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Original Article

The association between blood pressure and carotid intima-media thickness in children: a systematic review

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Abstract High blood pressure is a risk factor for atherosclerosis in adults, but whether the same is true in children and young people is not known. This is important to guide management of high blood pressure in children and young people. We aimed to investigate the association in children and young people between blood pressure and carotid intima-media thickness, a non-invasive marker of atherosclerosis, through a systematic review. Studies were retrieved from MEDLINE and EMBASE. Articles were eligible for inclusion if they included at least one measurement of blood pressure and at least one measurement of ultrasound-derived carotid intima-media thickness, both measured during childhood (0–19 years), and a measure of effect size or correlation between the two measurements. A total of 3748 studies were identified in the initial search, of which 28 studies were included in this review. The results were mixed, but the largest and highest-quality studies suggested an independent positive association between blood pressure and carotid intima-media thickness in children and young people, even after adjustment for other cardiovascular risk factors. There was no indication of a clear threshold level for the effect of blood pressure on carotid intima-media thickness, hence there are insufficient data to support a pharmacological treatment threshold for the treatment of high blood pressure in children and young people to prevent future cardiovascular disease. The studies included varied widely in terms of quality and design, and it was not possible to combine the data in a meta-analysis. There is likely to be an independent association between blood pressure and carotid intima-media thickness in childhood, but it is not clear at what point this should be treated.

Keywords: Hypertension; childhood; carotid intima-media thickness; atherosclerosis

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HYPERTENSION IS A KNOWN RISK FACTOR FOR THE progression of atherosclerosis in adults, along with other well-described cardiovascular risk factors such as obesity, age, and smoking. Hypertension in childhood and adolescence is associated with future risk of cardiovascular disease, but it is unclear whether this is initiated through direct vascular end organ damage at these ages or tracking of blood pressure and other related risk factors into adulthood and consequent acceleration of age-related vascular changes at older ages.[1–3] Knowing this could help guide management of high blood pressure in children and young people, particularly pharmacotherapy, for which there is considerable reluctance to initiate early treatment because of potential for lifelong therapy and adverse effects. This question has gained particular importance in recent years with the rising prevalence of high blood pressure in children and young people associated with the child obesity epidemic worldwide.

To address this question, we investigated the association between blood pressure and carotid intima-media thickness in children and young people

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through a systematic review of published evidence. In adults, carotid intima-media thickness measured non-invasively by ultrasound is frequently used as a surrogate marker of atherosclerosis: it has been shown to correlate well with atherosclerosis elsewhere and predicts cardiovascular events.[4] We hypothesised that a greater carotid intima-media thickness in children and young people could be indicative of vascular re-modelling, and therefore used to investigate a direct role of blood pressure in initiating atherosclerosis at younger ages. If a clear association was found between blood pressure and carotid intima-media thickness, our secondary objectives were to explore the potential impact on this association on age, type, systolic or diastolic, and level of blood pressure, and presence of other cardiovascular risk factors, notably obesity, as these would further guide decisions on early initiation of blood pressure control in children and young people.

Materials and methods

A systematic search was conducted for published English-language studies of the association between blood pressure and carotid intima-media thickness in childhood. Databases such as MEDLINE and EMBASE were used, limited from January, 1980 to June, 2013.

The following search terms were used for MEDLINE, and were adapted as necessary for EMBASE: 1. exp Child/, 2. exp Adolescent/, 3. juvenile.mp., 4. exp Infant/, 5. child$.mp., 6. adolescen$.mp., 7. infan$.mp., 8. teen$.mp., 9. P?ediatric$.mp., 10. Pediatrics/, 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10, 12. hyperten$.mp., 13. pre-hyperten$.mp, 14. exp Hypertension/, 5. exp Prehypertension/, 16. exp Blood pressure/, 17. 12 or 13 or 14 or 15 or 16, 18. exp Atherosclerosis/, 19. exp Arteriosclerosis/, 20. exp Carotid intima-media thickness/, 21. exp Carotid artery disease/, 22. atherosclero$.mp, 23. arteriosclero$.mp, 24. carotid intima-media thickness.mp, 25. carotid intima-media thickness.mp, 26. exp Carotid Arteries/ and exp Ultrasonography/, 27. Exp Carotid Arteries/us, 28. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27, 29. 11 and 17 and 28, 30. limit 29 to (humans and year = "1980 to Current").

Articles were eligible for inclusion if they included at least one measurement of blood pressure and at least one measurement of ultrasound-derived carotid intima-media thickness, both measured during childhood (0–19 years), and if a measure of effect size or correlation between the two measurements was included in the manuscript. Both cross-sectional and longitudinal studies were eligible, so long as both blood pressure and carotid intima-media thickness measures were obtained in childhood. Studies were excluded if they did not meet inclusion criteria, or if the population was recruited from specific disease groups such as children with CHD, endocrine diseases, or renal disorders, as the results of such studies may be confounded by disease-specific risk factors. Studies focussing on obese children were also included.

For a preliminary assessment of suitability, two independent reviewers – T.D. and M.H.P. – screened titles and abstracts. If deemed suitable, the full text of the articles was screened to determine whether the article met inclusion criteria. Any disagreements between the two reviewers were resolved by consensus.

Data were extracted using a pre-designed pro forma. For each study, the following was recorded: study population, country of residence, study design, study population recruitment method, subgroups of the study population, mean age, number and sex distribution of the study population, mean systolic and diastolic values blood pressure, blood pressure measurement method, carotid intima-media thickness measurement method, details of relationship between blood pressure and carotid intima-media thickness.

For studies that were eligible, study quality was assessed using 10 pre-defined criteria:

- Are the hypotheses/aims/objectives clearly described?
- Are the carotid intima-media thickness and blood pressure measurement methods clearly described?
- Are the age and sex of the study population clearly described?
- Have actual probability values been reported for the relationship between carotid intima-media thickness and blood pressure?
- Does the study include at least a group of subjects who are representative of the general population?
- Was the source of each group of subjects clearly defined?
- Was an attempt made to blind those measuring carotid intima-media thickness to the subject's blood pressure?
- Was linear regression used, rather than just a simple comparison of means?
- Was an attempt made to assess the internal validity of the carotid intima-media thickness measurement?
- Was an attempt made to adjust confounding factors in the analysis of the relationship between blood pressure and carotid intima-media thickness?

Data were synthesised in a narrative manner, and are summarised in tabular form.

Results

In total, 28 studies were eligible for inclusion in this review (see Fig 1). Detailed descriptions of each study

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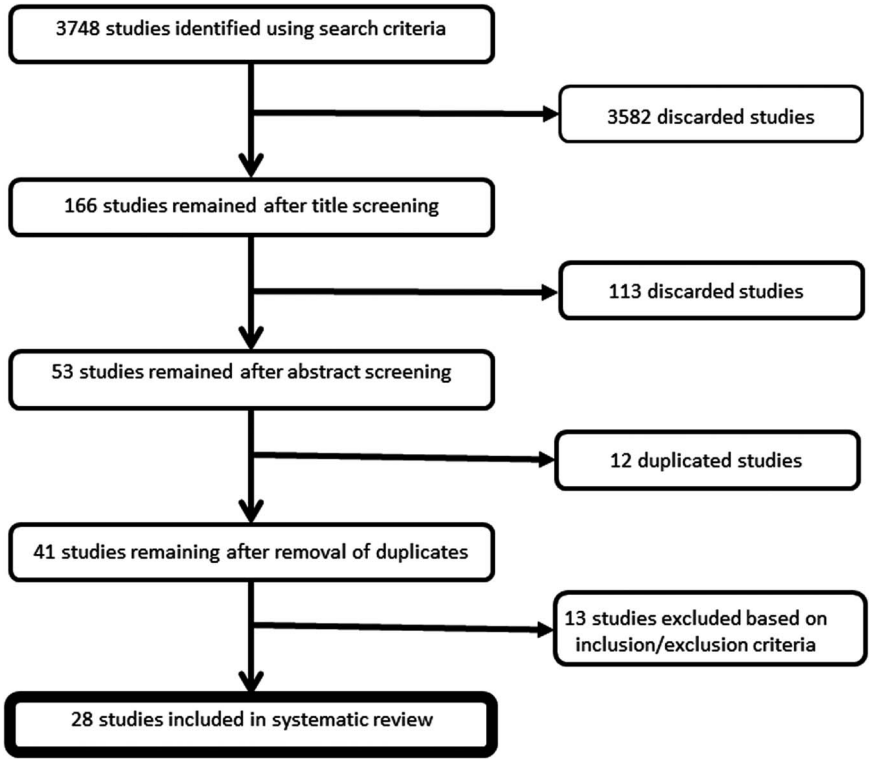

Figure 1.
Flow diagram indicating the number of studies included at each stage of the inclusion process.

are included in Table 1 (online supplement). Summaries of the main relevant findings of each study are included in Table 1. All included studies were cross-sectional in design – eight of these studies recruited healthy children from the community, a further eight were based on children identified as hypertensive recruited from clinics or following population screening, and nine studies were based on children identified as overweight or obese. A further three studies were miscellaneous: one was based on healthy children seen during a hospital "check-up", one was based on children identified as having high cholesterol, and one study did not specify how or why the study population was recruited.

Studies based on healthy children recruited from the community

All eight studies with a healthy study population recruited from the community showed a positive association between carotid intima-media thickness and systolic blood pressure and/or diastolic blood pressure. Only two studies found an association between both systolic blood pressure and diastolic blood pressure and carotid intima-media thickness: Whincup et al[5] used multilevel random effects modelling to adjust for sex, age, ethnicity, month, and random effect for school, showing an increase of 0.024 and 0.0027 mm for each standard deviation increase in systolic blood pressure and diastolic blood pressure, respectively. Castera et al[6] also showed a positive association between both systolic blood pressure and diastolic blood pressure with carotid intima-media thickness on univariate modelling. However, when multivariate modelling was used to adjust for potential confounders, only systolic blood pressure showed a robust association with carotid intima-media thickness ($\beta = 0.0004$, $p = 0.005$).

Among all three studies found positive associations between carotid intima-media thickness and systolic blood pressure but not diastolic blood pressure. Lim et al[7] used multivariate logistic regression – being in the top quartile of carotid intima-media thickness for age and sex was the outcome variable – showing an odds ratio of 1.7 (95% CI 1.2–2.41) per increase of 1 standard deviation of systolic blood pressure. Kollias et al[8] found that systolic blood pressure was positively correlated with carotid intima-media thickness ($r = 0.14$, $p < 0.01$). After adjusting for age, sex, and other cardiovascular risk factors, however, this association only remained for left-sided carotid intima-media thickness, but not for right-sided or mean carotid intima-media thickness. Mittleman et al[9] found that systolic blood pressure was positively associated with carotid intima-media thickness in both sexes, but when the analysis was restricted those

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with "healthy" weights, this association remained only for boys. Systolic blood pressure did not remain associated with carotid intima-media thickness after adjustment for potential confounders using a multiple regression model.

Two studies focussed on systolic blood pressure only and did not present data on diastolic blood pressure. Bohm et al[10] found that systolic blood pressure was significantly correlated with carotid intima-media thickness in both sexes, but when the used multiple regression this association remained only for boys ($\beta = 0.31$, $p \leqslant 0.001$). Sarkola et al[11] found an association between systolic blood pressure and carotid intima-media thickness in both univariate and multivariate models ($\beta = 3.1$, $p < 0.001$ and $\beta = 1.1$, $p = 0.03$, respectively).

The study by Ishuzu et al[12] found that diastolic blood pressure but not systolic blood pressure was associated with carotid intima-media thickness using a linear regression model; however, in a model adjusting for additional potential confounding factors, this association did not remain significant.

Studies based on hypertensive children

In all, eight studies were based on children identified as hypertensive, recruited either from hospital clinics (five studies), following screening of the general paediatric population (two studies), or a combination of the two methods (one study). The definition of hypertension varied between the studies – for example, if the systolic and/or diastolic blood pressure exceeded the 90th or 95th centile based on height, weight, and sex, or if the systolic blood pressure exceeded 140 mmHg (see online Table 1). Of these eight studies, seven found a positive association between blood pressure and carotid intima-media thickness; however in the four of these studies that adjusted for potential confounders, none found a significant association after adjustment.

Among children referred to secondary care for investigation of possible hypertension, Stabouli et al[13] found that systolic blood pressure and diastolic blood pressure, as well as 24-hour systolic blood pressure were positively correlated with carotid intima-media thickness. After adjusting for obesity and age however, these associations did not remain statistically significant. Lande et al[14] studied children with newly diagnosed untreated hypertension and age, sex, and body mass index-matched normotensive controls from a general paediatric clinic. They found that carotid intima-media thickness was significantly higher in the hypertensive group (0.67 versus 0.63 mm, respectively, $p = 0.045$), but there was no significant correlation between single office blood pressure measurement and carotid intima-media thickness. Ambulatory measurements however, were correlated with carotid intima-media thickness – for example daytime mean systolic blood pressure ($r = 0.43$, $p = 0.03$).

Similarly, Litwin et al[15] studied hypertensive children in secondary care and healthy normotensive controls from local schools. They found that carotid intima-media thickness was higher in the hypertensive group compared with controls (0.47 versus 0.43 mm, respectively in boys, $p = 0.0001$, similar results in girls). After adjustment for possible confounders however, this association did not remain significant. Loureiro et al[16] found that systolic blood pressure and diastolic blood pressure index were correlated with carotid intima-media thickness in hypertensive children, but this association disappeared when potential confounders were controlled for in a multiple regression model.

Sorof et al published two studies in 2003. The first,[17] studying patients referred to a secondary care hypertension clinic, found no association between blood pressure and carotid intima-media thickness. The second study[18] utilised data from hypertension clinics, but combined them with data on hypertensive children and normotensive controls from a population-based screening study. In contrast to the first study, this study found that the hypertensive subjects had higher carotid intima-media thickness compared with controls (0.62 versus 0.53 mm, $p < 0.0001$). When age and body mass index were taken into account however, blood pressure was no longer significantly associated with carotid intima-media thickness.

Pall et al[19] used data from children recruited from local schools. In unadjusted analyses, they found that carotid intima-media thickness was thicker in hypertensive subjects (both "white-coat" and sustained hypertensive combined) compared with normotensive controls. Gill et al[20] recruited hypertensive children after screening in schools, and in unadjusted analyses they found that carotid intima-media thickness was higher in the hypertensive group than among normotensive controls (0.62 versus 0.5 mm, $p < 0.05$).

Studies based on obese children

A total of nine studies focussed on overweight and obese children. Of these, eight included a normal-weight control group. Four studies recruited children directly from a weight management or obesity clinic, one from a paediatric cardiology clinic, and one from local schools, whereas three studies failed to report from where the subjects were recruited. Of the nine studies, all found a significant association between blood pressure and carotid intima-media thickness;

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Table 1. Summaries of the relevant findings from each study.

References	Population	Univariate association between BP and CIMT	Multivariate association between BP and CIMT
Studies based on healthy children recruited from the community			
Whincup et al (2012)	Primary school children	N/A	Multilevel random effects model: each SD increase of systolic BP increased CIMT by 0.0024 mm (95% CI 0.0002–0.0046), each SD increase of diastolic BP increased CIMT by 0.0027 mm (95% CI 0.0005–0.0048). Adjusted for sex, age, ethnicity, month, and random effect for school
Bohm et al (2009)	School children	SBP positively correlated with CIMT in both boys ($r = 0.31$, $p \leqslant 0.001$) and girls ($r = 0.24$, $p = 0.005$). DBP correlation not presented	Multivariable linear regression: SBP significantly associated with CIMT in boys but not girls ($\beta = 0.31$, $p \leqslant 0.001$), adjusted for height, weight, BMI, and body fat
Lim et al (2009)	Students at a rural high school	SBP positively correlated with CIMT ($r = 0.31$, $p \leqslant 0.01$). DBP not correlated	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)	Healthy children recruited schools	SBP significantly correlated with mean CIMT ($r = 0.14$, $p < 0.01$)	Multivariable linear regression: SBP significantly associated with left (but not right or mean) CIMT ($\beta = 0.002$, $p < 0.01$). DBP not significantly associated with CIMT
Caserta et al (2010)	Random selection of children from school census list	Univariate linear regression: both SBP and DBP significantly associated with CIMT ($\beta = 0.0006$, $p < 0.001$ and $\beta = 0.0005$, $p = 0.006$, respectively)	Multivariable linear regression: SBP but not DBP significantly associated with CIMT ($\beta = 0.0004$, $p = 0.005$), after adjusting for presence of fatty liver disease, BMI, waist circumference, liver enzyme levels, cholesterol, and C-reactive protein
Mittelman et al (2010)	Healthy subjects recruited from schools and universities	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 ($r = 0.15$, $p = 0.0364$)	Multivariable linear regression: BP is not significantly associated with CIMT, either in the group as a whole or the isolated healthy weight group
Sarkola et al (2012)	Healthy children recruited from local public schools, and from low-risk cardiology clinic (once cardiac disease excluded)	Univariate linear regression: SBP significantly associated with CIMT ($\beta = 3.1$, $p < 0.001$)	Multivariable linear regression: SBP significantly associated with CIMT ($\beta = 1.1$, $p = 0.03$), model adjusts for gender, age, and BSA
Ishizu et al (2004)	Healthy children recruited from schools	N/A	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
Studies based on children identified as hypertensive, either from clinic or following population screening (± a normotensive comparison group)			
Stabouli et al (2012)	Children referred to secondary care for investigation of possible hypertension (those with secondary hypertension excluded)	Both clinic SBP and DSP positively correlated with CIMT for both common carotid ($r = 0.41$ and 0.32, respectively) and internal carotid ($r = 0.33$ and 0.30,	ANCONA analysis: after adjusting for age and obesity, neither clinic nor 24-hour BP remained significantly associated with either CIMT measurement

Table 1. *Continued*

References	Population	Univariate association between BP and CIMT	Multivariate association between BP and CIMT
		respectively). 24-hour SBP correlated with CIMT ($r = 0.29$ for common carotid and 0.23 for internal). 24-hour DBP not significantly associated	
Pall et al (2010)	Healthy adolescent students included in the Debrecen hypertension study, recruited from local secondary schools	CIMT in both white-coat and sustained hypertensives significantly higher than normotensive controls when compared by t-test (0.056 and 0.054 mm, respectively, versus 0.048 mm, both $p \leqslant 0.001$). No significant difference between the two hypertensive groups	N/A
Gil et al (2008)	Hypertensive children identified after screening school children and normotensive controls (not mentioned how recruited)	Unadjusted CIMT greater in hypertensive versus controls (0.62 versus 0.50 mm, $p < 0.05$), compared by t-test	N/A
Lande et al (2006)	Newly diagnosed untreated hypertensive children recruited from hypertension or nephrology clinics. Age, sex, and BMI-matched healthy controls recruited from a general paediatric clinic	Average CIMT higher in the hypertensive group compared with controls (0.67 versus 0.63 mm, respectively, $p = 0.45$). No significant correlation between office BP and CIMT, but significant correlation seen between ABPM parameters in hypertensive group and CIMT, e.g., daytime systolic index ($r = 0.57$, $p = 0.03$), daytime mean SBP ($r = 0.43$, $p = 0.03$)	
Litwin et al (2006)	Newly diagnosed untreated children with essential hypertension referred to secondary care. Healthy control group recruited from schools	CIMT significantly higher in hypertensive patients versus controls in both boys (0.47 versus 0.43, respectively, $p = 0.0001$) and girls (0.47 versus 0.41, $p = 0.0001$)	Multivariable linear regression: BP not significant in model as predictor of CIMT
Sorof et al (2003) (Pediatr)	Newly diagnosed untreated hypertensive children referred to secondary care	CIMT not correlated with BP. Subjects in upper quartile of CIMT values did not have a significantly different BP compared with those in the bottom three quartiles	
Loureiro et al (2013)	Hypertensive children recruited from hospital nephrology and endocrinology clinics	SBP index and DBP index significantly correlated with CIMT ($r = 0.323$, $p < 0.01$ and $r = 0.304$, $p < 0.05$, respectively).	Multivariable linear regression: neither SBP index nor DBP index significantly associated with CIMT (model adjusts for BMI, serum aldosterone, and angiotensin/renin ration)
Sorof et al (2003) (Pediatr nephrol)	Hypertensive children recruited from both hypertension clinics and a school-based BP screening study. Control normotensive subjects recruited from a school-based study	Hypertensive subjects had greater CIMT compared with normotensives (0.62 versus 0.53 mm $p < 0.0001$). This effect remained when subjects were split into BMI overweight/normal weight groups. Using univariate linear regression, both SBP and DDP were significantly positively associated with CIMT ($r = 0.3$, $p = 0.001$ and $r = 0.22$, $p = 0.044$, respectively)	Multivariable linear regression: SBP was no longer associated with CIMT (model adjusting for age and BMI)
Studies based on children identified as overweight or obese, either from clinic or following population screening (± a normal BMI comparison group)			
Rheinehr et al (2007)	Consecutive patients from the outpatient obesity clinic	N/A	Multivariable linear regression: increase of 0.00018 and 0.00013 mm CIMT per increase of 1 mmHg in SBP and DBP, respectively ($p < 0.0001$ and 0.0104, respectively), adjusting for age and sex only
Hacihamdioglu et al (2011)	Consecutive patients recruited from hospital obesity clinics. Also, healthy age, sex, and pubertal stage-matched controls (not specified from where controls were recruited)	In the obese group, CIMT significantly correlated with SBP ($r = 0.19$, $p = 0.04$) but not DBP	"Linear logistic" regression: BP not significantly associated with CIMT

Ozcetin et al (2012)	Obese children recruited from secondary-care obesity clinics. Control group of "similar" age and sex distribution without obesity recruited (not specific how or from where)	Analysing all subjects together, SBP significantly correlated with CIMT ($r = 0.306$, $p < 0.05$), DBP not correlated	N/A
Casariu et al (2011)	Obese and non-obese children recruited (not specified how or from where)	Both SBP and DBP significantly correlated with CIMT ($r = 0.51$ and 0.41, respectively, p both <0.05)	N/A
Simsek et al (2010)	Obese and non-obese control subjects (not specified how or from where either group recruited)	DBP centile significantly correlated with CIMT ($r = 0.42$, $p < 0.001$). SBP not correlated	Multivariable linear regression: neither SBP nor DBP significantly associated with CIMT
Fang et al (2010)	Obese and non-obese control subjects (not specified how or from where either group recruited)	Both SBP and DBP significantly correlated with CIMT ($r = 0.27$, $p = 0.006$ and $r = 0.21$, $p = 0.033$, respectively)	Multivariable linear regression: neither SBP nor DBP significantly associated with CIMT
Yilmazer et al (2010)	Obese children recruited from paediatric cardiology clinics (reason for attending clinic not specified). Control subjects recruited from the group investigated for physiological murmur	Both SBP and DBP positively correlated with CIMT ($r = 0.38$, $p = 0.001$ and $r = 0.32$, $p = 0.005$, respectively)	Multivariable linear regression: neither SBP nor DBP significantly associated with CIMT
Elkiran et al (2013)	Healthy subjects recruited from random selection of primary schools in one city (not clear how the study population was selected from the overall population). Split into obese, overweight, and control groups based on BMI	In the obese group only, DBP was significantly correlated with CIMT ($r = 0.266$, $p = 0.03$)	Multivariable linear regression (again in obese group only): DBP is significantly associated with CIMT ($\beta = 0.301$, $p = 0.031$) after adjustment for SBP, BMI, waist circumference, fat mass, and CRP
Leite et al (2012)	Obese and overweight children recruited from hospital paediatric obesity clinics. Normal-weight control group recruited from same hospital, with "non-organic" disease	DBP positively correlated with CIMT ($r = 0.266$, $p = 0.001$), SBP not associated (data not presented)	Multivariable linear regression: DBP no longer significantly associated with CIMT (adjusting for waist circumference and BMI)
Miscellaneous studies			
Tamura et al (2011)	Healthy children seen at a hospital for a "health check-up"	DBP positively correlated with CIMT in girls only ($r = 0.563$ $p = 0.045$). SBP not correlated with CIMT in boys or girls	Multivariable linear regression: no association seen between BP and CIMT
Krebs et al (2009)	Consecutive patients seen in paediatric hospital clinics for hypercholesterolaemia, and a separate group of "healthy" children (not specified where recruited from)	In children with normal cholesterol, those with SBP >90th centile compared with population norms had mean CIMT not significantly different to those with BP <90th centile (0.542 versus 0.546 mm $p = 0.91$) In hypercholesterolaemic children, those with SBP >90th centile had significantly greater CIMT compared with those with SBP < 90th centile (0.594 versus 0.545 mm, $p = 0.006$). Also analysed using Spearman's correlation of SBP index with CIMT. In hypercholesterolaemic children significant correlation seen ($r = 0.358$, $p = 0.001$). No significant correlation seen in "control" children	N/A
Yang et al (2007)	Not specified from where or how subjects were recruited	In the younger age group, no significant difference in SBP or DBP in the normal versus abnormal CIMT groups. In the older age group, both SBP and DBP significantly higher in the abnormal CIMT groups (SBP: 116.8 versus 103.5, $p = 0.001$, DBP 77.4 versus 68.5, $p = 0.01$)	

ABPM = ambulatory blood pressure measurement; BMI = body mass index; BP = blood pressure; CIMT = carotid itima media thickness; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation

however in seven of these that performed statistical adjustment to control for potential confounding factors, only two found a significant association after adjustment.

Rheiner et al[21] recruited patients from a paediatric obesity clinic. In a multiple regression model adjusting for age and sex, both systolic blood pressure and diastolic blood pressure were significantly associated with carotid intima-media thickness. Leite et al[22] also recruited patients from a hospital obesity clinic, and recruited normal-weight controls from hospital clinics for "non-organic disease" such as attention deficit hyperactivity disorder and learning disability. They found that diastolic blood pressure but not systolic blood pressure was correlated with carotid intima-media thickness, but this association did not remain significant after adjusting for waist circumference and body mass index.

Both Hacihamdioglu et al[23] and Ozcetin et al[24] recruited subjects from obesity clinics and normal-weight controls. Hacihamdioglu et al found that in the obese group only, carotid intima-media thickness was positively correlated with systolic blood pressure but not diastolic blood pressure ($r = 0.19$, $p = 0.04$), but after adjustment for confounders this association did not remain significant. Ozcetin et al found that systolic blood pressure, but not diastolic blood pressure, was correlated with carotid intima-media thickness, but no attempt was made to adjust for confounders in this study.

Three studies recruited both obese and normal-weight children, but did not specify how each group was recruited. Casariu et al[25] found that in the obese group only, both systolic blood pressure and diastolic blood pressure were positively correlated with carotid intima-media thickness. Simsek et al[26] found that in the combined sample, diastolic blood pressure but not systolic blood pressure was positively correlated with carotid intima-media thickness ($r = 0.42$, $p < 0.001$), but this association did not remain in multiple linear regression analyses. Fang et al[27] similarly found that both systolic blood pressure and diastolic blood pressure were significantly associated with carotid intima-media thickness, but these associations did not remain after adjustment for potential confounders in a multiple regression model.

Among obese children recruited from a paediatric cardiology clinic[28], carotid intima-media thickness was positively correlated with both diastolic blood pressure and systolic blood pressure, but this association disappeared when adjustment was made in a multiple regression model. In obese children recruited from primary schools[29], diastolic blood pressure was positively correlated with carotid intima-media thickness ($r = 0.266$, $p = 0.03$). This association remained significant after adjustment for potential confounders ($\beta = 0.301$, $p = 0.031$).

Miscellaneous studies

Tamura et al[30] found that diastolic blood pressure, but not systolic blood pressure, was positively correlated with carotid intima-media thickness in girls only. This association did not remain significant after adjustment in multiple regression models. Krebs et al[31] recruited children with hypercholesterolaemia and a group of healthy controls. They found that in the control group those with higher systolic blood pressure did not have significantly different carotid intima-media thickness compared with the normotensive group. In the hypercholesterolaemic group, those with systolic blood pressure above the 90th centile had higher carotid intima-media thickness than those with lower systolic blood pressure (0.594 versus 0.545 mm, $p = 0.006$). Yang et al[32] found that at ages 10–18 years, systolic blood pressure and diastolic blood pressure were significantly higher among those with thickened carotid intima-media thickness, but this association was not detected in younger age groups.

Discussion

This review set out to characterise the relationship between blood pressure and atherosclerosis in children, with the aim of identifying possible indications and thresholds for the pharmaceutical management of paediatric hypertension. On the basis of the 28 studies included, there is consistent evidence for a positive association between blood pressure and carotid intima-media thickness among healthy, hypertensive, and overweight children, in unadjusted analyses. A similar relationship is well-described in adults,[3,32] and hypertension is recognised as a major risk factor for the development of atherosclerosis in the adult population.

Many of the studies included in this review attempted to control for potential confounding factors by adjusting for them in multivariable models. The evidence is mixed for an association between blood pressure and carotid intima-media thickness independent of other cardiovascular risk factors. In the population-based studies of healthy children, the majority – six out of eight – found a positive association between blood pressure and carotid intima-media thickness that remained after adjustment for possible confounders, most commonly obesity and age. In studies of hypertensive and obese populations however, the positive association between blood pressure and carotid intima-media thickness

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generally disappeared after adjusting for other cardiovascular risk factors.

The lack of positive associations after adjustment for confounding factors in some studies may suggest that blood pressure acts as a surrogate marker for another causal factor in the development of atherosclerosis, for example obesity. It is worth noting however that the group of population-based studies where this association persisted after adjustment for other risk factors were in general the largest and of the highest quality. It may therefore be possible that the studies that did not find an association in adjusted analyses were not sufficiently powered to do so, especially given the strong correlation between multiple cardiovascular risk factors which could result in over-adjustment.

The large group of studies included here varies widely in both quality and methodology. The patient groups included are heterogeneous, and both carotid intima-media thickness and blood pressure have been measured in many different ways. As a result of this, it was not possible to perform any quantitative meta-analysis of the results. Conclusions are also limited by the use of carotid intima-media thickness as a proxy for cardiovascular risk in children; however, cardiovascular events are rare in young people and more robust markers of future cardiovascular are generally unavailable.

In terms of clinical practice, this review does demonstrate some evidence that higher blood pressure is associated with increased carotid intima-media thickness even during childhood; however, with the present data, it is not clear whether this damage to the vasculature is of any clinical significance, as there are limited data linking carotid intima-media thickness in youth to cardiovascular events in later life. In their 2013 review, Juhola et al[33] found that, although hypertension in adulthood was clearly associated with increased carotid intima-media thickness, this did not seem to be influenced by the presence or absence of childhood hypertension. This does not completely negate the influence of childhood blood pressure however, as consistent tracking of hypertension form childhood to adult life is well described, meaning that childhood hypertension may well influence atherosclerosis risk in adult life via an increased risk of adult hypertension.[34] Furthermore, the correlation between childhood and adult hypertension may have contributed to insufficient study power to detect independent effects of the two in studies that tried to do so.

Another aim of this review was to attempt to define at what point blood pressure should be managed with anti-hypertensive pharmaceutical therapy in childhood. There are data to suggest that individuals who are hypertensive in childhood, whose blood pressures normalise by adulthood, have a carotid intima-media thickness that is no worse than those who were never hypertensive.[33] Although this may indicate that early treatment of hypertension in childhood is worthwhile, to intervene and prevent high blood pressure tracking into later life, the mechanism of the relationship between blood pressure and carotid intima-media thickness remains unclear. In addition, the studies included in this review largely assumed a linear association between carotid intima-media thickness and blood pressure, and none explicitly tested for a non-linear relationship or threshold effect; because of this it is not clear at which threshold carotid intima-media thickness begins to be adversely affected, and the question of when to treat remains unanswered. Further study is needed to answer this question. This would require a large cohort of children with a wide range of blood pressure measurements, but would certainly help guide the decision-making process with regards to anti-hypertensive therapy in children.

Our systematic review was limited by the use of only databases such as MEDLINE and EMBASE. Although we feel this would have included the majority of suitable studies, it is possible that some were missed. We did not attempt to include grey literature, or unpublished studies. We were not able to assess for the effect of publication bias on our results.

In conclusion, our review gave mixed results. On the basis of the largest and highest-quality population-based studies, there is consistent evidence that higher blood pressures are associated with increased carotid intima-media thickness in childhood, even after adjusting for other cardiovascular risk factors. Further study is needed to consolidate this evidence, and further delineate the values of blood pressure at which a clinically significant increase in carotid intima-media thickness is seen. If the level can be defined beyond which blood pressure starts to acutely affect carotid intima-media thickness, this would greatly aid clinicians in initiating pharmacological treatment of hypertensive for cardiovascular disease in children and young people.

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reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

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Conflicts of Interest

None.

Supplementary materials

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