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ORIGINAL RESEARCH

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The association of blood pressure, body mass index and carotid intima-media thickness as childhood predictors of cardiovascular disease risk: A systematic review and meta-analysis

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Abstract

Background and Aims: Blood pressure, body mass index (BMI), and carotid intima-media thickness (CIMT) are well-known independent predictors of cardiovascular disease especially in adulthood. However, there is insufficient evidence regarding the statistical significance of the relationship between childhood CIMT, blood pressure and BMI. This systematic review and meta-analysis was therefore conducted to ascertain the relationship.

Methods: This systematic review and meta-analysis was reported in accordance with the PRISMA statement. Three electronic databases were searched, namely EMBASE, MEDLINE and the Cochrane Library. Data were extracted independently by two review authors. Quantitative data were analyzed using Review Manager.

Results: The meta-analysis was conducted using a random effects model and standard mean difference. The results of the meta-analysis indicated a statistically significant difference in CIMT of 0.86 (95% CI: 0.41–1.31) between normotensive versus hypertensive children. Again, overweight and moderately obese children had higher CIMT values as compared to normal weight children with a pooled standard mean difference of 0.72 (95% CI: 0.24–1.20) and 2.75 (95% CI: 0.73–4.77) respectively. The pooled standard mean difference of systolic and diastolic blood pressures was found to be 2.44 (95% CI: 1.69–3.19) and 1.28 (95% CI: 0.65–1.92) respectively between normal weight and overweight/obese children.

Conclusion: The meta-analysis found a significant difference in CIMT between normotensive and hypertensive children, with overweight and moderately obese children having higher CIMT values. Thus, conducting CIMT screening for obese or overweight children and children with increased blood pressure can provide valuable information about their cardiovascular disease risk.

KEYWORDS

blood pressure, body mass index, carotid intima-media thickness, carotid ultrasound

1 | INTRODUCTION

Cardiovascular diseases (CVDs) cause more than 18.5 million deaths globally, making up over 31% of all deaths.[1] Atherosclerosis is the dominant form of CVD characterized by the accumulation of lipids and inflammation in the major arteries.[2,3]

Childhood and adolescent health behaviors have a direct effect on cardiovascular health in adulthood. Traditional risk factors for CVD, including hypertension, obesity, dyslipidemia, and unhealthy diets often stem from childhood or adolescence and subsequently worsens with advancing age. It is reported that the CVD health profile of most children and adolescents are not ideal.[4]

Therefore, it is of great public health importance to focus on the burden and trend of CVD during childhood. Early identification of children at risk for atherosclerosis allows for timely management to reduce advancement. The American Heart Association recommends eight Essentials of Life which must be closely monitored, including four health behaviors. The four easily measurable intermediate health factors are body mass, blood pressure, blood lipids, and blood glucose.[5] Among the four recommended risk parameters, body mass and blood pressure are much easier to determine because no invasive testing or blood analysis is required. In addition, the American Heart Association also recommends the noninvasive assessment of atherosclerosis in children with unhealthy CVD profiles. The carotid intima media thickness (CIMT) has been suggested as a viable tool for this purpose.[6] There is however the need for more research to ensure standardization and availability of normative data before the CIMT can be adopted into clinical practice.

CIMT assessment can be performed with B-mode ultrasound imaging as a relatively inexpensive, safe technique and is suitable for large-scale population studies.[7] CIMT is a useful subclinical indicator of atherosclerosis and predictive of cardiovascular events in the adult population.[8] Childhood diseases often associated with increased CIMT include chronic kidney disease,[9] type I diabetes,[10] familial hyperlipidemia,[11] obesity, and hypertension,[12] among others.

Obesity and hypertension are the main readily measurable, noninvasive physically assessed risk factors of CVD that are CIMT-related. Yet there is insufficient evidence of a statistically significant relationship between body mass, blood pressure and CIMT. Day, Park and Kinra,[13] conducted a systematic review on the relationship amongst these parameters, but there was no meta-analysis on the statistical significance of the relationship. Therefore, the purpose of this review is to assess the statistical significance of the relationship between body mass, blood pressure and CIMT.

2 | DESIGN AND METHODOLOGY

The systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14]

3 | ETHICS

Being a systematic review and meta-analysis of already existing data, ethical approval was not required for this study. There was also no need for informed consent.

3.1 | Data source and search strategy

Between 18th and 19th July 2023, three electronic databases were searched for relevant articles: Cochrane Library, Embase, and Medline databases. A combination of Medical Subject Headings (MeSH) and key words for carotid intima-media thickness and blood pressure in pediatrics were used. The chosen search phrases were merged using Boolean operators "AND" and "OR" to identify papers. No date restrictions were applied to the search. The data were exported to and managed in Endnote software version 20.2 The reference lists of the selected publications and Google scholar were searched to identify additional articles. The PICO (Population, Intervention, Comparator, Outcome) framework was used as a guide to develop the systematic review question (See Table 1).

3.2 | Outcomes

The primary outcome was to ascertain whether there is significant increase in CIMT with increasing blood pressure in children between the ages of 9 and 16 years. The secondary outcome was to ascertain whether there is significant increase in CIMT with increasing BMI in children between the ages of 9 and 16 years.

3.3 | Inclusion and exclusion criteria

This review included studies on CIMT in children, blood pressure measurements, demographic information, and control groups for analysis. Exclusion criteria included carotid ultrasound studies without measurements of CIMT and studies examining the relationship between CIMT and specific pediatric diseases. The criteria also excluded papers focusing on carotid ultrasound but not CIMT measurements. Papers not written in the English language were also excluded.

TABLE 1 PICO plan for the review.

Population (P)	Children
Intervention (I)	Carotid intima-media thickness measurement in children with high blood pressure.
Comparator (C)	Carotid intima-media thickness measurement in children with normal blood pressure.
Outcome (O)	Higher carotid intima-media thickness values.

3.4 | Study selection

After removal of duplicates, two review authors (BAA and YAW) independently screened the titles and abstracts of the articles to determine their relevance. Subsequently, the two reviewers reached a consensus over the results of the screening process. The full texts of articles that were identified as potentially relevant during the abstract assessment were obtained and evaluated by the same independent reviewers according to the predefined inclusion criteria. Articles that did not fit the inclusion criteria were eliminated from the analysis, and the reasons for their exclusion were appropriately justified. Any conflicts that arose between the two authors of the review were resolved through collaborative dialogue. The procedure of selecting review articles is further elucidated in the PRISMA flow diagram (Figure 1).

3.5 | Data extraction

The two authors (BAA and YAW) independently extracted pertinent data from the articles to be included in analysis. The data gathered included the name of the author, the year of publication, the country where the study was conducted, the study design, the number of participants, the size of the cohort, the measurements of blood pressure (both systolic and diastolic), the body mass index (BMI) as well as the CIMT values for each cohort (mean and standard deviation).

3.6 | Quality assessment

The quality assessment was performed by BAA. The quality of the included studies was assessed using the appropriate tool for quantitative studies provided by the Joanna Briggs Institute (JBI) Critical Appraisal Checklist (cohort studies). The risk of bias in studies was set at a cut-off point of 60%.

3.7 | Data analysis

Meta-analysis was employed for studies that reported quantitative data. The meta-analysis was performed using Review Manager version 5.

A random-effects meta-analysis was used to calculate the pooled data with 95% confidence intervals (CIs) because it allows for the possibility that studies in the meta-analysis have heterogeneous effects. The extracted data were utilized to compute the standard mean difference (SMD).[15] The studies incorporated in the analysis utilized a standardized scale but different techniques to assess the outcome. The heterogeneity among the studies was estimated using the I^2 index, with values classified as: "no heterogeneity (0%)", "low heterogeneity (25% to 50%)", "moderate heterogeneity (51%–74%)", and "high heterogeneity (greater than or equal to 75%)".[15] Forest plots were generated. Probability values below 0.05 were considered statistically significant.

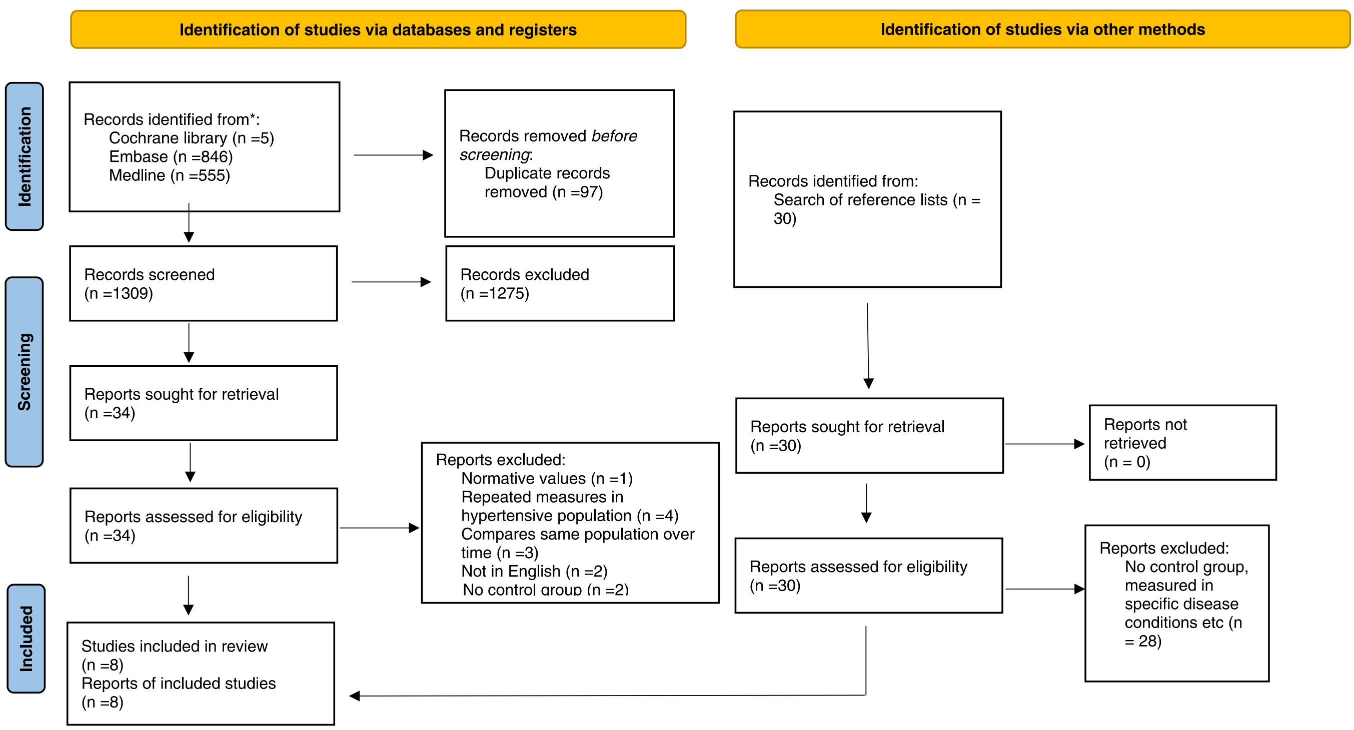

FIGURE 1 Prisma flow chart.

4 | RESULTS

The electronic database searches yielded 1,406 articles. A total of 97 articles were excluded due to duplication. The titles and abstracts of the remaining articles were screened, and 1,275 articles were excluded. The full texts of the remaining 34 articles were reviewed for eligibility of which 6 were found to be eligible for inclusion.

The hand search also identified 30 articles of which two were deemed relevant for inclusion. Finally, a total of 8 studies were included in this review (See Figure 1).

4.1 | Study characteristics

The 8 studies in this review enrolled a total of 1,013 participants. The studies were published between 2003 and 2022. All the studies were cross-sectional.

4.2 | Participants

The studies included in the analysis had sample sizes that varied from 32[16] to 254.[17] Except for one study that provided the mean age of participants as 14.0 ± 3.32[18] the remaining studies did not include information regarding the overall mean age of participants. The majority of studies provided reports regarding the average ages categorized by participant group.[17–23] The mean ages of the population, both as a whole and within their respective groups of normotensive and hypertensive individuals, were not reported in a particular study.[16] In general, the age range of the participants included in this review varied from 9.8 ± 4.1 years[17] to 15.8 ± 0.6 years[20] for individuals with normal blood pressure, and from 10.5 ± 4.0 years[17] to 16.5 ± 1.0 years[20] for individuals with high blood pressure.

4.3 | Settings

The studies included in this review were of European, Asian, and American origin (See Figure 2). No studies were undertaken in Africa or the Middle East. Concerning the sample selection in the research, the majority of the studies (*n* = 5) obtained their sample from a specialized clinic catering to pediatric patients with hypertension.[17,19,21–23] The remaining studies (3) relied on screening conducted within school settings.[16,18,20]

The results obtained from the research included in the analysis exhibited a range of outcomes. Initially, all the included studies reached a consensus about the observation that the hypertensive cohorts exhibited greater weight and height in comparison to the normotensive controls.[16–23] Once again, it was observed that the groups with hypertension exhibited larger values of CIMT in comparison to the control group. Two studies found that, there was no statistically significant difference in CIMT between the two groups that were examined.[19,21] However, the remaining studies did not provide any commentary on statistical significance. Instead, they simply confirmed the observation that individuals with hypertension had higher CIMT compared to those without hypertension.[16–18,20,22,23] Table 2 below illustrates the key findings in the included papers.

4.4 | CIMT in hypertensive and normotensive patients

Figure 3 shows the forest plot of CIMT in hypertensive and normotensive patients. Eight studies with 520 hypertensive and 495 normotensive children were analyzed.[16–23] The pooled standard mean difference in CIMT between hypertensive and normotensive children was 0.83 (95% CI: 0.47–1.19) by using a random effects model. There was a high heterogeneity amongst the studies ($I^2 = 84\%$, $p < 0.001$).

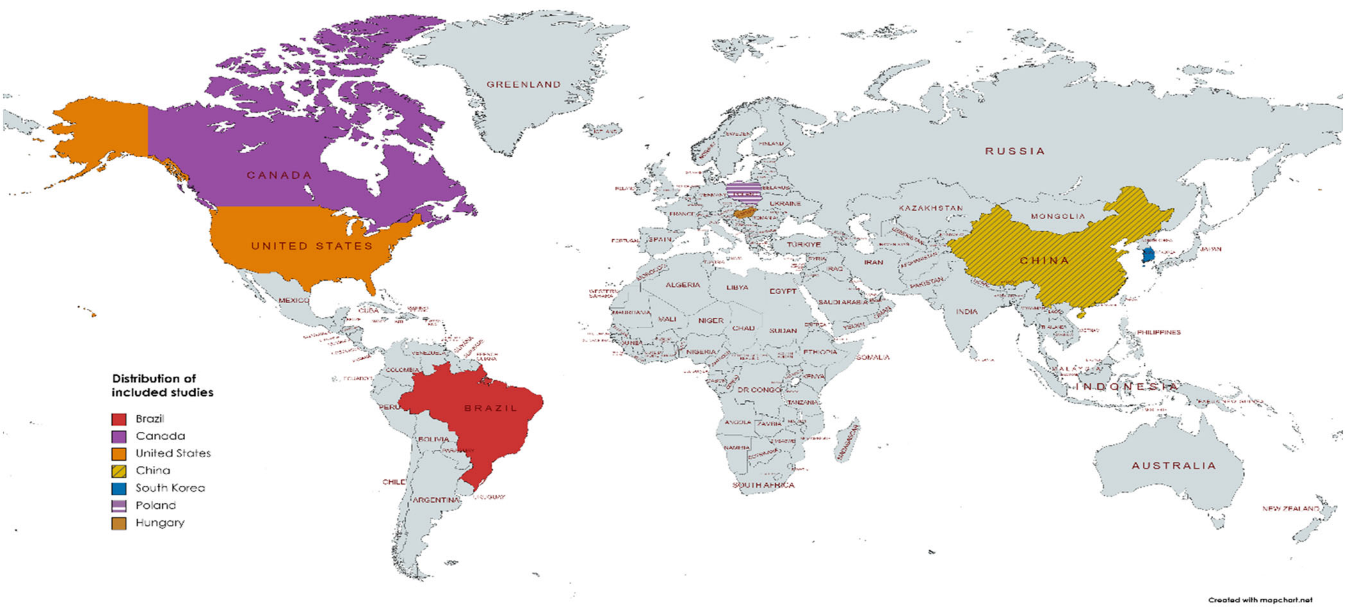

FIGURE 2 Map showing the distribution of included studies.

TABLE 2 Showing the key findings in the included studies.

Author	Year	Country	Study design	Aim	Sample Normotensive (NORM) Hypertensive (HPTN)	CIMT measurement technique	Key findings
BARONCINI, L	2017	BRAZIL	Cross-sectional	To assess CIMT as an early marker of atherosclerosis and vascular damage in hypertensive children and adolescents compared with non-hypertensive controls.	254 NORM: 121 HPTN:133	Manual	• Hypertensive children were either overweight or obese. • Hypertensive children had higher CIMT values compared to controls, regardless of weight, and BMI • After multiple linear regression CIMT remained independently associated with hypertension ($p < 0.001$)
LIU, W	2022	CHINA	Cross-sectional	To non-invasively investigate changes in cardiovascular structure and function in children with hypertension.	66 NORM:32 HPTN: 34	Automated	• There is a clear difference in CIMT between hypertensives and controls, though the difference may not be statistically significant. • Hypertension has an effect on target organ damage in children. The heart, and blood vessels of children with hypertension undergo functional and structural changes as proven by Doppler ultrasound.
PHILIPS, A	2015	CANADA	Cross-sectional	To identify the relationship between childhood BP and arterial markers of arteriosclerotic progression.	104 NORM:85 HPTN: 21	Manual	• Body mass and BMI were significantly elevated in high blood pressure group compared to the normal group. • There was no statistically significant difference between CIMT in high blood pressure and normal blood pressure groups. • High blood pressure individuals had significantly higher pulse wave velocity compared to the normal blood pressure group.
SKRZYPCZYK, P	2021	POLAND	Cross-sectional	To assess relation between subclinical inflammation and arterial damage in pediatric patients with Hypertension	164 NORM: 45 HPTN: 119	Manual	• BMI and BMI Z scores higher in hypertensive. • A number of the hypertensive group were also either overweight or obese. • Hypertension group had higher PWV, PWV Z score, CIMT and CIMT z score
SOROF, J	2003	USA	Cross-sectional	To determine: whether cIMT is increased in hypertensive compared with normotensive children and the extent to which overweight status modifies the relation-ship between hypertension and cIMT.	86 NORM: 33 HPTN: 53	Manual	• Hypertensive participants tended to be overweight when compared to normotensives. • Hypertensive subjects had higher CIMT as compared to normotensives (significant difference). • subgroup analysis of hypertensive and weight status showed that hypertensive- overweight

(Continues)

TABLE 2 (Continued)

Author	Year	Country	Study design	Aim	Sample Normotensive (NORM) Hypertensive (HPTN)	CIMT measurement technique	Key findings
							subjects had higher CIMT than normotensive overweight and normotensive normal weight. • Multiple regression comparing age, BMI SBP showed that only BMI is associated with CIMT
TAE, G	2008	KOREA	Cross-sectional	Investigate whether CIMT and pulse wave velocity are useful diagnostic markers in predicting early atherosclerosis in hypertensive adolescents	32 NORM: 17 HPTN: 15	Manual	• Hypertensive subjects had significantly higher weight, height, BMI obesity index and arm circumference, fat mass. • Hypertensives had significantly greater CIMT values than normotensives
LITWIN, M	2006	POLAND	Cross-sectional	Determine prevalence of left ventricular hypertrophy and CIMT in Caucasian children with Hypertension	175 NORM: 103 HPTN: 72	Manual	• standardized values of CIMT and Femoral intima media thickness(fIMT) were significantly higher in hypertensives than in controls.
PALL, D	2010	HUNGARY	Cross-sectional	Assess if there is a difference between intima–media thickness and the left ventricular mass index in healthy non-hypertensive, white-coat hypertensive and sustained hypertensive adolescents.	132 NORM: 59 HPTN: 73	Manual	• BMI, Height, weight are higher in hypertensive groups than normotensives. • CIMT was higher in hypertensives than in normotensives. Left ventricular mass index significantly higher in sustained hypertension groups.

Study or Subgroup	Hypertensive children Mean	SD	Total	Normotensive children Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Philips et al, 2015	0.43	0.05	21	0.42	0.06	85	12.5%	0.17 [-0.31, 0.65]
Liu et al , 2022	0.46	0.05	34	0.44	0.05	32	12.4%	0.40 [-0.09, 0.88]
Skrzypczyk et al , 2021	0.46	0.07	119	0.43	0.07	45	13.9%	0.43 [0.08, 0.77]
Pall et al, 2010	0.54	0.12	73	0.48	0.1	59	13.9%	0.53 [0.19, 0.88]
Baroncini et al, 2017	0.46	0.05	133	0.42	0.05	121	14.8%	0.80 [0.54, 1.05]
Sorof et al , 2003	0.62	0.11	53	0.53	0.06	33	12.7%	0.95 [0.49, 1.41]
Litwin et al, 2006	0.47	0.05	72	0.42	0.035	103	14.1%	1.19 [0.86, 1.52]
Tae et al , 2008	0.62	0.013	15	0.5	0.04	17	5.7%	3.83 [2.61, 5.05]
Total (95% CI)			**520**			**495**	**100.0%**	**0.83 [0.47, 1.19]**

Heterogeneity: Tau² = 0.21; Chi² = 44.83, df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.48 (P < 0.00001)

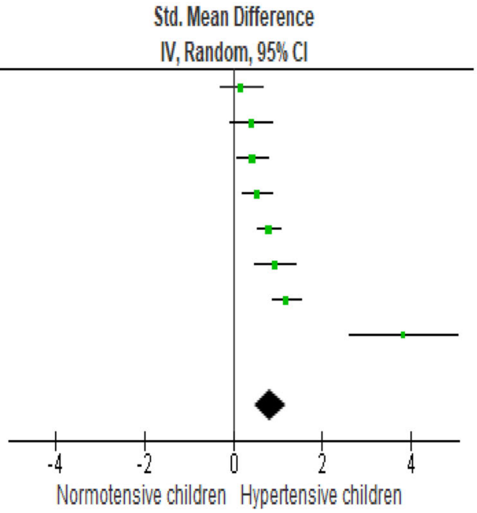

FIGURE 3 Showing plot of CIMT in hypertensive and normotensive children.

Study or Subgroup	BMI Hypertensive children Mean	SD	Total	BMI Normotensive children Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baroncini et al, 2017	21.9	6.3	133	19.9	4.4	121	15.3%	0.36 [0.12, 0.61]
Skrzypczyk et al , 2021	24.7	5.1	119	22.2	4	45	13.9%	0.52 [0.17, 0.86]
Sorof et al , 2003	27.9	6.9	53	22.7	4.8	33	12.3%	0.83 [0.38, 1.29]
Pall et al, 2010	23.4	4.2	73	20.2	2.7	59	13.8%	0.88 [0.52, 1.24]
Litwin et al, 2006	24.45	4.1	72	20	3.6	103	14.3%	1.16 [0.84, 1.49]
Liu et al , 2022	22.4	3.9	34	18	2.8	32	11.2%	1.27 [0.74, 1.81]
Tae et al , 2008	26.6	4.2	15	21.2	3	17	7.8%	1.46 [0.67, 2.25]
Philips et al, 2015	26.4	7.1	21	19.8	3.6	85	11.4%	1.46 [0.94, 1.98]
Total (95% CI)			**520**			**495**	**100.0%**	**0.94 [0.64, 1.24]**

Heterogeneity: Tau² = 0.14; Chi² = 31.32, df = 7 (P < 0.0001); I² = 78%
Test for overall effect: Z = 6.11 (P < 0.00001)

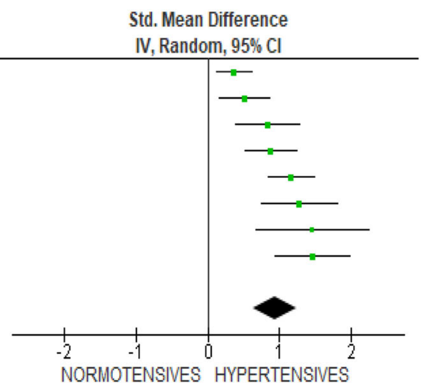

FIGURE 4 Showing BMI in hypertensive and normotensive children.

4.5 | BMI in hypertensive and normotensive children

Figure 4 shows the forest plot of BMI in hypertensive and normotensive children. Eight studies with 520 hypertensive and 495 normotensive children were utilized.[16–23] The pooled standard mean difference in BMI between hypertensive and normotensive children was 0.94 (95% CI: 0.64–1.24) by using a random effects model. There was a high between study heterogeneity ($I^{2=}$ 78%, $p<$ 0.001).

4.6 | Systolic blood pressure in hypertensive and normotensive children

Figure 5 shows the forest plot of systolic blood pressure in hypertensive and normotensive children. Seven studies reported on the mean blood pressure of the two cohorts with 387 hypertensive and 374 normotensive children.[16,18–23] The pooled standard mean difference in systolic blood pressure between hypertensive and normotensive children was 2.44 (95% CI: 1.69–3.19) by using a random effects model. There was a high between study heterogeneity ($I^{2=}$ 93%, $p < 0.001$).

4.7 | Diastolic blood pressure in hypertensive and normotensive children

Figure 6 shows the forest plot of diastolic blood pressure in hypertensive and normotensive children. Seven studies reported on the mean blood pressure of the two cohorts with 387 hypertensive and 374 normotensive children.[16,18–23] The pooled standard mean difference in diastolic blood pressure between hypertensive and normotensive children was 1.28 (95% CI: 0.65–1.92) by using a random effects model. There was a high between study heterogeneity ($I^{2} =$ 93%, $p < 0.001$).

4.8 | CIMT in overweight and normal weight children

Figure 7 shows the forest plot of CIMT in overweight and normal weight children. Three studies ([18,20,22]) reported on BMI values

Study or Subgroup	Hypertensives Mean	Hypertensives SD	Hypertensives Total	Normotensives Mean	Normotensives SD	Normotensives Total	Weight	Std. Mean Difference IV, Random, 95% CI
Skrzypczyk et al , 2021	132.3	12.5	119	122	10.8	45	15.2%	0.85 [0.49, 1.21]
Litwin et al, 2006	135.5	12.5	72	114	10.5	103	15.2%	1.88 [1.52, 2.25]
Tae et al , 2008	148.1	6.5	15	115.9	15.9	17	12.5%	2.52 [1.57, 3.48]
Liu et al , 2022	144.4	16.3	34	106.5	11.3	32	14.0%	2.66 [1.98, 3.33]
Pall et al, 2010	144.8	11.1	73	114.9	10	59	14.8%	2.80 [2.31, 3.28]
Sorof et al , 2003	139	10	53	113	7	33	14.3%	2.87 [2.25, 3.49]
Philips et al, 2015	111	7	21	91	5	85	13.9%	3.65 [2.96, 4.34]
Total (95% CI)			**387**			**374**	**100.0%**	**2.44 [1.69, 3.19]**

Heterogeneity: Tau² = 0.93; Chi² = 85.10, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.37 (P < 0.00001)

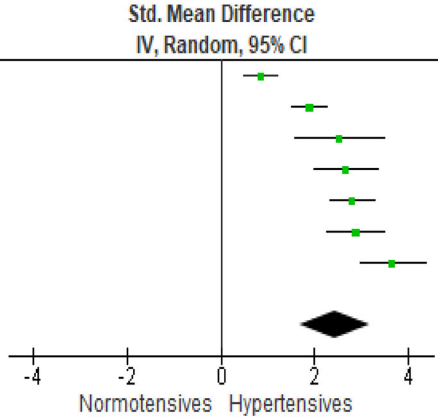

FIGURE 5 Showing systolic blood pressure in hypertensive and normotensive children.

Study or Subgroup	Hypertensives Mean	Hypertensives SD	Hypertensives Total	Normotensives Mean	Normotensives SD	Normotensives Total	Weight	Std. Mean Difference IV, Random, 95% CI
Tae et al , 2008	73.3	8	15	72.6	10.5	17	13.2%	0.07 [-0.62, 0.77]
Skrzypczyk et al , 2021	77.3	10.1	119	71.7	8.6	45	15.0%	0.57 [0.23, 0.92]
Litwin et al, 2006	63.5	11	72	58	7.5	103	15.1%	0.60 [0.29, 0.91]
Sorof et al , 2003	77	9	53	69	4	33	14.5%	1.06 [0.59, 1.52]
Liu et al , 2022	85.6	14.1	34	65.9	6	32	13.9%	1.78 [1.20, 2.35]
Pall et al, 2010	82.4	8.3	73	66.8	8.9	59	14.7%	1.81 [1.40, 2.22]
Philips et al, 2015	71	5	21	55	5	85	13.5%	3.18 [2.53, 3.82]
Total (95% CI)			**387**			**374**	**100.0%**	**1.28 [0.65, 1.92]**

Heterogeneity: Tau² = 0.68; Chi² = 83.76, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.94 (P < 0.0001)

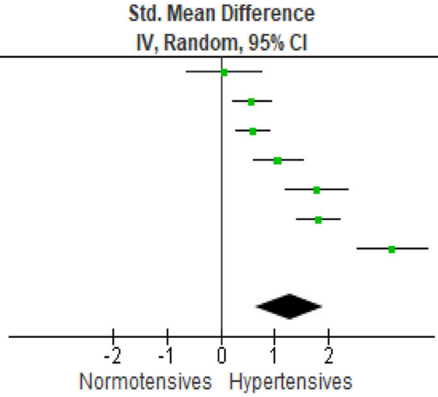

FIGURE 6 Showing diastolic blood pressure in hypertensive and normotensive children.

Study or Subgroup	Overweight Mean	Overweight SD	Overweight Total	Normal weight Mean	Normal weight SD	Normal weight Total	Weight	Std. Mean Difference IV, Random, 95% CI
Skrzypczyk et al , 2021	0.46	0.07	119	0.43	0.07	45	33.2%	0.43 [0.08, 0.77]
Pall et al, 2010	0.54	0.12	73	0.48	0.1	59	33.0%	0.53 [0.19, 0.88]
Litwin et al, 2006	0.47	0.05	72	0.42	0.035	103	33.8%	1.19 [0.86, 1.52]
Total (95% CI)			**264**			**207**	**100.0%**	**0.72 [0.24, 1.20]**

Heterogeneity: Tau² = 0.15; Chi² = 11.79, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 2.96 (P = 0.003)

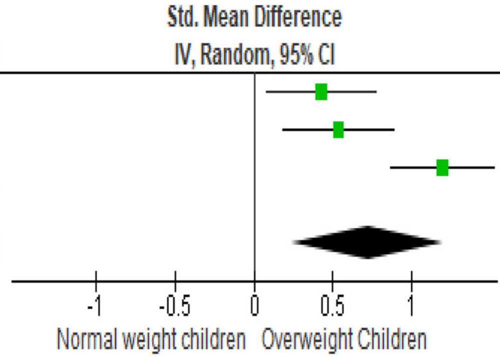

FIGURE 7 Showing CIMT in overweight and normal-weight children.

that fell within the overweight category.[24] There were 264 overweight children and 207 normal weight children. The pooled standard mean difference in CIMT for overweight and normal weight children was 0.72 (95% CI: 0.24–1.20) by using a random effects model. There was a high between study heterogeneity ($I^2 = 83\%$, $p = 0.003$).

4.9 | CIMT in moderately obese and normal weight children

Figure 8 shows the forest plot of CIMT in moderately obese and normal weight children. Three studies[16,21,23] reported on BMI values that fell within the moderately obese category.[24] There were 89 moderately

Study or Subgroup	Moderately obese children Mean	SD	Total	Normal weight children Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Philips et al, 2015	0.43	0.05	21	0.42	0.06	85	38.6%	0.17 [-0.31, 0.65]
Sorof et al , 2003	0.62	0.11	53	0.53	0.06	33	38.6%	0.95 [0.49, 1.41]
Tae et al , 2008	0.62	0.013	15	0.5	0.01	17	22.8%	10.17 [7.42, 12.92]
Total (95% CI)			89			135	100.0%	2.75 [0.73, 4.77]

Heterogeneity: Tau² = 2.70; Chi² = 51.39, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.67 (P = 0.008)

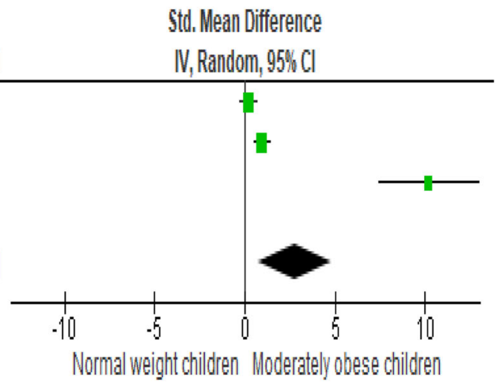

FIGURE 8 Showing CIMT in moderately obese and normal-weight children.

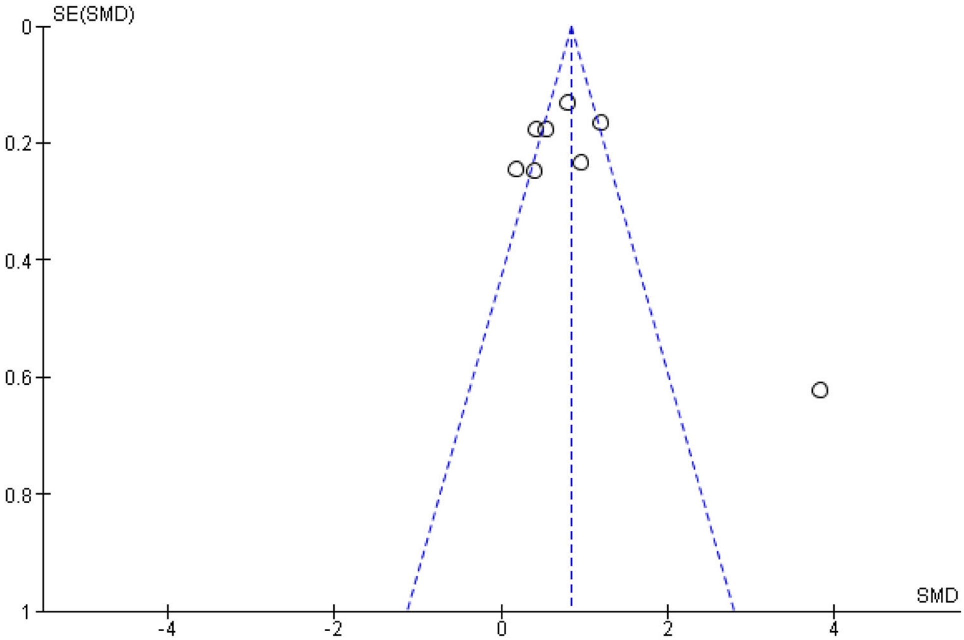

FIGURE 9 Funnel plot showing degree of bias.

obese children and 135 normal weight children. The pooled standard mean difference in CIMT for moderately obese and normal weight children was 2.75 (95% CI: 0.73–4.77) by using a random effects model. There was a high between study heterogeneity ($I^2 = 96\%$, $p < 0.001$).

4.10 | Publication bias

A funnel plot was used to assess the degree of bias in included studies. About 50% of the included studies are captured within the area of the funnel indicating a low level of bias (see Figure 9).

4.11 | Quality assessment

The details of the critical appraisal of the included studies are captured in Appendix 1. All the included studies were cohort studies and attained a 63.6% score across board. Confounding factors were identified in each of the studies and regression analysis were employed to ascertain their effect on the outcomes of interest.

5 | DISCUSSION

The present study is a systematic review and meta-analysis to examine the associations between blood pressure, BMI, and CIMT of children. The results of the meta-analysis indicate a statistically significant standard mean difference in CIMT of 0.83 (95% CI: 0.47–1.19) between normotensive and hypertensive children. The results of the meta-analysis indicate that children with hypertension had a higher CIMT value compared to those without hypertension.

Six of the included articles defined hypertension in children and adolescents as average systolic or diastolic blood pressure that is greater than or equal to the 95th percentile for sex, age, and height on at least three separate occasions. This is per the definition of hypertension as published in "The Fourth Report" by the National High Blood Pressure Education Program Working Group.[25] One included article by Litwin et al.,[18] defined hypertension based on data from another study which used ambulatory blood pressure values.[26] Another included study by Tae et al[16] defined hypertension as systolic blood pressure ≥ 140 mm/Hg and diastolic blood pressure ≥ to 90 mm/Hg.

The review also showed that the BMI of children with hypertension was significantly greater compared to those without hypertension with a standard mean difference of 0.94 (95% CI: 0.64–1.24). The pooled standard mean difference for systolic blood pressure was found to be 2.44 (95% CI: 1.69–3.19). The diastolic blood pressure exhibited a pooled standard mean difference of 1.28 (95% CI: 0.65–1.92). Again, overweight, and moderately obese children had higher CIMT values compared to normal-weight children with a pooled standard mean difference of 0.72 (95% CI: 0.24–1.20) and 2.75 (95% CI: 0.73–4.77) respectively. While most of the included studies did not specify their definitions of overweight and obesity, Liu et al.[19] defined obesity as a BMI greater than the 95th percentile for age, sex, and height.

Apart from the apparent higher CIMT in hypertensive children,[16–18,20,22,23] Litwin et al.,[18] also described the coexistence of an increased femoral intima-media thickness. Again, in two of the included studies by Litwin et al.[18] and Liu et al.,[19] children with high blood pressure also showed an increased incidence of left ventricular hypertrophy compared to those without hypertension. The prevalence of hypertension in children with obesity was quoted by Liu et al.[19] to be more than 10 times higher than in children with normal weight. Obese children with hypertension also had higher diastolic blood pressures as compared to their normal-weight counterparts.[19] These findings underscore the interplay between blood pressure, BMI, and early signs of vascular changes in children, emphasizing the importance of monitoring these factors for cardiovascular health in pediatric populations.

In this meta-analysis, it was also found that children with systolic blood pressure of 119 ± 9.9 and diastolic blood pressure of 66 ± 8.8 or above are candidates for CIMT assessment since they are at increased risk of having higher CIMT values. However as indicated by Touboul et al.,[27] this should be performed using the protocols outlined in the Mannheim consensus. Due to the operator-dependent nature of CIMT measurement and ultrasound in general, care should be taken to eschew biases in the analysis of derived values. Until there are region-specific BMI centile charts, children within the overweight and moderately obese weight categories as defined by Huang, Wan Mohamed Radzi and Salarzadeh Jenatabadi,[24] are also candidates for CIMT evaluation.

This systematic review underscores the need for region-specific and country-specific evaluations of cardiovascular disease risk in children using CIMT. Given the lack of literature from regions such as Africa and the Middle East, studies should be conducted to establish normative values for theirpediatric populations. Further investigation is needed to determine appropriate thresholds for pediatric blood pressure readings, as normative values may not be universally applicable across populations.[28] Additionally, there is the need to assess the effect of other established measures of obesity such as waist-hip ratio and ultrasound-measured abdominal adiposity since the BMI does not give information on body fat distribution.[29] Again, for individuals who are found to be overweight or obese, there is the need to conduct body composition analysis and blood tests. Homeostatic Model assessment for insulin resistance (HOMA-IR), lipid profiles, uric acid, and 25-OH vitamin D can help determine an individual's fat burden.[30]

The findings of this systematic review and meta-analysis also make it imperative for healthcare providers to diligently monitor the blood pressures and BMIs of pediatric patients. These should be based on region and gender-specific centile charts which are the current method of diagnosis of overweight or obesity status in pediatrics.[29,31,32] It is also recommended that children presenting with elevated blood pressure and BMI be provided with the opportunity to have a B-mode ultrasound of the common carotid, which can effectively measure their CIMT and evaluate their risk. Again, further research is needed to find out if weight loss through exercise or a healthy diet can reverse the CIMT changes seen in overweight and obese children.

The major strength of this review is the fact that all included studies performed their measurements in accordance with the Mannheim and American Society of Echocardiography consensus statements.[27,33] However, the systematic review had few limitations that should be highlighted. The included studies were mainly observational as there was no existing randomized controlled trial. It therefore calls for future studies that are randomized controlled trials. Similarly, there was also no uniformity in the methods used in blood pressure assessment. For example, two studies used ambulatory blood pressure measurements (ABPM) to assess hypertension,[17,18] while the remaining six articles used office blood pressure measurements. Also, a study conducted by Liu et al.[19] employed automated software to assess the CIMT, while the remaining relied on manual measurements[16–18,20–23]

6 | CONCLUSION

There is a significant association between increased CIMT, blood pressure and BMI in children. The evidence shows that children with higher blood pressure and BMI have significantly thicker CIMT than children with normal blood pressure and BMI. This suggests that CIMT screening for overweight/obese children and children with high blood pressure is valuable for assessing cardiovascular health. Additional research is needed to ascertain whether lifestyle modifications such as healthy diets and exercise can lead to the reversal of CIMT in overweight or obese children.

AUTHOR CONTRIBUTIONS

Benedict Apaw Agyei: Conceptualization; Formal analysis; Writing—review and editing; Writing—original draft; Methodology. **Yaw Amo**

Wiafe: Conceptualization; Writing—review and editing; Writing—original draft; Supervision. **Andrew Donkor**: Methodology; Writing—review and editing; Validation; Supervision. **Ijeoma Chinedum Anyitey-Kokor**: Writing—review and editing; Supervision. **Kataru Yahya**: Writing—review and editing; Validation. **Fred Stephen Sarfo**: Writing—review and editing; Conceptualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study. The authors confirm that the data supporting the findings of this study are available within the article.

TRANSPARENCY STATEMENT

The lead author Benedict Apaw Agyei affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks. *J Am Coll Cardiol*. 2020;76(25):2980-2981. Available at: doi:10.1016/j.jacc.2020.11.021
2. Björkegren JLM, Lusis AJ. Atherosclerosis: recent developments. *Cell*. 2022;185(10):1630-1645. doi1:0.1016/j.cell.2022.04.004
3. Tohirova J, Shernazarov F. Atherosclerosis: causes, symptoms, diagnosis, treatment and prevention. *Sci Innov*. 2022;1(D5):7-12.
4. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke Statistics-2017 update: A report from the American heart association. *Circulation*. 2017;135(10):e146-e603. Available at: doi:10.1161/CIR.0000000000000485
5. Lloyd-Jones DM, Allen NB, Anderson C, et al. Life's essential 8: updating and enhancing the American heart association's construct of cardiovascular health: A presidential advisory from the American heart association. *Circulation*. 2022;146(5):e18-e43. Available at: doi:10.1161/CIR.0000000000001078
6. Urbina EM, Williams RV, Alpert BS, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American heart association. *Hypertension*. 2009;54(5):919-950. Available at: doi:10.1161/HYPERTENSIONAHA.109.192639
7. Faita, F. et al. Real-time measurement system for the evaluation of the intima media thickness with a new edge detector. *Conference proceedings:… Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. IEEE Engineering in Medicine and Biology Society. Annual Conference, 2006; 2006:715-718. Available at: doi:10.1109/IEMBS.2006.260450
8. Drole Torkar A, Plesnik E, Groselj U, Battelino T, Kotnik P. Carotid Intima-Media thickness in healthy children and adolescents: normative data and systematic literature review. *Front Cardiovasc Med*. 2020;7:597768. Available at: doi:10.3389/fcvm.2020.597768
9. Lawal OM, Balogun MO, Akintomide AO, et al. Carotid Intima-Media thickness: A surrogate marker for cardiovascular disease in chronic kidney disease patients. *Clin Med Insights: Cardiol*. 2019;13:1179546819852941. Available at: doi:10.1177/1179546819852941
10. Epure AM, Anker D, Di Bernardo S, da Costa BR, Sekarski N, Chiolero A. Interventions to decrease Carotid-Intima media thickness in children and adolescents with type 1 diabetes: A systematic review and Meta-Analysis. *Front Clin Diabetes Healthc*. 2022;3:882504. Available at: doi:10.3389/fcdhc.2022.882504
11. Kusters DM, Wiegman A, Kastelein J, Hutten BA. Carotid intima-media thickness in children with familial hypercholesterolemia. *Circ Res*. 2014;114(2):307-310. Available at: doi:10.1161/CIRCRESAHA.114.301430
12. Lucas-Herald AK, Delles C. Carotid Intima-Media thickness is associated with obesity and hypertension in young people. *Hypertension*. 2022;79(6):1177-1179. Available at: doi:10.1161/HYPERTENSIONAHA.122.19163
13. Day TG, Park M, Kinra S. The association between blood pressure and carotid intima-media thickness in children: a systematic review. *Cardiol Young*. 2017;27(7):1295-1305. Available at: doi:10.1017/S1047951117000105
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Available at: doi:10.1136/bmj.n71
15. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
16. Gil TY, Sung CY, Shim SS, Hong YM. Intima-media thickness and pulse wave velocity in hypertensive adolescents. *J Korean Med Sci*. 2008;23(1):35-40. Available at: doi:10.3346/jkms.2008.23.1.35
17. Baroncini LAV, Sylvestre LC, Baroncini CV, Pecoits RF. Assessment of carotid intima-media thickness as an early marker of vascular damage in hypertensive children. *Arq Bras Cardiol*. 2017;108(5):452-457. Available at: doi:10.5935/abc.20170043
18. Litwin M, Niemirska A, Śladowska J, et al. Left ventricular hypertrophy and arterial wall thickening in children with essential hypertension. *Pediatr Nephrol*. 2006;21:811-819.
19. Liu W, Hou C, Hou M, et al. Ultrasonography to detect cardiovascular damage in children with essential hypertension. *Cardiovasc Ultrasound*. 2021;19(1):26. Available at: doi:10.1186/s12947-021-00257-y
20. Páll D, Juhász M, Lengyel S, et al. Assessment of target-organ damage in adolescent White-coat and sustained hypertensives. *J Hypertens*. 2010;28(10):2139-2144.
21. Phillips AA, Chirico D, Coverdale NS, et al. The association between arterial properties and blood pressure in children. *Appl Physiol Nutr Metab*. 2015;40(1):72-78. Available at: doi:10.1139/apnm-2014-0206
22. Skrzypczyk P, Zacharzewska A, Szyszka M, Ofiara A, Pańczyk-Tomaszewska M. Arterial stiffness in children with primary hypertension is related to subclinical inflammation. *Cent Eur J Immunol*. 2021;46(3):336-343. Available at: doi:10.5114/ceji.2021.109156

23. Sorof JM, Alexandrov AV, Garami Z, et al. Carotid ultrasonography for detection of vascular abnormalities in hypertensive children. *Pediatr Nephrol*. 2003;18(10):1020-1024. Available at: doi:10.1007/s00467-003-1187-0
24. Huang H, Wan Mohamed Radzi C, Salarzadeh Jenatabadi H. 'Family environment and childhood obesity: A new framework with structural equation modeling'. *Int J Environ Res Public Health*. 2017;14(2):181. Available at: doi:10.3390/ijerph14020181
25. A.National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and National High Blood Pressure Education Program Working Group. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 suppl 4th Report):555-576.
26. Soergel M, Kirschstein M, Busch C, et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. *J Pediatr*. 1997;130(2):178-184. Available at: doi:10.1016/s0022-3476(97)70340-8
27. Touboul P-J, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). an update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th european stroke conferences, mannheim, Germany, 2004, Brussels, Belgium, 2006, and hamburg, Germany, 2011'. *Cerebrovasc Dis*. 2012;34(4):290-296. Available at: doi:10.1159/000343145
28. Xi B, Zong X, Kelishadi R, et al. Establishing international blood pressure references among nonoverweight children and adolescents aged 6 to 17 years. *Circulation*. 2016;133(4):398-408. Available at: doi:10.1161/CIRCULATIONAHA.115.017936
29. Anderson LN, Carsley S, Lebovic G, et al. Misclassification of child body mass index from cut-points defined by rounded percentiles instead of z-scores. *BMC Res Notes*. 2017;10(1):639. Available at: doi:10.1186/s13104-017-2983-0
30. Mihuta MS, Paul C, Borlea A, et al. Unveiling the silent danger of childhood obesity: Non-Invasive biomarkers such as carotid Intima-Media thickness, arterial stiffness surrogate markers, and blood pressure are useful in detecting early vascular alterations in obese children. *Biomedicines*. 2023;11(7):1841. Available at: doi:10.3390/biomedicines11071841
31. Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment, and management. *Lancet Diabetes Endocrinol*. 2022;10(5):351-365. Available at: doi:10.1016/S2213-8587(22)00047-X
32. Lin X, Li H. Obesity: epidemiology, pathophysiology, and therapeutics. *Front Endocrinol*. 2021;12:706978. Available at: doi:10.3389/fendo.2021.706978
33. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American society of echocardiography carotid Intima-Media thickness task force. endorsed by the society for vascular Medicine'. *J Am Soc Echocardiogr*. 2008;21(2):93-111.; quiz 189-190 Available at: doi:10.1016/j.echo.2007.11.011

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APPENDIX 1

JBI question	BARONCINI et al, (2017)	LIU et al., (2022)	PHILIPS et al., (2015)	SKRZYPCZYK et al., (2021)	SOROF et al., (2003)	TAE et al., (2008)	LITWIN et al., (2006)	PALL et al., (2010)
Were the two groups similar and recruited from the same population?	YES	YES	YES	YES	YES	YES	YES	YES
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	YES	YES	YES	YES	YES	YES	YES	YES
Was the exposure measured in a valid and reliable way?	YES	YES	YES	YES	YES	YES	YES	YES
Were confounding factors identified?	YES	YES	YES	YES	YES	YES	YES	YES
Were strategies to deal with confounding factors stated?	YES	YES	YES	YES	YES	YES	YES	YES
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	NA	NA	NA	NA	NA	NA	NA	NA
Were the outcomes measured in a valid and reliable way?	YES	YES	YES	YES	YES	YES	YES	YES
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	NA	NA	NA	NA	NA	NA	NA	NA
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	NA	NA	NA	NA	NA	NA	NA	NA
Were strategies to address incomplete follow up utilized?	NA	NA	NA	NA	NA	NA	NA	NA
Was appropriate statistical analysis used?	YES	YES	YES	YES	YES	YES	YES	YES
Total number of yes response as %	63.60%	63.60%	63.60%	63.60%	63.60%	63.60%	63.60%	63.60%