertensive patients had significantly greater LVHI than controls (32.9±11.5 vs 28.8±1.55 p=0.01).

Meng et al (2015)[14] recruited 80 children aged 9-15 newly diagnosed with hypertension and 158 normotensive children who were available for baseline and follow up testing (2 years later). Children were classified as being normotensive (n=148), having sustained hypertension (n=48) or non-sustained hypertension (n=38) based on the consistency of their baseline and follow up results. At follow up LVMI was measured and significant differences detected between normotensive controls and both groups of sustained and non-sustained hypertension (both p<0.01).

Pieruzzi et al (2015)[15] studied 526 children aged 6 to 15 years to examine the role of BMI, BP and waist circumference on left ventricular mass, diastolic function and left ventricular geometry. Primary care referrals were made of 461 children for either elevated BP or overweight/obesity[16]. A further 65, normal weight normotensive children were also recruited and investigated. Multiple regression analysis showed that male gender (p<0.001, 1.98, 95%CI 1.03-2.93), systolic blood pressure z score (p=0.005, 0.94, CI 0.41-1.46) and weight class (normal weight vs overweight [p<0.001, 95%CI, 4.30, 3.09-5.5], normal weight vs obese, [p<0.001, 8.05, 95%CI, 6.86-9.24]) were independently associated with higher values of LVMI.

There are different forms of left ventricular hypertrophy changes. The 3 that were measured in this study were:

- concentric remodelling – changes in the left ventricle shape due to ongoing chronic high pressure and volume
- concentric hypertrophy – changes in ventricle shape due to pressure overload
- eccentric hypertrophy - changes in left ventricle shape due to volume overload.

Logistic regression showed that concentric remodelling was associated with systolic blood pressure but not weight category (see Table 6 below).

Concentric hypertrophy and eccentric hypertrophy were associated with hypertension, excess weight and waist circumference.

Table 6. Association of left ventricular hypertrophy, hypertension and weight

Variable	Concentric remodelling	Concentric hypertrophy	Eccentric hypertrophy
	Odds Ratio (95%CI)	Odds Ratio (95%CI)	Odds Ratio (95%CI)
Systolic BP (Zscore)	1.71 (1.29 2.26) p=0.0002	2.09 (1.48-2.95 p<0.0001	1.51 (1.10-2.09) p=0.0120
Over Weight vs Normal weight	0.57 (0.32-1.01) p=0.0528	2.78 (0.93-8.27) p=0.0669	6.82 (2.31-20.13) p=0.0005
Obese vs Normal weight	0.91(0.50-1.64) p=0.7506	17.15(6.23-47.20) p<0.0001	16.65 (5.69-48.74) p<0.0001
Waist circumference Z score	1.02 (0.91-1.15) p=0.7009	1.5 (1.28-1.76) p<0.0001	0.00 (0.00-0.00) p=0.0000

Source: Pieruzzi et al (2015)[15]

The results suggest that high BP and weight excess could have a different impact on cardiac morphology and diastolic function in children. Weight excess and fat distribution are associated with a worse diastolic function whereas hypertension induces more easily concentric remodelling.

Limitations

It is noted by Meng et al (2015)[14] and Pieruzzi et al (2015)[15] that the measurement and definition of LVH are important in the stratification of cardiovascular risk but there is a complex relationship between myocardial growth and body growth making indexing difficult in children. There is currently no consensus on how LVMI is calculated and this means it is difficult to compare studies.

Carotid Intima Media Thickness

The carotid intima-media thickness test (CIMT) is a measure of the thickness of the inner 2 layers of the carotid artery – the intima and media. Abnormal thickness is related to the extent of atherosclerosis.

Day et al (2017)[17] undertook a systematic review of the evidence of the association between blood pressure and CIMT thickness in children published between 1980 and 2013. Twenty eight studies were included of which 8 were based on healthy children recruited in the community, a further 8 included only hypertensive children and 9 studies recruited obese children from obesity clinics. A further 3 studies focussed on hypercholesterolemia, gender differences and age differences respectively and CIMT.

Of the 8 studies based on healthy children systolic blood pressure was correlated with CIMT in 5 studies, diastolic blood pressure in 1 study and both systolic and diastolic blood

pressure in 2 studies. When adjusted for confounding factors 1 study found the correlation disappeared for both SBP and DBP and 1 study found the correlation with DBP weakened.

The 8 studies recruiting only children with hypertension found the definition of hypertension varied between studies. Seven studies found a positive association between blood pressure and CIMT however where the studies had adjusted for confounders no association was apparent.

Of the 9 studies focused on overweight and obese children in 8 there was a healthy weight control group. All 9 studies initially found a significant association between blood pressure and CIMT. When 7 of the studies made adjustments for potential confounding factors only 2 studies continued to find a significant association.

Four studies identified by the Kollias et al (2014)[11] systematic review were suitable for meta–analysis and provided data about differences in carotid intima-media thickness(CIMT) between normotensive (n=277) and hypertensive (n=258) children. Carotid intima-media (CIMT) thickness was 0.03 mm higher in the hypertensive group (95% CI 0.02-0.04).

Stelcar et al (2017)[12] measured CIMT in 100 hypertensive and 50 normotensive children. CIMT on both left and right sides were significantly thicker in the total study group vs the control group (p<0.0001) and the sub-set of the study group who had a BMI≤90th percentile and the control group (Table 7).

Table 7. CIMT in hypertensive and normotensive children

Variable	CIMT right side mm	CIMT left side mm
CG - Control group(n=50)	0.35±0.05	0.36±0.050
SG1 -Study group 1 (n=100)	0.43±0.09	0.43±0.08
SG2 -Sub set of SG -BMI≤90th percentile (n=45)	0.42±0.09	0.42±0.07
CG vs SG	p<0.001	p<0.001
CG vs SG2	p<0.001	p<0.001

Source: Stelcar et al (2017)[12]

White et al (2017)[18] measured CIMT in left and right arteries of 123 children aged 10 and 11and examined the association with 7 cardiovascular risk factors:

- total cholesterol mg/dL
- HDL-C mg/dL
- Fasting glucose mg/dL

- BMI percentile
- BP(mm/HG)
- family history
- physical activity mins/day

A positive relationship was reported with fasting glucose (r=0.22, p<0.05), systolic BP (r=0.23, p<0.05) and BMI (r=0.41, p<0.41). There was also a significant increase in thickness of CIMT of those children with 0 cardiovascular risk factors compared to those with 3+ (p<0.05).

Mir et al (2016)[13] measured CIMT in 75 newly diagnosed children 13 (17.3%) of which were pre-hypertensive, 39 (52%) had stage I hypertension and 23 (30.7%) had stage II hypertension. A control group of 35 healthy children were also tested. CIMT in the study group was significantly thicker than those in the control group (0.46±0.06 vs 0.35±0.12 p=0.01).

Meng et al (2015)[14] measured CIMT in 80 hypertensive children (38 with non-sustained hypertension and 46 with sustained hypertension) and 148 normotensive controls. CIMT was 0.46 ±0.03 in the normotensive group, 0.47±0.03 in the non-sustained hypertensive group and 0.49±0.04 in the sustained hypertension group. There was a significant difference in thickness between the control group and each of the 2 study groups both with a p value of p<0.01.

BP trajectories and LVMI and CIMT

Hao et al (2017)[19] examined the association of blood pressure throughout childhood and young adulthood with LVMI and CIMT. The Georgia Stress and Heart longitudinal study was designed to evaluate the development of CVD risk factors in children and young adults. Participants were aged 5-16 in 1989, normotensive based on age and gender. They were included if considered healthy based on parental reports of the child's medical history. Over a 23 year period (1989-2012) participants were invited to 16 data collection appointments. Of the 683 participants meeting the inclusion criteria, over 75% had measurements taken 9 or more times with the remainder ≥3 to ≤ 8 times. Measurements taken include:

- height
- weight
- BMI
- body surface area
- blood pressure
- IMT and LVMI were measured at the 12th, 14th and 15th appointments.

Latent class modelling (a type of modelling used to find groups in multivariate categorical data) was used to identify 3 sub-groups that shared a similar underlying trajectory in BP then the association of these trajectory groups with IMT and LVMI were examined using a mixed linear regression model.

The first sub group, High Increasing (HI), comprised 83 participants (12.2%) who started at around the age of 10 with SBP of 116±10.4 which increased most steeply of the 3 groups, over the following 23 years to 138.5±15.4 (mean increase of 22.0 mmHg). The second sub group, Moderate Increasing (MI) comprised 266 (39.0%) participants who started the study with an SBP of 106±9.9 which increased over 23 years to 122.5±10.0 (mean increase13.9 mmHg). The final sub group, Low Increasing (LI) comprised 334 (48.9%) participants who started with an SBP of 99.8±8.6 which increased to 108.9±8.0 by the end of the study (mean increase of 9.1mmHg).

Participants in the HI sub group were more likely to be African American ($p<0.001$), male ($p<0.001$) have a higher BMI ($p<0.001$) and a father with a lower educational level ($p<0.05$). The percentage of participants with hypertension (SBP≥140mmHg or DBP ≥90mmHg) or taking hypertension medications was 42.2% in the HI group, significantly higher ($p<0.001$) than in the MI group (6.0%) and LI subgroups (1.8%).

Increased rate of growth in SBP (SBP trajectories) was significantly associated with increased CIMT and LVMI ($p<0.001$). Compared with the LI group individuals in the MI and HI showed higher IMT (MI is $\beta=0.019$; $p=0.007$ and HI is $\beta=0.051$; $p=0.012$). MI and HI groups were also associated with higher LVMI than the LI group (MI is $\beta=2.785$; $p=0.019$ and for HI $\beta=7.451$; $p<0.001$). The associations were independent of age, gender, race, BMI, fathers' education and BP levels.

Using mid-BP trajectories, compared to the LI group the MI group did not have a significant association with higher CIMT and LVMI values but the HI group did (CIMT adjusted $\beta=0.028$;$p=0.007$ and LVMI $\beta=3.672$;$p=0.035$).

The association of DBP trajectories with IMT or LVMI were not significant.

Retinal blood vessel changes

Five studies were identified that examined the relationship between hypertension and the microvascular changes of the diameter of the arterioles and venules of the retina. Retinal arteriolar narrowing has been associated with large artery stiffness (Lin et al 2015)[20]

Imhof et al (2016)[21] undertook an observational study of 391 primary school children (aged 6-8 years) measuring SBP, DBP, BMI, waist to height ratio and waist circumference. Retinal arteriole and venule diameters were measured from photographs and the central retinal arteriolar (CRAE) and central retinal venular (CRVE) equivalents calculated. The ratio of these measurements (arteriolar to venular diameter ratio or AVR) was also calculated.

The study reported that there were 291 (74.4%) normotensive, 45 pre-hypertensive and 55 hypertensive children in the cohort. Children with pre hypertensive or hypertensive SBP had narrower arterioles compared with normotensive children (-5.5µm, p=0.01 and -7.5µm, p<0.001 respectively). Similar associations were observed between retinal arteriole diameter and pre hypertensive and hypertensive DBP (p=.01 and p<0.001 respectively). No association was seen between SBP or DBP and retinal venule diameter.

Gopinath et al (2013)[22] examined 379 children aged 3-6 years and also found an inverse relationship between SBP and retinal arteriolar diameter (β= -1.70 p=0.02) but not DBP (β=-1.02 p=0.16). Neither SBP nor DPB was associated with retinal venular diameter. The same authors undertook a similar study (Gopinath et al 2010)[23] with 2272 12 year olds and reported that hypertensive stage as determined by quartiles of SBP, DBP and mean arterial blood pressure were associated with retinal arteriolar narrowing (p<0.001 in all cases) but not retinal venular diameter.

Murgan et al (2013)[24] surveyed 121 adolescents aged 13-19. A weak significant negative correlation with peripheral SBP and central SBP was reported (r=-0.201, p=0.43 and r=-0.205, p=0.041 respectively). Neither AVR or CVRE correlated with peripheral or central SBP or DBP.

Neurocognitive functioning

One study by Lande et al (2016)[25] tested neurocognitive function in children with primary hypertension and normotensive controls. A cohort of 75 children with newly diagnosed untreated hypertension and 75 matched normotensive controls (including for BMI) had baseline neurocognitive testing including tests of problem solving/planning, set shifting, response inhibition, vigilance and working memory. Testing of fasting lipid profile, insulin level, glucose, C-reactive protein and ambulatory BP was undertaken by all participants but only those in the study group with sustained hypertension had an echocardiograph. Multivariate analysis showed an overall main effect of hypertension on worse neurocognitive test performance for 3 areas, the Rey Auditory Verbal Learning Test (RAVLT β= -1.13, βSE=0.44 p=0.012), the composite CogState Groton Maze Learning Test (CogState GMLT β=4.2, βSE=1.96, p=0.031) and the Weschler Abbreviated Scales of

Intelligence, Full Scale Intelligence Quotient (WASI FSIQ β=-4.1, βSE=1.97, p=0.038). These measures are testing attention, learning, memory and fine motor dexterity. The effect sizes of the group differences were modest but increased for the RAVLT and CogState GMLT tests when the hypertension group was limited to those with severe ambulatory hypertension or LVH. Those with moderate hypertension scored better than those with severe hypertension and less well than the control group (RVLT moderate group mean difference from control group -1.8, p=0.32, severe group -1.3, p=0.007, CogState GMLT, moderate group mean difference from control group, 1.3 p=0.47, severe group 4.4, p<0.001).

Summary of Findings Relevant to Criterion 1: Criterion not met[b]

Question 1 – What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?

This element of criterion 1, addressed by question 1, is not met.
One study is included that reported prevalence of hypertension across 8 European countries in children aged 2 -9. Results were inconsistent with previous estimates of hypertension in the UK reported in the UK NSC review in 2010.The evidence indicates that prevalence estimates of essential hypertension in children aged 3 to 18 in the UK remain uncertain.

Question 2 –What is the association between primary hypertension in children and young people and the risk of adverse outcomes?

This element of criterion 1, addressed by question 2, is met. The focus of this question was the presence or absence of target organ damage in relation to blood pressure in children and young people.

Fourteen publications are included that report results of children with primary hypertension and LVM (4), CIMT(3), both LVM and CIMT (2) changes in the microvasculature of the retina (4) and neurocognitive changes(1).

- [b] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
- **Not Met** - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
- **Uncertain** -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

All publications reported observational case control or cohort studies and there were no obvious concerns about the internal quality of the study methodology as determined by the critical appraisal check lists.

For LVM, CIMT and retinal vasculature multiple reasonable quality papers included here have shown target organ damage to be independently associated with systolic blood pressure in children, which suggests that the selection bias common to observational studies is unlikely to account for the result.

Overall there is reasonable evidence to suggest that there is likely to be an increasing prevalence of elevated blood pressure in children and adolescents in the UK, however it is uncertain what this prevalence is. There is good quality evidence from Europe, the US and Australia that high blood pressure is an independent factor associated with target organ damage in children and adolescents.

As one of the two questions about criterion 1 is unmet, overall this criterion is not met.

Criterion 4

There should be a simple, safe, precise and validated screening test

Question 3: What is the accuracy of the screening tests for primary hypertension in children and young people?

In the previous UK NSC review (2010)[4] the question of accuracy of the test used to measure hypertension in children and young people was addressed. The author outlined the challenges in obtaining an accurate blood pressure result from children. These were:

- blood pressure rises naturally with age
- blood pressure changes in individuals constantly and can vary by time of day, anxiety levels, activity or food and drink consumed just prior to the test
- different methods of taking blood pressure in children report different results
- the definition of hypertension varies between studies.

The recommendations about how to take blood pressure in children were reported. BP should be measured:

- using a non-mercury ausculatory device validated against the British Hypertension Society
- after 5 minutes of sitting quietly with the right arm supported
- when the person has not had any stimulant medication or food
- three times on separate occasions.

The blood pressure measurement should be checked against a set of standard tables based on age, gender and height to determine whether the result is ≥95th percentile for a healthy cohort of children of normal weight5. These tables are based on information about 50,000 US children compiled in 1999-2000 from the National Health and Nutrition Survey (NHANES).

The evidence reported in the 2010 NSC review showed that the variation in an individual's blood pressure each day, its natural increase as children grow in height combined with factors such as white coat syndrome[c] mean there is a high likelihood of a high false positive rate. Additionally tables to determine hypertension cut offs are based on the distribution of measurements from US children in 1999-2000 which may not be valid when evaluating children with possible hypertension in the UK in 2010.

[c] White coat hypertension, more commonly known as white coat syndrome, is a phenomenon in which patients exhibit a blood pressure level above the normal range, in a clinical setting, though they don't exhibit it in other settings

The aim of addressing this question in this review update is to evaluate if more recent evidence has been published that points to increased accuracy in testing BP in children and young people.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- the target population is children and young people aged 3-18 years
- the condition is primary hypertension and in children and young people aged 3-18 years
- the intervention is BP measurements using ausculatory or oscillometric devices performed by a healthcare professional
- the comparator is ambulatory monitoring
- the outcomes of interest are measures of clinical validity of screening tests such as positive predictive value, negative predictive value, sensitivity and specificity
- the search should prioritise randomised controlled trials, observation studies with a comparison group and systematic reviews.

Description of the evidence

Of the 37 results identified for this question from the database search 12 were determined to be the highest quality evidence relevant from the abstracts. On receiving the full papers reasons for exclusion were:

- 2 studies had been superseded by a recent 2017 systematic review
- 1 was an overview rather than a study
- in 3 papers the tests or outcomes described were not listed in the PICO
    - 1 was a meta analysis of studies carrying out three blood pressure measurements in children. There was significant heterogeneity between the studies and there were differences in how blood pressure was measured which were not fully described.
    - 2 papers summarised results of using BMI, waist to height ratio and BP to height ratio to identify those with elevated blood pressure.
- 1 was a conference abstract
- 1 was a poster.

Summary of findings

A study-level summary of data extracted from each included publication is critically appraised and presented in the summary and appraisal of individual studies in Appendix 3.

Table 8. Studies included in evidence summary; Criterion 4 question 3

Study	number	Age	Test	Test performance
Flynn et al (2017) **Systematic review- recommendations and grade of evidence available only, technical detail of review yet to be published.**	Studies between 2004 and 2016	0 to 18	No search strategy available	**Evidence level B**: Oscillometric devices may be used for BP screening in children and adolescents [d] **Evidence level C**: Ambulatory Blood Pressure Monitoring should be performed for confirmation of hypertension in children and adolescents with office BP measurements in the elevated BP category for 1 year or more or with stage 1 hypertension over 3 clinic visits
Thompson et al (2013) **Systematic review**	Two studies Stergiou et al (2008) and Fixler et al (1983) see below	0 to 18	Blood pressure measurements using ausculatory or oscillometric systems that can be used in a primary care clinic	Test performance from Stergiou et al 2008 and Fixler et al 1983 set out separately below.
Stergiou et al 2008 **Prospective cohort study** **Greece**	105	6 to 18	24 hr ambulatory blood pressure compared with three averaged measurements in non dominant arm sitting with 5 mins of rest	Sensitivity 65%(CI 95% 45-80) Specificity 75% (CI 95% 63 to 84) PPV 37%(CI 95% 28 to 47) NPV 63%(CI 95% 53 to 72)
Fixler et al 1983 **Prospective cohort study** **USA**	9017	12/13 with follow up at age 14/15	3 measures with mercury sphygmomanometre measured at least 4 weeks apart then follow up screening of positives after 2 years	Sensitivity of initial positive screen vs subsequent screens 72%(CI 95% 65 to 78) Specificity of initial positive screen vs subsequent screen 92% (CI 95% 91 to 92) PPV initial positive screen vs subsequent screen 17% (CI 95%15 to 20) NPV Initial screen vs subsequent screen 99.3%(CI 95% 99.1 to 99.4)
Bloetzer et al (2017) **Prospective cohort study** **Switzerland**	5207	10-14	3x Oscillometric test plus weight, and parental history compared with confirmatory testing of those with an initial positive result.	Combining all factors(weight, parental history and blood pressure test result) with confirmatory testing: Sensitivity:64.6%(CI 95% 55.1 to 73.4) Specificity: 70.5%(CI 95% 69.2 to 71.7) PPV 4.6% (CI 95% 3.6 to 5.6) NPV 98.9%(CI 95% 98.5 to 99.2)
Negroni et al (2015) **Retrospective cohort study** **USA**	9870	10-19	4 blood pressure readings taken with oscillometric system a random selection of 287 had an ausculatory BP test	There was a nonlinear decrease in blood pressure over time. Average of 1st, 2nd and 3rd SBP results was closest combination to the ausculatory results (p=0.367) all combinations of DBP were significantly different from the ausculatory values.

[d] Evidence level B: Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies

Evidence level C: Single or few observational studies or multiple studies with inconsistent findings or major limitations.

Flynn et al (2017)[2] carried out a review of 15,000 published articles between January 2004 and July 2016 in order to update the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents published by the American Academy of Pediatrics. This recent systematic review focussed on the role of individual clinicians and their role in prevention of disease in the children under their care and although the recommendations have been published the detail of the systematic review has not.

The first question addressed by the publication is, '*How should systematic hypertension in children be diagnosed and what is the optimal approach to diagnosing hypertension in children and adolescents?*'. The authors acknowledged that BP varied continuously, illustrated by a range of studies including one by McNiece et al (2007)[26] who reported that only 56% of BP readings in adolescents had the same blood pressure category on 3 different occasions.

They reported studies that had evaluated the accuracy of the oscillometric devices and compared readings with those from ausculatory method. These studies demonstrated that oscillometric devices systematically overestimate SBP and DBP compared with readings from auscultation BP and that BP status can therefore be misclassified (Chio and Urbina 2011[27,] Ostchega et al 2011[28]).

In one study target organ damage such as LVMI and CIMT in adolescents was best predicted by BPs obtained using auscultation. BP measured with auscultation was able to distinguish differences in LVM for all 3 categories of hypertensive, pre hypertensive and normotensive ($p \leq 0.05$). Oscillatory measurements could not differentiate between pre hypertensive and hypertensive groups but could detect differences in LVM in normotensive and pre hypertensive and hypertensive groups (Urbina et al 2015)[29].

The review made a recommendation based on good quality evidence that oscillometric devices may be used for BP testing in children and adolescents. However, when doing so providers should use a device that has been validated in the paediatric age group. If elevated BP is suspected on the basis of oscillometric readings, confirmatory measurements should be obtained by auscultation.

In 2013 a systematic review was undertaken for the USPSTF by Thompson et al on the effectiveness of screening asymptomatic children and adolescents for hypertension in order to prevent cardiovascular disease**Error! Bookmark not defined.**. The focus of the review was appraisal of the evidence to inform policy about the implementation of a population based screening programme of blood pressure in children.

Key question 2 of the Thompson et al (2013)[Error! Bookmark not defined.] review searched for evidence to determine 'what is the diagnostic accuracy of screening tests for elevated blood pressure in children/adolescents'. They included 2 studies in the review that focussed on this question and reported that a further 12 had been excluded as they did not contain enough data to calculate sensitivity or specificity and were heterogeneous in the definition of a positive test result.

The first study (Stergiou et al 2008)[30] focussed on the accuracy of testing 105 Greek children referred with suspected hypertension. They reported that compared with a reference standard of 24 hour ambulatory monitoring at 20 minute intervals, office-based blood pressure measured at 3 times at each of 2 clinic visits had a sensitivity of 65% (95% CI, 45-80) and a specificity of 75% (95% CI, 63-84). The positive predictive value was 37 (95% CI, 28 -47) and negative predictive value was 63% (95% CI, 53- 72). Limitations of the study include testing a cohort that was already possibly symptomatic as they were referred to a hypertension clinic (ie; not a screen detected cohort) and different normative values were used for each of the 2 methods (24hr ambulatory monitoring and office based blood pressure testing) to determine a diagnosis of hypertension.

The second study (Fixler et al 1983)[31] tested 9017 12 and 13 year olds of whom 900/9017 (9.9%) had blood pressure >95th percentile and the remainder where normotensive. Blood pressure was checked three times at least 4 weeks apart using a mercury sphygnomometer. Those with a positive test result were followed up 2 years later and 152/900 were recorded with elevated blood pressure. The sensitivity and specificity of initial elevated blood pressure for persistently high blood pressure was 72% (95%CI, 65-78 and 92% (95% CI, 91-92) respectively. Positive predictive value was 17% (95% CI, 15-20). This study did not focus on a whole population cohort but only on a small sample of those who had a positive initial screen.

Bloetzer et al (2017)[32] reported the performance of targeted screening of 5207 children aged 10-14 in Swiss schools. Blood pressure was measured with a validated oscillometric system whilst the child was seated after a 5 minute rest. Three readings were obtained 1 minute apart and only the last 2 readings were used for analysis. For those children with elevated blood pressure of BP≥95% percentile for height, age and gender, BP was measured at up to 2 visits at 1 week intervals by a trained school nurse. Data about other cardiovascular risk factors including weight status (normal, overweight, obese) and parental history of hypertension were gathered. A questionnaire was also completed by the children to collect information about other potential confounding factors such as sedentary behaviour, physical activity and dietary habits.

Hypertension was diagnosed in 2.2% of children. The performance of screening for hypertension in children with a parental history of hypertension combined with the child being overweight or obese was a sensitivity of 64.6% (95% CI, 55.1-73.4) a specificity of 70.5% (95% CI, 69.2-71.7) a positive predictive value of 4.6% (95% CI, 3.6-5.8) and negative predictive value of 98.9% (95% CI, 98.5 -99.2).

By combining the strongest risk factors for hypertension in children (overweight/obesity and parental hypertension history) 65% of cases were identified but this leaves a third undetected. The low positive predictive value means a substantial number of children will be unnecessarily investigated further following a screening test.

Negroni-Balasquide et al 2015[33] carried out a retrospective analysis of data from multiple cross-sectional screenings carried out by the Houston Pediatric and Adolescent Hypertension Program (HPAHP). BP screenings were conducted at 15 urban and suburban public secondary schools from 2003 to 2012.

Automated BP measurements were obtained after a 5-minute rest on the non dominant arm. Four BPs were measured in seated participants 1 minute apart using a validated oscillometric system. A randomly
selected subset of children had 1 additional BP measurement by auscultation performed by trained paediatric hypertension specialists in a separate room before the series of 4 oscillometric BPs were taken.

Systolic and diastolic BP decreased nonlinearly over repeated measurements, but this decrease was more pronounced with systolic BP. The largest decrease in systolic BP occurred from the first to the second measurement (3.8 mm Hg) followed by a smaller, yet statistically significant, decreases from second to third (2 mm Hg), and third to fourth (1.2 mm Hg). Diastolic BP did not change significantly between first and second measurement; the biggest decline was seen from second to third (3.3 mm Hg) followed by third to fourth (0.8 mm Hg).

For systolic BP, the second measurement alone, the average of first and second and the average of first, second, and third were statistically similar to the auscultatory BP (mean differences of 0.65 mm Hg, 0.74 mm Hg, and 0.50 mm Hg;). The other 4 comparisons of ausculatory versus oscillometric BP (OBP) readings were not similar (first OBP, p=0.001, average of second and third OBP, p=0.002, average of first, second, third, and fourth OBP, p=0.01 average of second, third, and fourth OBP p<0.001).

For diastolic BP, no oscillometric measure or average was similar to the ausculatory BP, oscillometric measurement was consistently lower than ausculatory readings (all p values<0.036).

Limitations

There were issues with the methodology of both school based studies in that the reference standard BP was only carried out in those children who tested positive in Bloetzer et al 2017[32] and a 30% sample in Negroni-Balasquide et al 2015[33]. Additionally in the latter[33] study only one reference standard ausculatory reading was taken whereas the standard methodology would be to take three readings some time apart and average the two lowest figures. This ausculatory reading was always taken before the other readings and this may be an additional confounding effect.

Summary of Findings Relevant to Criterion 4: Criterion not met

What is the accuracy of the screening tests for primary hypertension in children and young people?

The systematic review by Flynn et al 2017[2] recommends testing blood pressure in children from age 3 at routine clinic appointments to case find those with hypertension. It is recognised that blood pressure varies continually and therefore, it is important to obtain multiple measurements over time before making a diagnosis. This good quality systematic review goes into detail about the exact method needed to be able to take the most accurate blood pressure readings and the clinical work up required for its confirmation.

The good quality UPSTF systematic review**Error! Bookmark not defined.** included 2 papers reporting the accuracy of BP screening tests, one of which was 24 hour ambulatory testing andone used auscultation. The studies reported similar sensitivities of 65% and 72%, and varying specificities of 75% and 92%. A more recent study using validated oscillometric systems to measure BP reported a sensitivity of 65% and a specificity of 70%. Positive predictive values in all studies were low (37% and 17% and 5%). In a clinical setting hypertension may be identified using current standard techniques, from the perspective of population screening these methods would result in many children being identified with elevated blood pressure who did not have hypertension and a significant proportion of children who would remain with undetected hypertension.

Overall based on current available evidence this criterion is not met as the current accepted clinical test for BP would not meet adequate sensitivity and positive predictive values for a test used for population screening.

Criterion 9

There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldnot be further considered here should be a simple, safe, precise and validated screening test

Question 4 – What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young people?

Sub: question: What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions in children and young people for preventing hypertension in adulthood?

In the previous NSC review (2010) the question of effective treatment of children and young people was briefly addressed citing the guidance at that time in the UK, Europe and the US but concluded that these were not fully evidence based.

The aim of addressing this question in this review update is to evaluate if more recent evidence has been published to more accurately determine what intervention would reduce hypertension in UK children and young people.

The sub- question about evidence for interventions started in childhood that will go on to prevent hypertension in adulthood was not addressed in the previous NSC 2010 review.

The aim of addressing this sub question in this review update is to evaluate if evidence has been published to determine what intervention started in children and young people would reduce the risk of hypertension developing in adulthood.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- the target population is children and young people aged 3-18 years
- the condition is primary hypertension and prehypertension in children and young people aged 3-18 years
- the interventions include:
    - pharmacological interventions
    - non pharmacological interventions
    - combination of both pharmacological and non pharmacological interventions

- the comparator if applicable is pharmacological, non pharmacological, or placebo interventions
- the outcomes of interest are changes in:
    - blood pressure
    - retinal vascular changes
    - cognitive changes
    - cardiovascular end organ damage
- the search should prioritise randomised controlled trials, observation studies with a comparison group and systematic reviews.

Description of the evidence

Of the 74 results identified for this question from the database search 22 were determined to be relevant from the abstracts. On receiving the full papers

- 16 were excluded as they were incorporated into the latest systematic review
- 1 was excluded as it was a set of guidelines
- 1 paper was excluded because it was a conference poster

4 articles were included. These were:

- 2 systematic reviews of pharmacological and non pharmacological interventions
- 1 systematic review of pharmacological approaches only
- 1 observational study.

Where large systematic reviews had been included for a particular question, evidence older than the systematic review publication date was checked to see if it had been included in their analysis. If it had been included in the systematic review then the paper was excluded. Appendix 2 contains a full PRISMA flow diagram along with a table of the review questions and publications identified that relate to them.

Summary of findings

The table below details the four publications included in this review focused on the pharmacological, non pharmacological and combined interventions for management of hypertension in children with primary hypertension.

Table 9. Studies included in evidence summary following search and selection; Criterion 9 question 4

Study	Intervention	Number	Age group	Outcome
Chaturvedi et al (2014) **Systematic review**	Pharmacological	21 trials 6 included		
Oosterhoff et al (2016) **Meta analysis of RCTs**	Non-pharmacological	85 trials between 1980 and 2011	4 to 12	Pooled effects for: SBP of -0.182 (95%CI -0.266;-0.098) and for DBP-0.144 (95%CI -0.230;-0.057). Equates to a 1.9mmHg and 1.2mmHg favourable change in SBP and DBP respectively (both p<0.001).
Thompson et al (2013) **Systematic review**	a) Non pharmacological b) Combined pharmacological and non pharmacological	a) 6 trials b) 1 trial(n=150)	a) 9 to 15 b) age 12	a) 2/6 trials showed some decrease in SBP due to lifestyle change b) Decrease in both SBP (mean change -7.6mmHg,p<0.001) and DBP (mean change -6.9mmHg,p<0.01) at 6 month follow up compared to the control group
Litwin et al (2010) **Poland**	Combined pharmacological and non pharmacological	86 children	6 to 17	Reduction from baseline to 12 months : Number with severe LVH from 10 to 1 (p<0.006) Number with severe hypertension from 36 to 1 (p=0.004) Number with ambulatory hypertension from 50 to 21 (p=0.004)

Non pharmacological treatment for hypertension in children and adolescents

One meta-analysis and one systematic review that addressed the effectiveness of non pharmacological approaches to the treatment of hypertension in children and adolescents were included (Oosterhoff et al 2016[36],Thompson et al, 2013[Error! Bookmark not defined.]).

The focus of the Thompson et al (2013)[Error! Bookmark not defined.] review was appraisal of the evidence to inform policy about the implementation of a population based screening programme of blood pressure in children.

Osterhoff et al 2016[36] carried out a meta-analysis of the effects of school based lifestyle interventions on body mass index(BMI) and blood pressure reported by randomised controlled trials (RCTs) in children aged 4 to 12 carried out between 1980 and 2011. They identified 23 trials and carried out a meta-analysis on effect size reported. Interventions were either dietary, increased physical activity or education. Due to the dependency between SBP and DBP (ie when one rises the other is likely to rise) the authors used a multivariate 3 layer model to estimate the mean changes and reported pooled effects for SBP of -0.182 (95%CI -0.266;-0.098) and for DBP-0.144 (95%CI -0.230;-0.057). This translated to a 1.9mmHg and 1.2mmHg favourable change in SBP and DBP respectively (both p<0.001). The authors noted that it remains unclear the extent to which the reductions translate into meaningful clinical outcomes later in life.

There was significant heterogeneity across the trial results and the authors investigated the study quality characteristics (moderators) in an attempt to understand the sources of heterogeneity. Overall around 80-85% of heterogeneity could be accounted for by the study characteristics (e g different interventions between studies such as education, physical activity, diet or a combination of interventions) chosen. Inclusion of parental involvement accentuated the beneficial effects of the intervention on the effect on BP in the children. The outcomes suggest that changes in BP from the interventions may be achieved beyond the effect on BMI.

The Thompson et al review in 2013[Error! Bookmark not defined.] included 6 studies of trials using lifestyle interventions. One Danish study from 1991 reported significant reductions in blood pressure compared with untreated controls in a school based study (n=137) comparing 5 versus 3 weekly physical education classes over an 8 month period (mean group difference at end of trial for SBP was -4.9mmHg and for DBP -3.8 mmHg, p<0.05 for both outcomes). One other study from 1993 reported that girls (but not boys) on a low sodium diet showed a slight decrease in SBP compared to placebo groups whose SBP increased significantly from baseline (no data was reported in Thompson et al 2013[Error! Bookmark not

defined.). The remaining 4 studies using meditation, relaxation and dietary changes showed no significant changes between intervention and control groups.

Pharmacological treatment of hypertension in children and adolescents

One systematic review was included that addressed the effectiveness of pharmacological treatment for hypertension in children and adolescents due to primary and some secondary causes. Children with secondary hypertension associated with kidney transplant, nephrotic syndrome, malignant hypertension and children requiring perioperative management of high blood pressure were excluded.

Chaturvedi et al (2014)[34] carried out a systematic review of pharmacological interventions for hypertension in children for the Cochrane collaboration. Twenty one RCTs evaluated anti hypertensive medications of various drug classes in a total of 3454 hypertensive children with varying periods of follow up between 3 to 24 weeks. There were 5 trials using drug versus placebo whilst the remainder were dose response studies measuring change in blood pressure in children from baseline for different dosages. From the 5 trials using a placebo authors reported that the use of candesartan led to a significant reduction in systolic (mean difference -6.50mmHg, 95%CI -9.44 to -3.56) and diastolic blood pressure (mean difference -5.50mmHg, 95%CI -9.62 to -1.38) when compared to placebo. High dose of telmisartan reduced SBP (mean difference -8.5, 95%CI -13.79 to -3.21) but not DBP pressure (-4.80, 95% CI -9.50 to 0.10).

The adverse events associated with the antihypertensive agents were mostly minor and occurred in approximately 3% to 40% of all patients studied. The most common adverse events included headaches, dizziness and upper respiratory infections. Six trials tested the safety of angiotensin receptor blockers in six to 16-year olds. Angiotensin receptor blockers were well tolerated with headache being the most commonly observed adverse event, affecting up to a third of participants The 6 trials had between 90 to 304 participants and reported between 1 and 7 people dropping out due to adverse effects of the medication.

The dose response studies found that angiotensin-converting enzyme inhibitors showed a good reduction in systolic and diastolic blood pressure compared to baseline, although there was no consistent dose response relationship when pooling the data.

None of the included RCTs reported target organ damage markers such as the change in left ventricular hypertrophy, change in retinopathy or change in cardiac output, and systemic vascular resistance.

The authors conclude that results of the analyses are not robust enough to provide firm recommendations for first-line agents in children with hypertension from primary causes. There is a suggestion, however, that those medications that act through the renin-angiotensin pathway may lower blood pressure more than other pharmacological interventions. There is a need for more long-term trials to determine the efficacy and safety of antihypertensive agents in reducing target organ damage.

Pharmacological combined with non pharmacological treatments for treating hypertension in children and adolescents

Thompson et al (2013)[Error! Bookmark not defined.] reported data from 2 papers from 1 RCT of combined pharmacological and non pharmacological interventions held in the early 1980's. The dietary/Exercise Alteration Programme Trial examined the effectiveness of multi-component school based interventions including, nutrition and diet education for parents and 150 children aged 12. This was a school based exercise programme and treatment with propranodol and chlorthalidone compared to a no intervention group. The complex intervention resulted in a significant decrease in both SBP (mean change -7.6mmHg, p<0.001) and DBP (mean change -6.9mmHg,p<0.01) at 6 month follow up compared to the control group. At 30 months follow up SBP increased from baseline in both the intervention (1.4mm Hg) and control groups (3.5mm Hg). DBP in the intervention and control group remained below baseline level (-4.2mmHg and -3.3mmHg respectively).

One small observational study by Litwin et al (2010)[35] enrolled 86 children and adolescents (aged 5-17) newly diagnosed with untreated primary hypertension. At baseline CIMT, LVMI and LVH were measured. All children were referred to an external consultant for lifestyle advice that reduces CVD risk factors. Pharmacological treatment was immediately started in those who had severe target organ damage (LVMI>51h/height 2.7 and/or CIMT>2 standard deviations) and/or severe ambulatory hypertension. Table 10 shows the significant improvements observed at 12 month follow up.

Table 10. Blood pressure and target organ damage at baseline and at 12 months of treatment

N=86	Baseline number	12 months intervention number (%)	P value
Normotensive number participants (%)	0	54(62.8%)	0.0001
Pre hypertension number participants (%)	0	10(11.6)	0.0001
Ambulatory hypertension Number of participants (%)	50(58.1)	21(24.4)	0.004
Severe hypertension number of participants (%)	36(41.9)	1(1.2)	0.004

CIMT mm	0.44±0.05	0.42±0.04	0.0001
CIMT SDS	1.4±1.5	0.9±1.3	0.001
LVH (age and gender adjusted) number participants (%)	39(45.3)	24(27.9)	0.0001
Severe LVH	10(11.6)	1(1.2)	0.006
LVMI (g/height$^{2.7}$)	38.5±10	35.2±7.5	0.0001

Source: Litwin et al (2010)[35]

This study was not focussed on controlling the intervention to determine what specific treatment was associated with a reduction in target organ damage but rather was concerned with showing that target organ damage could regress in children and adolescents.

Pharmacological and non-pharmacological and/or combination interventions in childhood for preventing hypertension in adulthood

No studies were found that addressed the question of treatment for hypertension during childhood that would prevent hypertension in adulthood.

Summary of Findings Relevant to Criterion 9: Criterion not met

Question 4 – What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young people?

Sub: question: What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions in children and young people for preventing hypertension in adulthood?

Non- pharmacological interventions

A meta analysis by Oosterhoff et al 2016[36] analysed data from 23 RCTs about the reduction in BP using non pharmacological interventions. Overall results did show some impact on BP although it was not clear if this would result in a clinically meaningful change.

Pharmacological interventions

Evidence from the Chaturvedi et al (2014)[34] Cochrane systematic review reported that some types of antihypertensive medication can reduce blood pressure in children in the short term. The evidence is reported as low quality according to the GRADE Working group grades of evidence (Guyatt et al 2008)[37] which infers that further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. The trials included children with symptomatic primary or secondary hypertension,

and were of a short duration with a mean of 7 weeks. The results are therefore not generalizable to children with hypertension detected via a population based screening programme.

Combined pharmacological and non pharmacological interventions

There is limited evidence from 1 RCT reported in the Thompson et al 2013 systematic review and the study by Litwin et al (2010)[35] that BP is lowered by a combination of pharmacological and non pharmacological interventions. The small observational study by Litwin et al (2010)[35] was showed promising results as it included changes to level of target organ damage as an outcome of combined pharmacological and non pharmacological treatment.

Pharmacological, non pharmacological and combined interventions in childhood that show an in impact on hypertension in adulthood

There was no evidence identified considering the effect that pharmacological, non pharmacological or a combination of both interventions begun in childhood has in reducing hypertension in adulthood.

Criterion 11

There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Question 5: Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?

The previous NSC review in 2010[4] reported available evidence for criterion 11 but did not directly address question 5. The review reported no high quality RCTs that a screening programme would effectively reduce mortality or morbidity in either children or adults. The review described commentary from researchers with the opinion that effective evidence based screening strategies did not exist which would identify and treat children with high blood pressure at risk of developing cardiovascular disease in adulthood.

In the US the USPSTF (2003)[38] evidence review concluded that it was not possible to balance the harms versus benefits of routine screening of blood pressure in children. In contrast the US Fourth report (2004)[5] recommended that at preventative visits asymptomatic children from age 3 should have their BP checked.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- the target population is children and young people aged 3-18 years
- the condition is primary hypertension and prehypertension in children and young people aged 3-18 years
- the interventions include:
    - pharmacological interventions
    - non pharmacological interventions
    - combination of both pharmacological and non pharmacological interventions
- the comparator if applicable is pharmacological, non pharmacological, or placebo interventions
- the outcomes of interest are changes in:
    - blood pressure
    - retinal vascular changes
    - cognitive changes
    - cardiovascular end organ damage

- the search should prioritise randomised controlled trials, observation studies with a comparison group and systematic reviews.

Description of the evidence

Database searches yielded 30 results, of which 6 were judged to be relevant to this question. Appendix 2 contains a full PRISMA flow diagram
along with a table of the review questions and the publications identified that related to them.

Of the 6 results identified for this question from the database search 1 systematic review (Thompson et al 2013)[Error! Bookmark not defined.] was determined to be relevant from the abstracts and was included in this review. The remaining 5 studies were not designed to demonstrate effectiveness of a particular screening strategy as evidenced by prevention of hypertension in later life.

Summary of findings

The systematic review by Thompson et al (2013)[Error! Bookmark not defined.] searched for evidence to compare health outcomes related to hypertension in screened versus non screened child or adolescent populations and found no randomised controlled studies designed to show the effectiveness of screening.

Summary of Findings Relevant to Criterion 11: Criterion not met

Question 5: Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?

One systematic review addressed the question of the effectiveness of BP screening in children and adolescents to reduce and delay adverse health outcomes related to hypertension. No studies demonstrating effective BP screening strategies in children and adolescents were identified.

No relevant studies published since the systematic review were identified.

This criterion is not met.

Criterion 12

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

Question 6 – What are the optimal ages to initiate screening?
What are the optimal time intervals at which to repeat screening?
Who should do the screening; general paediatricians, renal physicians, other?

This question was not addressed by the UK NSC 2010 review of evidence of screening for hypertension in children.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- the target population is children and young people aged 3-18 years
- the condition is primary hypertension and prehypertension in children and young people aged 3-18 years
- the interventions include:
  - pharmacological interventions
  - non pharmacological interventions
  - combination of both pharmacological and non pharmacological interventions
- the comparator if applicable is pharmacological, non pharmacological, or placebo interventions
- the outcomes of interest are changes in:
  - blood pressure
  - retinal vascular changes
  - cognitive changes
  - cardiovascular end organ damage
- the search should prioritise randomised controlled trials, observation studies with a comparison group and systematic reviews.

Description of the evidence

Database searches yielded 31 results, of which 6 were judged to be relevant to this question. Appendix 2 contains a full PRISMA flow diagram
along with a table of the included the review questions and the publications identified that were relevant to them.

Of the 6 results identified for this question from the database search 1 was determined to be relevant from the abstracts. This 1 publication was included in the review.

Summary of findings

No studies were identified that addressed optimal ages to initiate a population based screening programme, the optimum time intervals or who should carry out the screening test within that programme.

One systematic review (Flynn et al 2017)[2] provided guidance to clinicians in healthcare settings about checking BP in children. The following recommendations were made based on evidence from the systematic review (technical details not yet been published):

- BP should be measured annually in children and adolescents ≥3 years of age
- BP should be checked in all children and adolescents ≥3 years of age at every health care encounter if they have obesity, are taking medications known to increase BP, have renal disease, a history of aortic arch obstruction or coarctation, or diabetes
- trained health care professionals in the office setting should make a diagnosis of hypertension if a child or adolescent has auscultatory confirmed BP readings ≥95th percentile at 3 different visits.

The recommendations were based on level C evidence which was defined as *'single or few observational studies or multiple studies with inconsistent findings and major limitations'*.

Summary of Findings Relevant to Criterion 12: Criterion not met

Question 6 – What are the optimal ages to initiate screening?
What are the optimal time intervals at which to repeat screening?
Who should do the screening; general paediatricians, renal physicians, other?
No evidence was identified that addressed the question of optimal ages to initiate a population based screening programme, optimum time intervals between tests or who should carry out the screening test.
This criterion is not met.

Review summary

Conclusions and implications for policy

This report is an update review on systematic population screening for hypertension in children and young people against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine if new evidence published since 2010 suggests that reconsideration of the current recommendation for screening for hypertension in children and young people in the UK is required.

What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?

There is reasonable evidence to suggest that there is likely to be increasing prevalence of elevated blood pressure in children and adolescents in the UK, however it is uncertain what this prevalence is.

What is the association between primary hypertension in children and young people and the risk of adverse outcomes?

There is good quality evidence from Europe, the US and Australia that high blood pressure is an independent factor associated with target organ damage in children and adolescents.

What is the diagnostic accuracy of the screening tests for primary hypertension in children and young people?

Hypertension may be identified in individuals using current standard techniques in a clinical setting; however, from the perspective of population screening these methods would result in many children being identified with elevated blood pressure who did not have hypertension and a proportion of children who would remain with undetected hypertension.

What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young people?
Some types of non pharmacological interventions showed some reduction in BP, but it was not clear if this would result in any clinically meaningful change and could be maintained over the long term.

Evidence for effectiveness of use of pharmacological interventions for children with hypertension detected via a population screening programme was limited in that the trials reported:

- included children with symptomatic primary or secondary hypertension
- were typically of a short duration with a mean of 7 weeks
- showed a modest short term effect of two drugs that were evaluated.

The trials were graded by the authors of the systematic review as low quality using the GRADE working group grades of evidence. This infers that further research is very likely to have an important impact on confidence in the estimate effect and is likely to change that estimate.

The evidence for combined interventions was limited to 1 RCT reported in the a systematic review and a small promising observational study that BP is lowered by a combination of pharmacological and non pharmacological interventions.

Overall there wasnot robust evidence of interventions that could be generalised to effectively manage children with hypertension detected from a population based screening programme

What is the effectiveness of pharmacological and non pharmacological and /or combination interventions in children and young people for preventing hypertension in adulthood?

There was no evidence that pharmacological, non pharmacological or a combination of both interventions begun in childhood were effective in reducing hypertension in adulthood.

Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?
No studies demonstrating effective BP screening strategies in children and adolescents were identified

What are the optimal ages to initiate screening?
What are the optimal time intervals at which to repeat screening?
Who should do the screening; general paediatricians, renal physicians, other?

No evidence was identified that addressed the questions of optimal ages to initiate a population based screening programme, optimum time intervals between tests or who should carry out the screening test.

The volume, quality and direction of new evidence published since 2010 does not indicate that there have been significant changes in the evidence base. This particularly relates to the accurate identification of children and young people with hypertension and an effective intervention which would reverse or stop the progression of adverse outcomes such as target organ damage and decrease the rate of progression of hypertension from children to adults.

The current recommendation not to introduce a UK systematic population screening programme for hypertension in children and young people should be retained.

Limitations

This rapid review was conducted in line with the UK NSC requirements for evidence summaries, as described at https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/appendix-f-requirements-for-uk-nsc-evidence-summaries.
This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by 1 information scientist, and further appraisal and study selection by 1 reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Appendix 1 — Search strategy

Electronic databases and Search Terms

Separate searches were undertaken for question 1, question 2, question 4 and questions 3,5,6 and search strategies applied to Embase, Cochrane and PubMed databases. Search terms for the Embase searches for each question are detailed in the tables below. The searches identified all relevant publications from 2010 to the present and were carried out on October 24th 2017.

Table 11. Embase search strategy for question1 – prevalence

#	Search terms	Results
# ▲	Searches	Results
1	hypertension/ or prehypertension/	489842
2	*blood pressure/	66747
3	(hypertension or pre-hypertension or prehypertension).ti,ab.	469020
4	((high or elevated) adj3 (blood pressure or bp)).ti,ab.	36231
5	(blood pressure or bp).ti.	70733
6	1 or 2 or 3 or 4 or 5	740140
7	adolescent/ or child/	2312329
8	(child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti,ab.	1847512
9	7 or 8	3015617
10	prevalence/	557106
11	prevalence.ti,ab.	694058
12	epidemiolog*.ti.	117793
13	10 or 11 or 12	921721
14	exp United Kingdom/	398374
15	(united kingdom or uk or britain or gb or wales or scotland or england or ireland).ti,ab.	457146
16	national health service/	63534
17	(national health service or nhs).ti,ab.	45828
18	(national health service or nhs*).in.	175785
19	14 or 15 or 16 or 17 or 18	855957
20	6 and 9 and 13 and 19	365
21	conference*.pt.	3472094
22	20 not 21	302
23	limit 22 to english language	293

24	limit 23 to yr="2010 -Current"	165

Table 12. Embase search strategy for question 2 – adverse outcomes

#	Search terms	
# ▲	Searches	Results
1	*hypertension/ or *prehypertension/	197727
2	*blood pressure/	84050
3	(hypertensi* or pre-hypertensi* or prehypertensi*).ti.	230025
4	(blood pressure or bp).ti.	73959
5	1 or 2 or 3 or 4	380415
6	(adolescent/ or child/) and (child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti,ab.	1192487
7	(child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti.	1152890
8	6 or 7	1502057
9	5 and 8	13652
10	organ injury/	4540
11	((organ or organs) adj3 (damag* or injur* or failure)).ti,ab.	55055
12	exp heart ventricle hypertrophy/	57201
13	((heart or cardi* or ventric*) adj3 hypertroph*).ti,ab.	65460
14	arterial wall thickness/	17632
15	exp atherosclerosis/	193805
16	(atheroscleros?s or arterioscleros?s or (arterial adj3 (thickness or diameter? or plaque?))).ti,ab.	152183
17	(carotid adj3 (wall or plaque? or thickness or diameter?)).ti,ab.	20403
18	*retina blood vessel/	5254
19	exp retinopathy/	84787
20	(retinopath* or (retina* adj5 (chang* or damag* or injur* or diameter*))).ti,ab.	67252
21	cognition/	205549
22	cognitive defect/	134943
23	mild cognitive impairment/	18645
24	cognition assessment/	2103
25	((cognitive or cognition) adj3 (chang* or deteriorat* or defect* or impair* or assess*)).ti,ab.	116467
26	*cardiovascular disease/	86050
27	*cerebrovascular disease/ or exp brain infarction/ or exp cerebrovascular accident/	234839
28	exp ischemic heart disease/	592344

29	(((cardiovascular or cardio-vascular or coronary or heart or myocardi* or cardi* or isch?mic or cerebrovascular or cerebro-vascular) adj (disease? or disorder? or health)) or cvd or chd).ti,ab.	469919
30	((cardiovascular or cardio-vascular or coronary or heart or myocardi* or cardi* or isch?mic or cerebrovascular or cerebro-vascular) adj risk).ti,ab.	103697
31	(myocardi* adj (infarct* or isch?emi*)).ti,ab.	271852
32	angina.ti,ab.	66996
33	acute coronary syndrome.ti,ab.	30608
34	((adverse or longterm or long-term) adj3 outcome?).ti,ab.	152690
35	outcome?.ti.	385343
36	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2295189
37	9 and 36	3454
38	Case Study/ or case report.tw. or abstract report/ or letter/ or conference*.pt. or editorial.pt. or letter.pt. or note.pt.	6139202
39	37 not 38	2274
40	limit 39 to (english language and yr="2010 -Current")	1000

Table 13. Embase search strategy for question 3, 5, 6 – testing and screening

# ▲	Searches	Results
1	*hypertension/ or *prehypertension/	197788
2	*blood pressure/	84070
3	(hypertensi* or pre-hypertensi* or prehypertensi*).ti.	230209
4	(blood pressure or bp).ti.	74000
5	1 or 2 or 3 or 4	380602
6	(adolescent/ or child/) and (child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti,ab.	1192527
7	(child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti.	1153412
8	6 or 7	1502398
9	exp screening/ or exp screening test/ or diagnostic test/	683364
10	*blood pressure measurement/	9954
11	(screen* or test*).ti.	615244
12	((blood pressure or bp) adj5 (screen* or test* or measur* or monitor*)).ti,ab.	70835
13	((hypertens* or prehypertens* or pre-hypertens*) adj5 (screen* or test* or measur* or monitor*)).ti,ab.	17592
14	((oscillomet* or auscultat*) adj3 (device? or machine?)).ti,ab.	1061

15	9 or 10 or 11 or 12 or 13 or 14	1200895
16	*diagnosis/ or diagnostic accuracy/ or diagnostic test accuracy study/	328255
17	"sensitivity and specificity"/	286447
18	predictive value/	122233
19	diagnos*.ti.	636128
20	(sensitivity or specificity or predict* or npv or ppv or accura* or valid*).ti,ab.	3659685
21	16 or 17 or 18 or 19 or 20	4308844
22	5 and 8 and 15	4154
23	limit 22 to (english language and "reviews (maximizes specificity)" and yr="2010 -Current")	29
24	((child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people) and (blood pressure or bp or hypertens* or prehypertens* or pre-hypertens*) and (screen* or diagnos* or test*)).ti.	510
25	5 and 8 and 15 and 21	1207
26	24 or 25	1536
27	limit 26 to (english language and yr="2010 -Current")	844
28	Case Study/ or case report.tw. or abstract report/ or letter/ or conference*.pt. or editorial.pt. or letter.pt. or note.pt.	6140909
29	27 not 28	456

# ▲	Searches	Results
1	*hypertension/ or *prehypertension/	197828
2	*blood pressure/	84075
3	(hypertensi* or pre-hypertensi* or prehypertensi*).ti.	230281
4	(blood pressure or bp).ti.	74031
5	1 or 2 or 3 or 4	380715
6	(child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti.	1154217
7	exp *screening/ or exp *screening test/	176855
8	screen*.ti.	194414
9	7 or 8	278518
10	5 and 6 and 9	195
11	limit 10 to (english language and yr="2010 -Current")	102

Table 14. Embase search strategy for question 4 – treatment

# ▲	Searches	Results
1	*hypertension/ or *prehypertension/	197811
2	*blood pressure/	84071
3	(hypertensi* or pre-hypertensi* or prehypertensi*).ti.	230255
4	(blood pressure or bp).ti.	74016
5	1 or 2 or 3 or 4	380669
6	(adolescent/ or child/) and (child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti,ab.	1193054
7	(child* or schoolchild* or boys or girls or pediatric* or paediatric* or adolescen* or teen* or youth? or young people).ti.	1153776
8	6 or 7	1502963
9	exp *antihypertensive agent/	285201
10	(antihypertensive* or anti hypertensive* or pharmacolog* or therap* or treatment? or intervention?).ti.	2308215
11	((antihypertensive* or anti hypertensive* or pharmacolog*) adj3 (therap* or treatment? or intervention?)).ti,ab.	108527
12	exp diet therapy/	311479
13	exp kinesiotherapy/	66155
14	lifestyle modification/	30508
15	weight loss program/	1195
16	weight reduction/	146884
17	sodium restriction/	9103
18	((nonpharma* or non-pharma* or diet* or nutrition* or exercise* or physical activity or salt or sodium or lifestyle or life-style) adj3 (therap* or treatment? or intervention? or program* or modif*)).ti,ab.	170237
19	((weight loss or weight reduction or weight management) adj3 (intervention? or program*)).ti,ab.	8991
20	((sodium or salt) adj2 reduc*).ti,ab.	8234
21	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	3124696
22	5 and 8 and 21	2580
23	limit 22 to (english language and "reviews (maximizes specificity)" and yr="2010 -Current")	21
24	limit 22 to (english language and "therapy (maximizes sensitivity)" and yr="2010 -Current")	335
25	23 or 24	339
26	Case Study/ or case report.tw. or abstract report/ or letter/ or conference*.pt. or editorial.pt. or letter.pt. or note.pt.	6143299
27	25 not 26	226

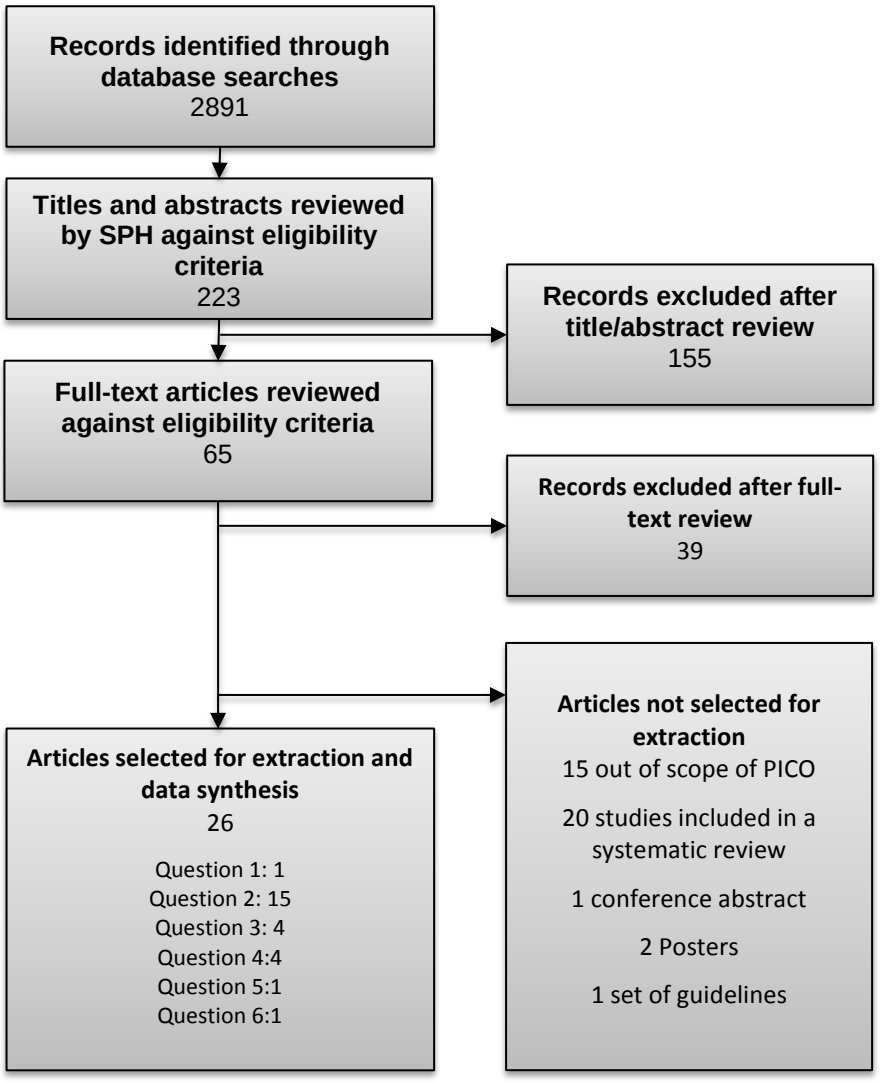
Duplicate references were removed.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. 65 publications were ultimately judged to be relevant to 1 or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 1. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

The publications included after review of full-texts are summarised below. Two systematic reviews were relevant to multiple questions and each section is extracted in a separate table for each question. The flow diagram in Figure 1 therefore counts each of these articles twice to ensure the numbers reconcile. Table 11 below lists each of the studies once.

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

Meta-analyses and systematic reviews would be considered the highest quality of evidence if any were found. Following this, study designs would be prioritised for each question in the order listed in Tables 12 to 25 respectively.

Studies relating to epidemiology would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK.

In addition, the following criteria were applied after assessing the overall volume of evidence identified in the review:

Table 15. Summary of publications included after review of full-text articles, and the criteria each publication was identified as being relevant to

	Study	Natural history	The test	The intervention	The screening programme
1	De Moraes et al (2014)	X			
2	Kollias et al (2014)	X			
3	Stelcar et al (2017)	X			
4	Gupta-Malhotra et al (2016)	X			
5	Mir et al (2016)	X			
6	Meng et al (2015)	X			
7	Pieruzzi et al (2015)	X			
8	Day et al (2017)	X			
9	White et al (2017)	X			
10	Hao et al (2017)	X			
11	Imhof et al (2016)	X			
12	Gopinath et al (2016)	X			
13	Gopinath et al (2010)	X			
14	Murgan et al (2013)	X			
15	Lande et al (2017)	X			
16	Flynn et al (2017)		X		X
17	Thompson et al (2013)		X	X	
18	Bloetzer et al (2017)		X		

19	Negroni et al (2015)	X	
20	Chaturvedi et al (2014)		X
21	Oosterhoff et al (2016)		X
22	Litwin et al (2010)		X

Appendix 3 — Summary and appraisal of individual studies

Natural history- Data extraction and quality assessment for studies relevant to criteria 1; questions 1 and 2.

Question 1 – What is the reported prevalence of primary hypertension in children and young people (3 to 18 years of age) in the UK?

Table 16. De Moraes et al (2015)[6]

Publication	De Moraes ACF, Carvalho HB, Siani A, Barba G, Veidebaum T, Tornaritis M, et al. Incidence of high blood pressure in children - Effects of physical activity and sedentary behaviors: The IDEFICS study: High blood pressure, lifestyle and children. International Journal of Cardiology. 2015;180:165-70		
Study details	Prospective epidemiological cohort study		
Study objectives	To measure blood pressure in a cohort of children aged 2 to 9 over a 2 year period and describe incidence of pre hypertension and hypertension and to evaluate the impact of physical activity and sedentary behaviours on these rates.		
Inclusions	General population of 2 to 9 year old children from 8 European countries		
Exclusions	None stated		
Population	5221 children aged 2-9		
Test	Two blood pressure readings taken after 10 minutes rest and 5 minute interval between readings at baseline and 2 years Pre hypertension =systolic or diastolic blood pressure between 90th and 95th percentile for height and age Hypertension = systolic or diastolic blood pressure >95th percentile for height and weight		
Comparator	None		
Outcomes		Male n=2638	Female n=2583
	Blood pressure	% (95% confidence intervals)	% (95% confidence intervals)
	Normal	78.8 (77.2-80,4)	75.5 (73.8-77.2)
	Pre hypertension	12.1 (10.9-13.4)	13.2(11.8-14.5)
	Hypertension	9.1(7.9-10.2)	11.3(10.0-12.5)
Quality appraisal	The JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data was used to assess the quality of the study – there were no areas of concern.		

Question 2 –What is the association between primary hypertension in children and young people and the risk of adverse outcomes?

Table 17. Kollias et al (2014)[11]

Publication	Kollias A, Dafni M, Poulidakis E, Ntineri A, Stergiou GS. Out-of-office blood pressure and target organ damage in children and adolescents: A systematic review and meta-analysis. Journal of Hypertension. 2014;32(12):2315-31.
Study details	Systematic review and meta-analysis
Study objectives	To review the literature of the relationship between out of office blood pressure and target organ damage in children
Inclusions	Full text articles in English, presenting data from observational, longitudinal, retrospective and prospective studies of children and adolescents. Which included ambulatory/home BP as well as indices of preclinical organ damage
Exclusions	See inclusion criteria
Population	93 studies published between 1974 and June 2012, 11 of which were relevant to this question.
Test	Ambulatory/home BP monitoring
Comparator	N/A
Outcomes	Eleven studies from 1998 to 2011 provided data on the Left Ventricular Mass Index differences between normotensive (n=432) and hypertensive children (n=428) Pooled difference 6.53 $gm^{2.7}$(4.73-8.33) (I^2=51%, p=0.03)
Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern. Authors noted the limitations of the review including a high level of heterogeneity of the studies.

Table 18. Stelcar et al (2017)[12]

Publication	Stelcar A, Homsak E, Marcun Varda N. Assessment of Early Cardiovascular Risk in Children and Adolescents with Essential Hypertension. Klinische Padiatrie. 2017;229(5):286-92
Study details	Prospective case control
Study objectives	To investigate early markers of hypertensive organ damage in children and adolescents
Inclusions	Children aged 5-20 years
Exclusions	Children with any cardiovascular risk factors (apart from primary hypertension in the study group)
Population	Intervention group: 100 Males and females aged 5 to 20 who were healthy apart from confirmed hypertension defined as average systolic or diastolic blood pressure >95th percentile for age, gender height carried out on 3 separate occasions Control group: 50 healthy males and females aged 5-20 normal BP with no cardiovascular risk factors
Test	CIMT and LVM
Comparator	50 healthy children without hypertension
Outcomes	**Control group compared with study group and sub set of study group (n=45) whose BMI was below 90th percentile.**

Parameters	Control group(CG n=50)	Study group(SG n=100)	P value (CG vs SG)	Study group BMI<90th percentile (SG<BMI) n=45)	P value 2 (CG vs SG<BMI)
Left ventricular mass(g/m^2)	31.0±6.0	37.2±11.5	<0.001	35.3±8.0	0.003
CIMT right side(mm)	0.35±0.05	0.43±0.09	<0.001	0.42±0.09	<0.001
CIMT left side (mm)	0.36±0.05	0.43±0.08	<0.001	0.42±0.07	<0.001

Quality appraisal The CASP case control studies guide checklist was used and there were no areas of concern

Table 19. Gupta-Malhotra et al (2016)[10]

Publication	Gupta-Malhotra M, Hashmi SS, Poffenbarger T, McNiece-Redwine K. Left Ventricular Hypertrophy Phenotype in Childhood-Onset Essential Hypertension. Journal of Clinical Hypertension. 2016;18(5):449-55
Study details	Cohort study
Study objectives	Determine the risk factors associated with LVH in children with hypertension
Inclusions	Children with untreated hypertension
Exclusions	Secondary hypertension
Population	89 children aged 9-18 with high blood pressure defined as average systolic or diastolic blood pressure >95th percentile for age, gender height carried out on 3 separate occasions. Children were drawn from those referred with hypertension to a clinic setting and those recruited from a high school screening programme
Test	Detection of left ventricle hypertrophy with transthoracic echocardiogram and vascular ultrasound
Comparator	None
Outcomes	32 of 89 children had LVH. Those who had LVH were more likely to have higher: BMI, (p=0.001), higher weight (p=0.0004) and higher CIMT (p=0.002)
Quality appraisal	The CASP cohort study checklist was used and areas of concern include small sample size

Table 20. Mir et al (2016)[13]

Publication	**Mir S, Sozeri B, Deveci M, Ozdemir K, Gun ZH, Dincel N, et al. Cardiovascular functional and structural changes in children with primary hypertension. Minerva Pediatrica. 2016;68(1):27-35.**
Study details	Case control study
Study objectives	Determine early cardiovascular changes in children with hypertension
Inclusions	Children aged 5 to 17
Exclusions	Secondary hypertension
Population	Children aged 5-17 (n=75) with elevated blood pressure either pre hypertension or hypertension. Pre hypertension defined as diastolic or systolic BP ≥90th and ≤95th percentile for age, gender and height and hypertension defined as ≥95th percentile from 3 BP measurements taken at least 1 minute apart using oscillometric monitors. Normotensive controls (n=35) defined with similar methodology with BP readings <90th percentile.

Test	LVH and CIMT measured using ultrasound and oscillometric device
Comparator	Healthy normotensive controls
Outcomes	

	Controls (n-35)	Patients n=75	P value
CIMT	0.35±012	0.46±0.06	0.01
LVMI	28.8±1.55	32.9±11.5	0.01

Quality appraisal:	The CASP case control study checklist was used and areas of concern include small sample size

Table 21. Meng et al (2015)[14]

Publication	Meng L, Hou D, Zhao X, Hu Y, Liang Y, Liu J, et al. Cardiovascular target organ damage could have been detected in sustained pediatric hypertension. Blood Pressure. 2015;24(5):284-92.
Study details	Case control study
Study objectives	To assess the impact of sustained hypertension on cardiovascular target organ damage
Inclusions	Children with primary hypertension
Exclusions	Secondary hypertension, previously diagnosed with hypertension and self-report diagnosis of hypertension
Population	At baseline 128 children aged 9 to 15 with hypertension defined as systolic or diastolic blood pressure ≥95th percentile by age and gender measured on 3 separate occasions at 15 day intervals
Test	LVMI and CIMT measured using ultrasound and echocardiography
Comparator	158 normotensive children matched for age and gender
Outcomes	All children were tested in 2009 and at follow up in 2011. Normotensive controls were children who remained normotensive at baseline and follow up. Non sustained hypertension was defined as children with hypertension at either baseline or follow up but were normotensive at the other reading. Level of target organ damage at baseline is set out below.

Measure	Normotensive BP control group(n=148)	Non-sustained hypertension(n=38)	Sustained hypertension(n=46)	P value
LVM(g)	90±26	106±34*	126±32*	0.015
LVMIg/m^2	28±6	32±6*	34±5*	0.016
CIMT	0.46±0.03	0.47±0.03*	49±0.04*	0.007

*p<0.01 compared to normotensive control group

Changes in prevalence of target organ damage between baseline and follow up (2 years) is set out below.

Measure	Normotensive BP control group(n=148)	Non-sustained hypertension(n=38)	Sustained hypertension(n=46)	P value
LVM elevated	12(7.9%)	16(42.1%)*	16(33.3%)*	<0.001
LVMI elevated	3(7.2%)	4(10.5%)*	7(14.6%)*#	0.001
Coronary arteriosclerosis	19(12.5%)	12(31.6)*	23(47.9%)*#	<0.001

*p<0.01 compared to normotensive control group

#p<0.01 non sustained hypertensive group as control

Quality appraisal	The CASP case control study checklist was used and there were no areas of concern

Table 22. Pieruzzi et al (2015)[15]

Publication	Pieruzzi F, Antolini L, Salerno FR, Giussani M, Brambilla P, Galbiati S, et al. The role of blood pressure, body weight and fat distribution on left ventricular mass, diastolic function and cardiac geometry in children. Journal of Hypertension. 2015;33(6):1182-92
Study details	Case control study
Study objectives	To determine the effects of different factors on cardiac morphology and function
Inclusions	Referral by primary care doctor for suspected hypertension or overweight/obesity
Exclusions	Secondary hypertension, impaired glucose tolerance or diabetes
Population	461 Children aged 6-15 years
Test	Echocardiography and aneroid sphygmomanometer
Comparator	65 normotensive, normal weight children
Outcomes	Blood pressure measured as a mean of 3 measurements: normotensive = systolic and diastolic BP <90th percentile , transient elevation =BP raised in primary care but neither diastolic not systolic raised at referral unit<90th percentile, pre hypertensive = if systolic and/or diastolic ≥90th <95th and hypertension = systolic and/or diastolic ≥95th percentile.

Prevalence of LVH %

	Normotensive	Transient hypertensive	Pre hypertensive	Hypertensive
Males	19%	30%	35%	40%
Females	22%	32%	30%	50%

Association of left ventricular hypertrophy morphology, hypertension and weight is set out below.

Variable	**Concentric remodelling**	**Concentric hypertrophy**	**Eccentric hypertrophy**
	Odds Ratio (95%CI)	**Odds Ratio (95%CI)**	**Odds Ratio (95%CI)**
Systolic BP (Zscore)	1.71 (1.29 2.26) **p=0.0002**	2.09(1.48-2.95 **p<0.0001**	1.51(1.10-2.09) p=0.0120
Over Weight vs Normal weight	0.57(0.32-1.01) p=0.0528	2.78((0.93-8.27) p=0.0669	6.82(2.31-20.13) **p=0.0005**
Obese vs Normal weight	0.91(0.50-1.64) p=0.7506	17.15(6.23-47.20) **p<0.0001**	16.65 (5.69-48.74) **p<0.0001**

Waist circumference Z score	1.02(0.91-1.15) p=0.7009	1.5(1.28-1.76) **p<0.0001**	0.00(0.00-0.00) p=0.0000
Quality appraisal	The CASP case control study checklist was used and there were no areas of concern.		

Table 23. Day et al (2017)[17]

Publication	Day TG, Park M, Kinra S. The association between blood pressure and carotid intima-media thickness in children: A systematic review. Cardiology in the Young. 2017;27(7):1295-305.
Study details	Systematic review
Study objectives	Investigate the relationship between CIMT and blood pressure in children
Inclusions	English language articles with at least 1 measurement of BP and 1 measurement CIMT both measured in childhood 0 to 19 years and if effect size or correlation was included, between January 1980 and June 2013
Exclusions	See inclusions
Population	28 studies published between January 1980 and June 2013 of which 8 (from 2004-2013) were based on healthy children recruited from the community (ie screen detected).
Test	Blood pressure and CIMT
Comparator	N/A
Outcomes	All studies were cross sectional in design The definition of hypertension varied between studies One study found an association between both SBP and DBP and CIMT. **Wincup et al (2012**)[39] Multilevel random effects model: each SD increase of systolic BP increased CIMT by 0.0024mm (95% CI 0.0002–0.0046), each SD increase of diastolic BP increased CIMT by 0.0027mm (95% CI 0.0005– 0.0048). Adjusted for sex, age, ethnicity, month, and random effect for school Four studies found an association with SBP but not DBP **Lim et al (2009)[40]** Multiple logistic regression (with having a top quartile IMT for sex as outcome): OR of 1.7 (95% CI 1.2–2.41) per SD of SBP increase, adjusted for age, sex, BMI, waist circumference, fasting plasma glucose, cholesterol. Effect of DBP not significant **Kollias et al (2013**)[41] Multivariable linear regression: SBP significantly associated with left (but not right or mean) CIMT (β=0.002, p <0.01). DBP not significantly associated with CIMT **Castera et al (2010)[42]** Multivariable linear regression: SBP but not DBP significantly associated with CIMT (β= 0.0004, p =0.005), after adjusting for presence of fatty liver disease, BMI, waist circumference, liver enzyme levels, cholesterol, and C-reactive protein **Mittelman et al (2010)[43]** Univariate association between BP and CIMT: SBP significantly correlated with CIMT in boys and girls (r=0.17, p=0.043, r= 0.16, p= 0.0062, respectively). DBP not correlated. When the group with "healthy" weights (BMI <85th centile), are analysed separately, SBP is only correlated with CIMT in boys (r=0.15, p= 0.0364)

	Two studies reported an association with SBP but did not report DBP **Bohm et al (2009[44])** Multivariable linear regression: SBP significantly associated with CIMT in boys but not girls (β=0.31, p ⩽0.001), adjusted for height, weight, BMI, and body fat **Sarkola et al (2012)[45]** Multivariable linear regression: SBP significantly associated with CIMT (β= 1.1, p=0.03), model adjusts for gender, age, and BSA One study found a weak association with DBP but not SBP which disappeared when other factors added to the model. **Ishizu et al(2004)[46]** Multivariable linear regression: SBP is not significantly associated with mean CIMT, however DBP is significantly associated (r=0.46, p =0.049). Adjustment for age only. In a larger model adjusting for gender, parental smoking, BMI, age, and serum lipids, neither SBP nor DBP are significantly associated with CIMT
Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern.

Table 24. White et al (2017)[18]

Publication	White D, Place R, Michael T, Hoffman E, Gordon PM, Visich P. The Relationship between Coronary Artery Disease Risk Factors and Carotid Intima-Media Thickness in Children. Journal of Pediatrics. 2017 Nov;190:38-42
Study details	Prospective cohort
Study objectives	To determine cardiovascular disease risk factors and CIMT in a screened population of healthy school children
Inclusions	Children aged 9-10 who completed all the study tests
Exclusions	See inclusion criteria
Population	119 fifth grade pupils attending elementary schools in southern Maine during spring 2016
Test	CIMT measured using portable ultrasound, BP measured using aneroid sphygmomanometer
Comparator	N/A
Outcomes	Systolic BP was associated with left + right mean CIMT thickness – r=0.23, P<0.05
Quality appraisal using CASP cohort checklist and studies guide found no areas of concerns	

Table 25. Hao et al (2017)[19]

Publication	Hao G, Wang X, Treiber FA, Harshfield G, Kapuku G, Su S. Blood pressure trajectories from childhood to young adulthood associated with cardiovascular risk. Hypertension (Dallas, Tex : 1979). 2017;69(3):435-42.
Study details	Longitudinal observational study
Study objectives	Identify sub groups of individuals with similar trajectories in blood pressure from childhood to young adulthood and relationship with CIMT and LVMI

Inclusions	Children aged 5-16 in 1989 with European or African ancestry, normotensive for age and gender, reportedly healthy and parents interested to participate in health research who have participated in the Georgia Stress and Heart Study over a 23 year period
Exclusions	See inclusions
Population	683 participants from the Georgia Stress and Heart Study
Test	BP measured with an automated oscillimetary system CIMT measured by ultrasound.
Comparator	N/A
Outcomes	Relationship of sub groups of low increasing, moderate increasing and high increasing SBP from baseline to final follow up (23 years).

	Low increasing(n=334)	Moderate increasing(n=266)	High increasing(n=83)
Baseline	99.8±8.6	106±9.9	116±10.4
Follow up (23 years)	108.9±8	122.5±10.0	138.5±15.4
Mean increase (Hgmm)	9.1	13.9	22.0
Taking BP meds at 23 years %	1.8%	6.0%	42.2%
Assoc with higher CIMT at 23 yrs	Reference	B=0.019 p=007	B=0.051 p=0.012
Assoc with LVMI at 23 yrs	Reference	β=2.785 p=0.019	β=7.451 p<0.001

Participants in the high increasing sub group were more likely to be African American (p<0.001), male (p<0.001) have a higher BMI (p<0.001) and a father with a lower educational level (p<0.05).

Quality appraisal using CASP cohort checklist and studies guide found no areas of concerns

Table 26. Imhof et al (2016)[21]

Publication	Imhof K, Zahner L, Schmidt-Trucksass A, Hanssen H. Association of body composition and blood pressure categories with retinal vessel diameters in primary school children. Hypertension Research. 2016;39(6):423-9.
Study details	Prospective cohort study
Study objectives	Examine impact of BP on retinal microvasculature
Inclusions	Children taking part in the Sport check study in Switzerland
Population	391 first grade pupils (aged 4-5 years from primary schools taking part in the Sport Check study in 1 canton in Switzerland
Test	BP measured with an oscillometric system, retinal vasculature measured using static retinal vessel analyser retinal camera
Comparator	N/A
Outcomes	BP was measured 5 times and the lowest 3 measurements averaged. Children were pre-hypertensive if between ≥90th <95th and hypertensive if ≥95th percentile.

	CRAE (mu)	CRVE(mu)	AVR
	Mean(CI 95%)	Mean(CI 95%)	Mean (CI 95%)

SBP			
Normotensive(n=291)	207.2(205.6-208.7)	232.2(230.6-233.8)	0.89(0.89-0.90)
Pre-hypertensive(n=45)	201.7(197.8-205.7)	229.2(225.2-233.2)	0.88(0.87-0.90)
Hypertensive (n=55)	199.7(196.2-203.3)	230.1(226.5-233.7)	0.87(0.86-0.89)
P value (normotensive vs pre-hypertensive)	0.01	0.2	0.1
P value (normotensive vs hypertensive)	<0.001	0.3	<0.001
DBP			
Normotensive(n=280)	207.5(205.9-209.0)	232.1(230.5-233.7)	0.90(0.89-0.90)
Pre-hypertensive(n=39)	201.7(197.5-205.9)	228.8(224.6-233.1)	088(0.87-0.90)
Hypertensive(n=72)	200.0(196.9-203.1)	230.8(227.7-234.0)	0.87(0.86-0.88)
P value (normotensive vs pre-hypertensive)	0.01	0.2	0.1
P value (normotensive vs hypertensive).	<0.001	0.5	<0.001

AVR, arteriolar to venular ratio, CI, confidence interval, CRAE, central retinal arteriolar equivalent, CRVE, central retinal venular equivalent.

Quality appraisal	Quality appraisal using CASP cohort checklist and studies guide found no areas of concerns.

Table 27. Gopinath et al (2013)[22]

Publication	Gopinath B, Wang JJ, Kifley A, Tan AG, Wong TY, Mitchell P. Influence of blood pressure and body mass index on retinal vascular caliber in preschool-aged children. Journal of Human Hypertension. 2013;27(9):523-8.
Study details	Prospective cohort
Study objectives	Use population based cohort to examine association between BP and retinal vascular caliber
Inclusions	Children recruited via door to door census
Exclusions	None
Population	379 children aged 3 to 6 years old who were part of the Sydney Pediatric Eye Disease Study
Test	BP taken with automated sphygmomanometer and retinal photographs taken with digital fundus camera
Comparator	N/A
Outcomes	Hypertension was defined as ≥95th percentile for SBP or DBP from mean of 2 readings adjusted for height and sex. Association between SBP and DBP and mean arterial blood pressure (MABP) and retinal vascular calibre in children aged 3 to 6 is set out below.

Per 10mmHg increase in BP	**Retinal arteriolar diameter**		**Retinal venular diameter**	
N=379	β	P value	β	P value
SBP	-1.70	0.02	-0.95	0.27
DBP	-1.02	0.16	-0.50	0.55

MABP	-1.48	0.06	-0.77	0.41
Quality appraisal	Quality appraisal using CASP cohort checklist and studies guide found no areas of concerns			

Table 28. Gopinath et al (2010)[23]

Publication	Gopinath B, Baur LA, Wang JJ, Teber E, Liew G, Cheung N, et al. Blood pressure is associated with retinal vessel signs in preadolescent children. Journal of Hypertension. 2010;28(7):1406-12.
Study details	Prospective cohort
Study objectives	Use population based cohort to examine association between BP and retinal vascular caliber
Inclusions	Child and parental agreement to participate
Exclusions	None
Population	2272 children aged 12 years old who were part of the Sydney Pediatric Eye Disease Study
Test	BP taken with automated sphygmomanometer and retinal photographs taken with digital fundus camera
Comparator	N/A
Outcomes	Hypertension was defined as ≥95th percentile for SBP, DBP or both from mean of 3 readings adjusted for height and sex. Increasing levels of SBP and DBP and MABP were significantly associated with narrower retinal arteriolar calibre. Higher BP associated with wider retinal venules in males but not females. Association between SBP and DBP and mean arterial blood pressure (MABP) and retinal vascular calibre stratified by sex aged 12 years is set out below.

Per 10mmHg increase in BP	**Retinal arteriolar diameter**		**Retinal venular diameter**	
N=2272	B	P value	β	P value
SBP Males	-1.49	<0.0001	1.39	0.003
SBP Females	-1.57	<0.0001	-0.51	0.34
DBP Males	-1.91	<0.0001	1.85	0.001
DBP females	-1.56	0.005	0.10	0.90
MABP Males	-2.29	<0.0001	2.10	0.0003
MABP females	-1.96	0.001	-0.20	0.79

Quality appraisal	Quality appraisal using CASP cohort checklist and studies guide found no areas of concerns

Table 29. Murgan et al (2013)[24]

Publication	Murgan I, Beyer S, Kotliar KE, Weber L, Bechtold-Dalla Pozza S, Dalla Pozza R, et al. Arterial and retinal vascular changes in hypertensive and prehypertensive adolescents. American Journal of Hypertension. 2013;26(3):400-8
Study details	Prospective cohort study

Study objectives	Examine association of BP and retinal vascular changes in adolescents
Inclusions	High school students who agreed to participate
Exclusions	No prior BP related medical conditions or current conditions (especially the eyes)
Population	121 participants aged 13 to 19 from Munich high schools.
Test	BP measured with a sphygmomanometer and retinal vasculature measured with a Dynamic Vessel Analyser retinal camera
Comparator	N/A
Outcomes	Normotensive participants were those with the mean of 3 readings of both SBP and DBP <90th percentile. Using the same method pre hypertension was defined as SBP and/or both ≥90th <95th percentile and hypertension was >95th percentile.

	CRAE	CRVE	AVR
Normotensive(NT)	198.0±2*$^{\#}$	221.1±22.7	0.89±0.10*
Prehypertensive(PHT)	190.2±19.4*	219.3±14.9	0.88±0.10*
Hypertensive(HT)	193.6±14.7*$^{\#}$	220.4±18.5	0.87±0.10

*NT and PHT p<0.05

NT and HT p<0.05

Quality appraisal	Quality appraisal using CASP cohort checklist and studies guide found no areas of concerns

Table 30. Lande et al (2017)[25]

Publication	Lande MB, Batisky DL, Kupferman JC, Samuels J, Hooper SR, Falkner B, et al. Neurocognitive Function in Children with Primary Hypertension. Journal of Pediatrics. 2017;180: 148-55.e1.
Study details	Case control study
Study objectives	To compare neurocognitive test performance of children with primary hypertension with normotensive controls
Inclusions	Children with newly diagnosed untreated hypertension
Exclusions	Those on medication for ADHD, those with learning disability
Population	75 children aged 10 to 18 with newly diagnosed untreated hypertension
Test	Blood pressure measured by 24 hr ambulatory blood pressure monitoring Neurocognitive tests including: Rey Auditory Verbal Learning Test (RAVLT) for Attention learning and memory Connors Continuous Performance Test-II (CPT-II) -for attention and vigilance Wechslar Abbreviated Scales Intelligence(WASHI FSIQ) – General intelligence) Delis Kaplan Executive Function system(DKEFS) – Planning/problem solving Tower test – Problem solving Grooved peg board test – Fine motor dexterity CogState Groton Maze Learning Test(GMLT) – Planning/problem solving memory CogState Set shifting – set shifting Parent BRIEF – Behavioural correlates of executive function
Comparator	75 frequency matched normotensive controls

Outcomes	Sustained hypertension confirmed with 24 hr ambulatory monitoring with BP≥95th percentile awake and asleep and normotension = both SBP and DBP to be <95th percentile. This excluded people with white coat hypertension and prehypertension. Hypertension was independently associated with worse performance for: RAVLT - β=-1.13 p=0.012 CogState GMLT β=4.2, p=0.031 WASHI FSIQ – β=-4.1, p=0.038 Hypertension was associated with worse performance on overall measures of verbal, and visual learning, recall and verbal reasoning. There was no association with performance tasks of vigilance, visumotor reaction time, auditory and visual attention and working memory, problem solving and planning and shifting between different problem solving rules.
Quality appraisal	Quality appraisal The CASP case control study checklist was used and there were no areas of concern. Authors noted there was no imaging component to the study so no anatomic basis for the differences could be determined.

Screening Test: Data extraction and quality assessment for studies relevant to criterion 4

Question 3: What is the accuracy of the screening tests for primary hypertension in children and young people?

Table 31. Flynn et al (2017)[2]

Publication	Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017 September;140 (3) (no pagination)(e20171904).
Study details	Systematic review
Study objectives	To inform and update the American Academy of Pediatrics Guideline for screening and management of high blood pressure in children and adolescents.
Inclusions	Studies of children aged 0-18 with any form of hypertension and co-morbidity
Exclusions	See inclusions
Population	Children aged 0-18
Test	N/A
Comparator	N/A
Outcomes	The following recommendations were made based on evidence from the systematic review (technical details not yet published) **Evidence level B**: Oscillometric devices may be used for BP screening in children and adolescents. When doing so, providers should use a device that has been validated in the pediatric age group. If elevated BP is suspected on the basis of oscillometric readings, confirmatory measurements should be obtained by auscultation. **Evidence level C**: Ambulatory Blood Pressure Monitoring should be performed for confirmation of hypertension in children and adolescents with office BP measurements in the elevated BP category for 1 year or more or with stage 1 hypertension over 3 clinic visits.
Quality appraisal	The technical detail of the systematic review has not yet been published to enable a check using the CASP systematic review checklist for elements indicating a good quality review. The level of evidence grades have been provided and are as follows: Level A: Intervention: well designed and conducted trials, meta analyses on applicable populations. Diagnosis; Independent gold standard studies of applicable populations Level B: Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies Level C: Single or few observational studies or multiple studies with inconsistent findings or major limitations. Level D: Expert opinion, case reports, reasoning from first principles Level X; Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates.

Table 32. Thompson et al (2013)[Error! Bookmark not defined.]

Publication	Thompson M, Dana T, Bougatsos C, Blazina I, Norris SL. Screening for hypertension in children and adolescents to prevent cardiovascular disease. Pediatrics. 2013 March; 131(3):490-525.
Study details	Systematic review

Study objectives	To inform policy and update the US Preventative Services Task Force on the evidence about population screening for hypertension : Key question 2: What is the diagnostic accuracy of screening tests for elevated blood pressure in children and adolescents?
Inclusions	Studies in primary care clinics well child/adolescent visits or school based screening Asymptomatic or otherwise healthy children and adolescents 0-18 with no known diagnosis of hypertension Blood pressure measurements using ausculatory or oscillometric devices that can be performed in a primary care clinic Measures of predictive validity of screening tests eg: predictive value, likelihood ratios, sensitivity and specificity Studies of predictive validity that compare with a reference standard (eg ambulatory monitoring)
Exclusions	Paediatric specialty or subspecialty clinics, inpatient or long term care settings emergency or urgent care facilities Pregnant adolescents 24h ambulatory, or home based blood pressure measurements. Diagnostic tests or investigations used to identify, confirm possible causes of secondary hypertension Studies that do not provide enough data to recreate the 2x2 tables or calculate sensitivity or specificity Studies that do not use a true reference standard for comparison
Population	Children and adolescents in studies meeting the inclusion criteria
Test	N/A
Comparator	N/A
Outcomes	2 fair quality studies[31,30] provided data on accuracy of screening tests 12 studies did not meet inclusion criteria as they failed to apply reference tests to participants who initially screened negative or they didnot use an acceptable reference standard.
Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern.

Table 33. Bloetzer et al (2017)[32]

Publication	Bloetzer C, Bovet P, Paccaud F, Burnier M, Chiolero A. Performance of targeted screening for the identification of hypertension in children. Blood Pressure. 2017 04 Mar;26(2):87-93.
Study details	Prospective cohort study
Study objectives	Assess the performance of combined risk factors for hypertension for the identification of hypertension in children
Inclusions	All children from all public 6th grade classes in a Swiss canton
Exclusions	None
Population	5207 children aged 10-14 years
Test	Blood pressure monitored 3 times using validated oscillometric system
Comparator	None
Outcomes	The data below reports the 2x2 tables for children with and without hypertension using a combination of factors (parental history of hypertension, obesity, or those overweight plus those obese) to determine if targeted screening would improve screening test performance.

	Children with hypertension	Clinical performance (95% CI)

Parental history of hypertension	No	Yes	Total	sen	40.7%(31.6-50.4)
No	4111	67	4178	spec	80.7%(79.6-81.8)
Yes	983	46	1029	PPV	4.5%(3.3-5.9)
Total	5094	113	5207	NPV	98.4%(98.0-98.8)
Overweight/obese				Sen	43.4%(34.1-53.0)
No	4401	64	4465	Spec	86.4%(85.4-87.3)
Yes	693	49	742	PPV	6.6%(4.9-8.6)
Total	5094	113	5207	NPV	98.6% (98.2-98.9)
Obesity				Sen	24.8%(17.1-33.8)
Yes	4934	85	5019	Spec	96.9%(96.3-97.3)
No	160	28	188	PPV	14.9%(10.1-20.8)
Total	5094	113	5207	NPV	98.3%(97.8-98.6)
Combined factors				Sen	64.6%(55.1-73.4)
No	3591	40	3631	Spec	70.5%(69.2-71.7)
Yes	1503	73	1576	PPV	4.6%(3.6-5.6)
Total	5094	113	5207	NPV	98.9%(98.5-99.2)
Sens- sensitivity, Spec- specificity, PPV – Positive predictive value, NPV-negative predictive value CI – Confidence interval					

Quality appraisal: **QUADAS 2 table for test studies**

Question	**Assessment (Y, N, unclear)**	**Risk of Bias (low, high, unclear)**	**Supporting info**
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Large size all pupils in one year invited to participate
Case-control design avoided?	Y	Low	Prospective cohort
Inappropriate exclusions avoided?	Y	Low	No exclusions
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	N	High	No blinding
Threshold pre-specified?	Y	Low	Those above≥95% percentile for height gender and age
Domain II: Reference standard			
Reference standard likely	Unclear	High	Reference standard comprises multiple testing

to correctly classify condition?			with same test as index
Reference standard results interpreted without knowledge of index test results?	N	High	No blinding
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Y	Low	1 week
Did all participants receive same reference standard?	N	High	Only those above the specified threshold
All patients included in analysis?	Y	Low	
Applicability			
Applicable to UK screening population of interest?	Y	Low	European population
Applicable to UK screening test of interest?	Y	Low	Yes would be a test used in the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	Reference standard would be used in UK

Table 34. Negroni-Balasquide et al (2015)[33]

Publication	Negroni-Balasquide X, Bell CS, Samuel J, Samuels JA. Is one measurement enough to evaluate blood pressure among adolescents? A blood pressure screening experience in more than 9000 children with a subset comparison of auscultatory to mercury measurements. Journal of the American Society of Hypertension. 2016 01 Feb;10(2):95-100
Study details	Longitudinal study
Study objectives	To examine if early BP readings using oscillometric systems are artificially elevated
Inclusions	All students invited from Houston area schools
Exclusions	Those who did not volunteer, those who did not return a signed consent form
Population	9870 children and adolescents aged 10 19 from Houston area schools
Intervention	Multiple BP readings using oscillometric systems
Comparator	Ausculatory BP measured in sample n=287
Outcomes	The main outcomes are set out in the table below. As no threshold for high blood pressure was defined it was not possible for authors to report sensitivity and specificity.

Mean difference of OBP combinations and single ausculatory measurement

	Systolic		Diastolic	
	Mean(95%CI)	P value	Mean (95%CI)	P value
1st OBP	-2.13(-3.33,-0.92)	0.006	2.06(0.81,3.31)	0.001
2nd OBP	0.65(-0.54,1.83)	0.282	4.82(3.54,6.10)	≤0.001

Mean of 1st and 2nd OBP	-0.74(-1.86,0.38)	0.195	3.44(2.25,4.64)	≤0.001
Mean 1st, 2nd & 3rd OBP	0.50(-0.59, 1.60)	0.367	4.41(3.26,5.57)	≤0.001
Mean 2nd&3rd OBP	1.82(0.69,2.95)	0.002	5.59(4.41,6.77)	≤0.001
Mean 1st, 2nd, 3rd, 4th OBP	1.33(0.25,2.41)	0.016	4.92(3.76.6.09)	≤0.001
Mean 2nd, 3rd, 4th OBP	2.48(1.37,3.59)	<0.001	5.88(4.70,7.06)	≤0.001
OBP – Oscillometric blood pressure, CI- Confidence interval				

Quality appraisal	There were some major limitations to this study (see QUADAS table below) including a reference standard obtained from 1 ausculatory measurement when the clinical standard is to take an average of the 2 lowest of 3 readings. Not all children who were negative on initial screen were tested against the reference standard.

QUADAS 2 table for test studies

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Large size all pupils in invited to participate
Case-control design avoided?	Y	Low	Prospective cohort
Inappropriate exclusions avoided?	Y	Low	No exclusions
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	N	High	No blinding
Threshold pre-specified?	Unclear	unclear	No threshold either pre specified or following testing the study was checking agreement of index with reference standard but not about definition of hypertension which would result in applying a threshold.
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Unclear	Unclear	Reference standard was only one measurement using ausculation
Reference standard results interpreted without knowledge of index test results?	N	High	No blinding
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Unclear	Ausculatory test taken just before oscillometric tests
Did all participants receive same reference standard?	N	Low	Random sample of 30% of total participants

All patients included in analysis?	Y	Low	
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	US population 36% Caucasian
Applicable to UK screening test of interest?	Y	Low	Yes would be a test used in the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	Reference standard would be used in UK

Treatment: Data extraction and quality assessment for studies relevant to criterion 9

Question 4 – What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions for treating primary hypertension in children and young people?

Sub: question: What is the effectiveness of pharmacological and non-pharmacological and/or combination interventions in children and young people for preventing hypertension in adulthood?

Table 35. Chaturvedi et al (2014)[34]

Publication	Chaturvedi S, Lipszyc DH, Licht C, Craig JC, Parekh R. Pharmacological interventions for hypertension in children. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD008117. DOI: 10.1002/14651858.CD008117.pub2.
Study details	Systematic review
Study objectives	To determine strength of evidence of effectiveness of pharmacological treatment for children with hypertension
Inclusions	Children and young people aged 0 to 18 with primary or secondary causes
Exclusions	Children with secondary hypertension from: kidney transplant, nephrotic syndrome, on calcineurin inhibitors on high dose steroids, with malignant hypertension perioperative control of BP
Population	Children and young people aged 0 to 18
Intervention	Anti hypertensive medication
Comparator	Placebo or range of dosages
Outcomes	Table below extracted directly from Chaturvedi et al (2014)

Antihypertensive drug class compared to placebo for hypertension in children: diastolic blood pressure reduction			
Patient or population: children (f rom 1 to 18 years of age) with hypertension f rom primary or secondary causes **Settings:** outpatient **Intervention:** antihypertensive drug class **Comparison:** placebo			
Outcomes	Magnitude of reduction in diastolic blood pressure mmHg in treatment group minus placebo response	No of participants (studies)	Quality of the evidence (GRADE)

	Mean difference with 95%CI		
Angiotensin receptor blocker (any dose) Mean duration of 4 weeks	-5.50 (-9.62 to -1.38) 240	240(1 study)	Very low
Angiotensin receptor blocker for hypertension in children: dose response in systolic blood pressure			
Angiotensin receptor blocker >/= 6 years			
Angiotensin receptor blocker (high- versus low-dose)	4.16 (-5.47 to -2.86)	418 (5 studies)	Low
Angiotensin receptor blocker (high- versus medium-dose)	-0.46 (-2.44 to 1.53)	237 (3 studies)	Very Low
Angiotensin receptor blocker (medium- versus low-dose)	-3.13 (-5.43 to -0.83)	160 (3 studies)	Very Low
Angiotensin receptor blocker < 6 years			
Angiotensin receptor blocker (high- versus low-dose)	-3.01 (-8.79 to 2.76)	67 (2 studies)	Very Low
Angiotensin receptor blocker (high- versus medium-dose)	-1.76 (-4.80 to 1.29	67 (2 studies)	Very Low
Angiotensin receptor blocker (medium- versus low-dose)	-1.32 (-4.54 to 1.90)	50 (2 studies)	Very Low
Angiotensin receptor blocker for hypertension in children: dose response in diastolic blood pressure			
Angiotensin receptor blocker >/= 6 years			
High- versus low-	dose -3.48 (-5.00 to -1.95) ⊕⊕	418 (5 studies)	Low
High- versus medium dose	-0.59 (-2.49 to 1.32)	237 (3 studies)	Very low
Medium- versus low dose	-3.04 (-5.67to -0.40)	160 (3 studies	Very low
Angiotensin receptor blocker < 6 years			
High- versus low-dose -	2.85 (-8.63 to 2.92)	67 (2 studies)	Very low
High- versus medium dose	-0.56 (-4.42 to 3.29)	67 (2 studies)	Very low
Medium- versus low dose	-1.31 (-3.74 to 1.12)	50 (2 studies)	Very low
Angiotensin converting enzyme inhibitor for hypertension in children: dose response in systolic blood pressure			

Angiotensin-converting enzyme inhibitor			
High- versus low-dose	-5.20 (-10.46 to 0.06)	187 (3 studies)	Very Low
High- versus medium dose	-2.72 (-5.83 to 0.40))	187 (3 studies)	Very Low
Medium- versus low dose	-2.01 (-6.07 to 2.05)	139 (3 studies)	Very Low
Angiotensin converting enzyme inhibitor for hypertension in children: dose response in diastolic blood pressure			
High- versus low-dose	-5.81 (-11.87 to 0.26) ⊕	187 (3 studies)	Very Low
High- versus medium dose	-4.31 (-8.59 to -0.03)	187 (3 studies)	Very Low
Medium- versus low dose	-0.46 (-2.19 to 1.27)	139 (3 studies)	Very Low

* The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

CI: confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Comments:

1. Evidence based on only one study.
2. “Industry-funded study. Industry-funded studies are at risk of over-estimating effect size.”
3. “Wide confidence interval.”
4. “High risk of publication bias.”
5. “Unclear method of randomisation and allocation concealment”

Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern.

Table 36. Osterhoff et al (2016)[28]

Publication	Oosterhoff M, Joore M, Ferreira I. The effects of school-based lifestyle interventions on body mass index and blood pressure: A multivariate multilevel meta-analysis of randomized controlled trials. Obesity Reviews. 2016 Nov;17(11):1131-1153
Study details	Meta-analysis
Study objectives	Assess the impact of school based lifestyle interventions on children’s BMI and BP
Inclusions	Children aged 4-12 enrolled in RCT with control group with no intervention, outcomes were BMI and cardiovascular risk factors implemented in a school setting and data included at least 1 follow up point since start of intervention
Exclusions	See inclusions
Population	Children aged 4 - 12
Test	Non pharmacological interventions in school settings

Comparator	No intervention
Outcomes	

Outcome	Multivariate analysis	
	β(95% CI)	P value
SBP	-0.182(-0.266,-0.098)	<0.001
DPB	-0.144(-0.230, -0.057)	<0.001

CI Confidence interval

Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern.

Table 37. Thompson et al (2013)[Error! Bookmark not defined.]

Publication	Thompson M, Dana T, Bougatsos C, Blazina I, Norris SL. Screening for hypertension in children and adolescents to prevent cardiovascular disease. Pediatrics. 2013 March;131(3):490-525.
Study details	Systematic review
Study objectives	To inform policy and update the US Preventative Services Task Force on the evidence about population screening for hypertension: **Key question 5**: What is the effectiveness of drug, non drug and combination interventions for treating primary hypertension in children and adolescents. **Key question 6**: What is the effectiveness of drug, non drug and combination interventions for treating primary hypertension in children and adolescents for reducing blood pressure and other intermediate outcomes in adults?
Inclusions	Studies in primary care clinics well child/adolescent visits or school based screening Primary hypertension defined as average blood pressure between 95th percentile and 5mmHg above the 99th percentile Drug antihypertensive medications which are currently FDA approved for use with children and adolescents Outcomes include blood pressure, LVH(based on LVMI) and microalbuminuria, CIMT and retinal vascular changes RCTs controlled clinical trials observational studies with a comparison group and systematic reviews.
Exclusions	Paediatric specialty or subspecialty clinics, inpatient or long term care settings emergency or urgent care facilities When the majority of the study population included has secondary hypertension Interventions for treatment of secondary hypertension Outcomes where reduction in blood pressure is not the primary objective of the study, measures of cognitive function, variations in blood pressure such as diurnal or nocturnal changes, arterial stiffness, metabolic measures, uric acid levels, inflammatory markers weight changes or BMI.
Population	Children aged 0 to 18 enrolled in studies meeting the above inclusion and exclusion criteria
Test	N/A
Comparator	N/A
Outcomes	Pharmacological interventions – 7 trials examining 7 drugs with a follow up of up to 4 weeks Non pharmacological interventions - 6 trials Combined pharmacological and non pharmacological studies -1 trial. For many studies, the proportion of children with secondary hypertension was unclear Children achieving normotensive status (on the basis of varying definitions) ranged from15% to 86%inpatientstakingdrugtreatmentsand 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 from0 to 9mm Hg for SBP and 0.5 to 10mm 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. No studies were found that assessed effectiveness of any intervention or combination of interventions in childhood that reduced adverse outcomes in adults.
Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern

Table 38. Litwin et al (2010)[35]

Publication	Litwin M, Niemirska A, Sladowska-Kozlowska J, Wierzbicka A, Janas R, Wawer ZT, et al. Regression of target organ damage in children and adolescents with primary hypertension. Pediatric nephrology (Berlin, Germany). 2010 Dec;25(12):2489-99
Study details	Prospective cohort
Study objectives	Examination of pharmacological and non pharmacological anti hypertensive therapy on target organ damage and metabolic status
Inclusions	All children with newly diagnosed untreated primary hypertension
Exclusions	Presence of any chronic disease apart from primary hypertension including diabetes, chronic kidney disease and any acute disease including infections
Population	86 children aged 6 to 17
Test	Pharmacological or non pharmacological or a combination of interventions to treat hypertension
Comparator	NA
Outcomes	**Blood pressure and target organ damage at baseline and at 12 months of treatment**

N=86	**Baseline number**	**12 months intervention number (%)**	**P value**
Normotension number participants (%)	0	54(62.8%)	0.0001
Pre hypertension number participants (%)	0	10(11.6)	0.0001
Ambulatory hypertension	50(58.1)	21(24.4)	0.004
Number of participants (%)			
Severe hypertension number of participants (%)	36(41.9)	1(1.2)	0.004
CIMT mm	0.44±0.05	0.42±0.04	0.0001
CIMT SDS	1.4±1.5	0.9±1.3	0.001

	LVH (age and gender adjusted) number participants (%)	39(45.3)	24(27.9)	0.0001
	Severe LVH	10(11.6)	1(1.2)	0.006
	LVMI (g/height$^{2.7}$)	38.5±10	35.2±7.5	0.0001

SDS – Standard deviations, LVH – Left ventricular hypertrophy, LVMI – Left ventricular mass index, CIMT – Carotid- intima media thickness

Quality appraisal	Quality appraisal using CASP cohort checklist and studies guide found no areas of major concern although the combination of different types of intervention means it is not clear what type of treatment might be associated with a reduction in target organ damage.

Screening programmes: Data extraction and quality assessment for studies relevant to criterion 11

Question 5: Is there an effective screening strategy for hypertension in children and young people to prevent hypertensive disorders in later life?

Table 39. Thompson et al (2013)[Error! Bookmark not defined.]

Publication	Thompson M, Dana T, Bougatsos C, Blazina I, Norris SL. Screening for hypertension in children and adolescents to prevent cardiovascular disease. Pediatrics. 2013 March;131(3):490-525.
Study details	Systematic review
Study objectives	To inform policy and update the US Preventative Services Task Force on the evidence about population screening for hypertension. **Key question 1**; Is screening for hypertension in children and adolescents effective in delaying the onset or reducing adverse health outcomes related to hypertension?
Inclusions	Studies in primary care clinics well child/adolescent visits or school based screening Asymptomatic or otherwise healthy children and adolescents 0-18 with no known diagnosis of hypertension Blood pressure measurements using ausculatory or oscillometric devices that can be performed in a primary care clinic Outcomes - morbidity that covers: 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. All cause and disease specific mortality. RCTs controlled clinical trials observational studies with a comparison group and systematic reviews
Exclusions	Paediatric specialty or subspecialty clinics, inpatient or long term care settings emergency or urgent care facilities Pregnant adolescents 24h ambulatory, or home based blood pressure measurements. Diagnostic tests or investigations used to identify, confirm possible causes of secondary hypertension
Population	Children enrolled in studies meeting the inclusion and exclusion criteria
Test	N/A
Comparator	N/A
Outcomes	No studies were identified that met the inclusion and exclusion criteria.
Quality appraisal	The CASP Systematic Review checklist was used to assess if all the expected elements of good quality systematic review were present in the publication. The systematic review included all the elements of the checklist and there were no areas of concern

Screening programmes: Data extraction and quality assessment for studies relevant to criterion 12

Question 6: What are the optimal ages to initiate screening?
What are the optimal time intervals at which to repeat screening?
Who should do the screening; general paediatricians, renal physicians, other?

Table 40. Flynn et al (2017)[2]

Publication	Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017 September;140 (3) (no pagination)(e20171904).
Study details	Systematic review
Study objectives	To inform and update the American Academy of Pediatrics Guideline for screening and management of high blood pressure in children and adolescents: Key question: How should systematic hypertension (primary, renovascular, white coat, and masked) in children be diagnosed and what is the optimal approach to diagnosing hypertension in children and adolescents?
Inclusions	Studies of children aged 0-18 with any form of hypertension and co-morbidity.
Exclusions	See inclusions
Population	Children aged 0-18
Test	N/A
Comparator	N/A
Outcomes	The following recommendations were made based on evidence from the systematic review (technical details not yet published) **Evidence level C:** BP should be measured annually in children and adolescents ≥3 y of age. **Evidence level C:** BP should be checked in all children and adolescents ≥3 y of age at every health care encounter if they have obesity, are taking medications known to increase BP, have renal disease, a history of aortic arch obstruction or coarctation, or diabetes. **Evidence level C**: Trained health care professionals in the office setting should make a diagnosis of HTN if a child or adolescent has auscultatory confirmed BP readings ≥95th percentile at 3 different visits.
Quality appraisal	The technical detail of the systematic review has not yet been published to enable a check using the CASP systematic review checklist for elements indicating a good quality review. The level of evidence grades were provided and are as follows: Level A: Intervention: well designed and conducted trials, meta analyses on applicable populations. Diagnosis; Independent gold standard studies of applicable populations Level B: Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies Level C: Single or few observational studies or multiple studies with inconsistent findings or major limitations. Level D: Expert opinion, case reports, reasoning from first principles Level X; Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates.

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Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 36.

Table 41. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	7
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	12
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	17
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	21
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	61

3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	67
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	67
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 70 Quality assessment:
4.2	Additional analyses	Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer.	N/A
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	24
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	24
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	25
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	58
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	60

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2 Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017 September;140 (3) (no pagination)(e20171904).

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