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Blood pressure in children and adolescents: Moving forward

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Blood pressure in children and adolescents: Moving forward

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Editorial: Blood pressure in children and adolescents: Moving forward

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Editorial on the Research Topic
Blood pressure in children and adolescents: Moving forward

Cardiovascular disease to which hypertension (HTN) is a major contributor, has been named as the largest epidemic known to humankind. High blood pressure is a clearly established, modifiable risk factor for early disability and death. Although most of the adverse cardiovascular outcomes occur in adulthood, it has become clear that high blood pressure (BP) is a problem across the course of life that may become evident in early life. Since the 1970s, the prevalence of HTN in children has increased about 4-fold. This data is highly concerning as HTN in childhood is typically associated with intermediate markers of hypertension mediated organ damage (HMOD). As such, further research focusing on early life and assessing the origins of this epidemic is a key issue. The current interest in the field of HTN in youth, could lead to improvements in the quality and efficacy of care provided to patients and lead to secondary prevention of adverse cardiovascular events in later life. There is strong evidence that early identification of high BP and early intervention, can lead to successful management, which has an important impact on long-term cardiovascular health outcomes in adulthood.

The importance of a Research Topic on Blood Pressure in Children and Adolescents can hardly be overemphasized. This Research Topic of Frontiers in Cardiovascular Medicine addresses key issues on the front line of the field of pediatric HTN, highlighting emerging research in the identification, evaluation, and management of high BP in youth, opening the way to make progress on many aspects in the field. Clinical evidence has progressed considerably, and it is now known that HTN in children and adolescents is not at all uncommon and its origin is by no means limited to renal, endocrine, or other diseases but extends to primary HTN which in adolescents and children has a prevalence that makes regular BP measurements mandatory.

The accurate measurement of BP is a prerequisite in children for the reliable diagnosis of HTN and the avoidance of misdiagnosis and over-or under-treatment. In this way Stabouli et al. focused on the named topic as the diagnosis of HTN is critically dependent upon the accuracy of the BP measuring device. The validation criteria for BP measuring devices among consensus documents from different scientific organizations emphasizing on the pediatric population are highlighted and the gaps targeting the needs for validated BP measuring devices are discussed.

The role of primary HTN has gained ground over the last decades, and it is now known that it is the leading cause of childhood HTN, especially in adolescents. The phenotype of primary HTN in childhood and recent findings are discussed in depth by Falkner. For children and adolescents with secondary HTN, the treatment can focus on managing the underlying cause of HTN. Less is known about managing primary HTN in childhood, including diagnosis, evaluation, treatment, and possibilities for prevention.

Evidence has been obtained on the multifold structural and functional abnormalities of the cardiovascular system that can be seen in young hypertensive individuals. Considering its relevance, better knowledge about the natural history of early HMOD is needed. The assessment of HMOD needs to be optimized, looking for early markers in different organ systems. Better knowledge of all of these may contribute to optimize interventions, reducing HMOD and improving long-term prognosis. As summarized by Sinha et al., left ventricular hypertrophy is the main marker of HMOD in children and young people and is evident in at least one-fifth of children and young adults with primary HTN and in nearly a third of those referred to specialty clinics with a predominant eccentric LVH pattern in the latter. Similarly, children and adolescents with primary HTN could be expected to underperform during neuropsychological evaluations when compared with healthy peers. Lucas et al. point-out that evidence relating primary HTN with poor cognitive functioning among youth is usually based on indirect measures of executive functions (e.g., self-reported) rather than objective neuropsychological performance-based tasks. Future prospective studies should consider using common standardized neuropsychological batteries as well as adjust the assessing results for obesity and sleep disorders.

Exercise stress testing as a rather non-invasive procedure to add additional information with regard to cardiovascular risk profile is a relevant tool as expressed by Alvarez et al.. The interpretation of BP values in response to exercise during childhood and adolescence is discussed considering the available reference values and their limitations with regard to device, exercise protocol and normalization. Based on the existing data future studies are needed to extend our current knowledge on possible links between the presence of certain clinical conditions, the detectability of an exaggerated BP response during childhood and adolescence and the risk of developing cardiovascular morbidity and mortality in later life.

A further contribution is devoted to clinical trials with antihypertensive drugs. Redon et al., reinforce that pharmacological treatment in children and adolescents is still limited because there are few randomized clinical trials, hampering appropriate management. Given the increasing prevalence and under treatment of HTN in this age group, innovative solutions including new study designs and optimizing the use of digital health technologies could provide more precise and faster information about the efficacy of each antihypertensive drug class and the potential benefits according to patient characteristics.

The global prevalence of childhood HTN is increasing, yet its investigation has been rather sporadic in Eastern Europe. The calculated prevalence of childhood HTN in Hungary has been assessed by Kovács et al. using data mining methods. Results were comparable to data from other European countries. Higher BMI values were found in hypertensive children as compared to non-hypertensives in all age groups and is associated with early metabolic disturbances.

Furthermore, the relevance of perinatal programming opening up new ways to understand the early-life origins of diseases such as high BP has been covered by Crivelli-Meyer et al.. The authors conducted an inquiry among all employees of public hospitals to assess how many adults remember their own birth weight, an important anamnestic item for cardiovascular and renal disease risk stratification. Waist-to-Height-Ratio is associated with sustained HTN in children and adolescents with high office PB, as presented by Nimkarn et al..

The Research Topic presented here provides an overview of the subject that is difficult to find elsewhere and represents not only up-to-date advice for medical practice but also a source of critical information on issues of great potential interest. We very much hope you enjoy reading this Research Topic.

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Blood pressure response to exercise in children and adolescents

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Blood pressure changes during exercise are part of the physiological response to physical activity. Exercise stress testing can detect an exaggerated blood pressure response in children and adolescent. It is applied for certain clinical conditions, but is also commonly used as part of the assessment of athletes. The interpretation of blood pressure values in response to exercise during childhood and adolescence requires appropriate reference data. We discuss the available reference values and their limitations with regard to device, exercise protocol and normalization. While the link between an exaggerated blood pressure response and cardiovascular events and mortality has been demonstrated for adults, the situation is less clear for children and adolescents. We discuss the existing evidence and propose that under certain circumstances it might be reasonable to have children and adolescents undergo exercise stress testing as a rather non-invasive procedure to add additional information with regard to their cardiovascular risk profile. Based on the existing data future studies are needed to extend our current knowledge on possible links between the presence of certain clinical conditions, the detectability of an exaggerated blood pressure response during childhood and adolescence and the risk of developing cardiovascular morbidity and mortality in later life.

KEYWORDS

blood pressure (BP), exercise, stress test, children, adolescents, arterial hypertension, cardiovascular risk

Introduction

The changes in blood pressure (BP) during exercise are mainly seen as part of the physiological toward an increased demand. Standardized exercise protocols are used as part of certain clinical investigations, but also to assess cardiorespiratory fitness in athletes. The interpretation of BP values in children and adolescents upon exposure to different protocols is hampered by the scarcity of respective reference values. While data from adults suggest a relationship between an exaggerated BP response to exercise and the risk of developing arterial hypertension (HTN), the situation is less clear in children and adolescents.

This narrative review intends to provide an overview of the physiology behind the BP changes detected during exercise, the available reference data for children and adolescents to assess BP after engagement in different exercise protocols, potential clinical conditions that may predispose toward an exaggerated BP response as well as the implications such an exaggerated BP response might have.

Physiology of blood pressure changes during exercise

Blood pressure changes during exercise are part of the complex physiological response of the cardiovascular (CV) system to physical activity (**Figure 1**). To preserve cellular oxygenation and acid-base homeostasis during exercise, metabolic, CV, and respiratory responses must adapt rapidly to these changes. This task is accomplished by increases of heart rate and stroke volume and decreases in systemic as well as pulmonary vascular resistance. Precise control mechanisms are required for this process to balance systemic vascular resistance (SVR) in context of metabolic vasodilation at the muscle. In general, the increment in cardiac output with exertion is larger than the rise in mean systemic BP reflecting a decrease in SVR (1). The ability to decrease SVR has been correlated with exercise performance (2). Changes in the sympathetic and parasympathetic nervous systems are responsible for the CV adjustment during exercise such as increased cardiac output, skeletal muscle flow, and BP. Damage to the neurophysiological mechanisms could result in an inadequate blood supply to the muscle and the brain. Circulation control and control of the BP is a multifactorial process and complex interaction of peripheral reflexes (exercise pressor reflex, arterial and cardiopulmonary baroreflexes) and higher brain centers (central command, see below). During mild to moderate exercise in healthy subjects, BP is well maintained by increasing heart rate and cardiac output. With increased duration and intensity exercise is accompanied by vasoconstriction in many organs, especially the splanchnic region and kidneys (3). The exercise pressor reflex (EPR), which is the most important peripheral reflex response during physical activity, consists of two components: the mechanoreflex and the metaboreflex. Afferent fibers from skeletal muscle of groups III (mechanoreceptors) and IV (metaboreceptors) are excitable by mechanical and chemical stimulation (4). Mechanoreceptors are activated by mechanical deformation induced by pressure or stretch. Metaboreceptors are sensitive neural fibers activated by metabolites (lactic acid, potassium, bradykinin, arachidonic acid products etc.) accumulating in the muscle during contraction. Although mechano- and metaboreceptor stimulation occur mainly simultaneously, activation is different in different types of physical activity, i.e., reflecting dynamic or static exertion. Mechano- and metaboreflex also interact with other reflexes induced by baroreceptors and chemoreceptors. Baroreceptors, located in the carotid sinuses and aortic arch, are a part of the vascular system's autoregulation toward hemodynamic changes. They reduce fluctuations in arterial pressure by lowering sympathetic activity as arterial pressure rises. During the exercise, however, the baroreceptor reflex is not inhibited or overridden, but is reset and allows increases in BP, heart rate and sympathetic activity (5). In addition to reflex stimuli, the central neural mechanism so-called *central command* is involved in controlling the CV response to the muscular effort. Neurons of the motor cortex together with the medulla oblongata activate the CV response to exertion (6). Their role is to coordinate and transmit excitatory impulses to descending somato and locomotor neurons in parallel to activate the somatomotor-, respiratory- and CV systems simultaneously. Alterations in these control mechanisms could result in an inadequate blood supply to the muscle and the brain.

Changes in the sympathetic and parasympathetic nervous systems are responsible for the CV adjustment during exercise such as increased cardiac output, skeletal muscle flow, and BP. The hemodynamic status during dynamic exercise is regulated by integrated signals from the brain and periphery, which increases the activity of the sympathetic and reduces the parasympathetic nervous system. As a consequence, heart rate, myocardial contractility, stroke volume, and cardiac output are increased. At the same time, significant metabolic vasodilation and a decrease in SVR occur in the large muscles involved in physical activity.

Another important factor contributing to the regulation of BP during exercise is process of vasodilation. The key regulator of that process is Nitric oxide (NO). It is a soluble gas continuously synthesized from the amino acid L-arginine in endothelial cells by the constitutive calcium-calmodulin-dependent enzyme nitric oxide synthase (eNOS). This substance has a wide range of biological properties that maintain vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injurious consequences of platelets and cells circulating in blood, playing in this way a crucial role in the normal endothelial function (7). It has been shown, that as a response

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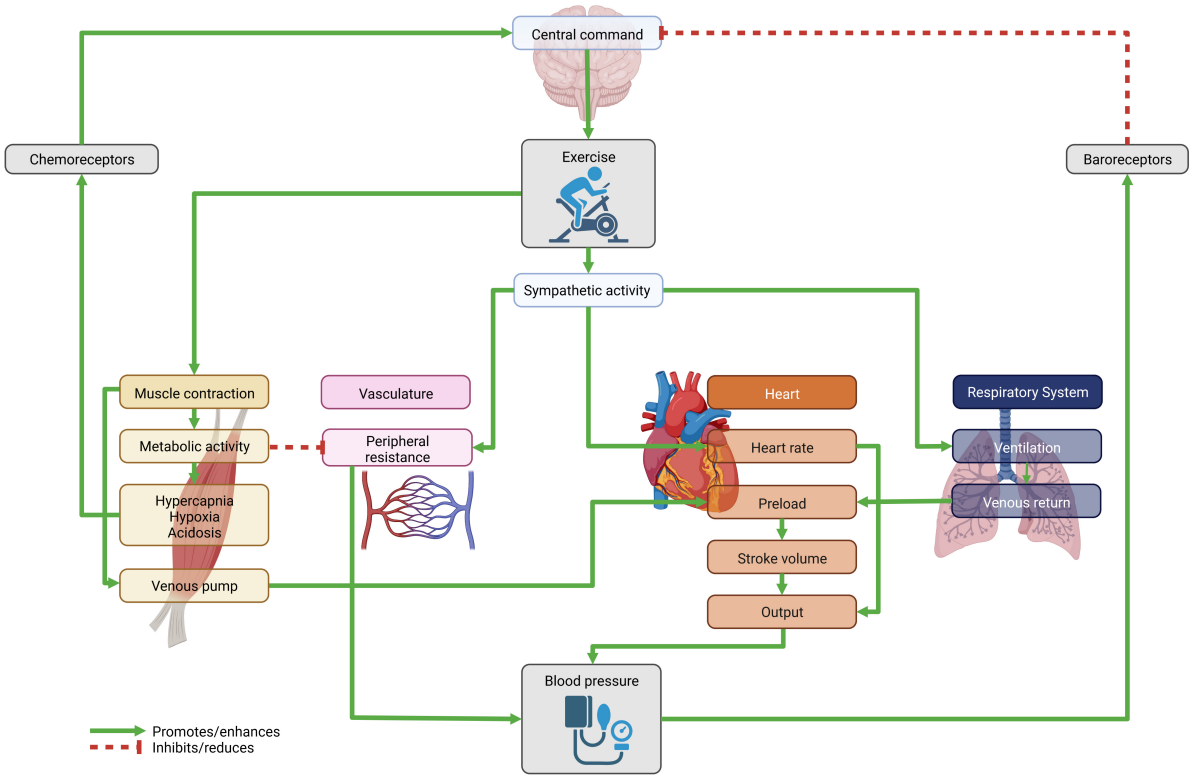

FIGURE 1
Feedback loop as the physiological response to physical activity. The central command initiates muscle activity via somatomotor neurons. Simultaneously the vascular, heart and respiratory systems are activated, in part through the increasing sympathetic activity. This leads to a surge in cardiac output and peripheral vascular resistance, which in turn raises (systolic) blood pressure. The change in hemodynamics triggers the baroreceptor reflex, while the metabolic activity of muscle exertion is sensed by chemoreceptors. Figure created with BioRender.com.

to the mechanical stimuli the activity of eNOS is increasing (8). A recently published study found that response to nitric oxide production may vary with age. The vasodilatory response to 30 min of cycling at 60% $\dot{V}O2_{max}$ was greater and occurred earlier in boys compared with men (9). The beneficial effect of different types of physical activity on endothelial function in both adults and children and adolescents is known (10, 11). But preliminary studies indicate that even in children and adolescents with some degree of endothelial dysfunction (such as children with obesity or with abnormal BP), physical activity improves endothelial function (12–14).

Mean arterial pressure (MAP) is therefore only slightly elevated during physical activity, diastolic pressure does not change, while systolic pressure increases during exercise. Vasoconstriction occurs in organs and tissues that are not directly involved in the exercise. This arterial vasoconstriction in non-exercising organs together with the activation of the muscle and respiratory pump and sympathetic venoconstriction increases cardiac preload and consequently stroke volume (6).

The CV response toward static exercise differs significantly from that observed during dynamic exercise. During static exercise, in contrast to dynamic, there is no significant vasodilation in the muscles due to intramuscular pressure produced by isometric contractions. Peripheral systemic resistance decreases but not as much as in dynamic exercise. Cardiac output increases during static contractions due to increased heart rate. The increased cardiac output without a significant decrease in peripheral vascular resistance causes an increase in BP with increases in systolic BP, diastolic BP and MAP. These changes occur in an attempt to maintain adequate perfusion of muscle during static exercise (15). Stroke volume is relatively constant during low-intensity contractions and decreases during high-intensity contractions. It is probably the result of decreased preload because of high intrathoracic pressure, and an increased afterload. Static exercise is characterized by a rapid increase in both systolic and diastolic pressure, termed the *pressor response*, which appears to be inappropriate for the amount of work produced by the contracting muscle. Compared to the slight increase in MAP during dynamic exercise, MAP is markedly elevated in static exercise (16). Considering the described pathophysiological mechanism of static loading in exercise, traditionally aerobic exercise has been shown to be beneficial in lowering blood pressure. It was recommended that children do not engage

in sports with predominantly static loading until they have completed their physical and skeletal maturity. This particularly applied to children with uncontrolled hypertension, seizure disorders, pulmonary hypertension, and children treated with cardiotoxic drugs (17). However, a positive effect of static load on arterial pressure values was observed in adults. Although the positive effects of resistance training on BP values was registered in adults there is limited understanding about the static loading on BP in children and adolescents. The recently published meta-analysis of Guillem et al. (18) did not clearly confirm the positive effect of static exercise in young people on BP, but a non-significant decrease in both, systolic and dyastolic BP was observed. Authors explained that although there is limited research in this topic, the results of their research suggest that "resistance training does not have an adverse effect on the BP of children and adolescents and may be beneficial in lowering BP and improving BMI in this population." In general, today's scientific research supports the acceptance that children and adolescents can participate in static sports if the activities are performed with an emphasis on proper technique and under good supervision (19). Nevertheless, and following the recommendations of the American Academy of Pediatrics, "athletes with poorly controlled, preexisting hypertension require consultation with a medical professional because of the risk of marked elevation of BP during resistance training with weights. Using one's own body weight is an acceptable alternative until a consultation can be obtained" (20).

After the exercise is terminated, the impulses of the metabo- and mechanoreceptors cease as well as the stimulus from the central command. This leads to a decrease in sympathetic activity and an increase in parasympathetic activity. Consequently, heart rate, myocardial contractility, stroke volume, cardiac output, and MAP rapidly decline. Cessation of muscle pump activity leads to decreased cardiac filling resulting in a decrease in stroke volume and the consequent reduction in MAP if baroreflex-mediated peripheral vasoconstriction does not contemporary adjust heart rate and SVR (4).

A phenomenon called post-exercise hypotension refers to a sustained decrease in BP after a single episode of exercise (21). Post-exercise hypotension is consistently elicited after longer (30–60 min) bouts of moderate-intensity exercise (22). The hypotensive effect during the post- period is observed in both, hypertensive and normotensive subjects, and may last nearly 120 min (23). The mechanisms responsible for BP reduction after aerobic training are not clear. Hypertension has a multifactorial etiology and, therefore, several mechanisms may be involved in the hypotensive effects of aerobic training. The cause of the vasodilatation underlying post-exercise hypotension in humans remains largely unexplained (24). It does not depend on the decease of adrenergic receptor responsiveness, neither on nitric oxide level (23). It has been suggested, that the phenomenon may be associated with ineffective transduction of sympathetic nerve activity into vasoconstriction and lesser neurotransmitter release (25). Sympathetic nerve terminals possess pre-synaptic inhibitory opioid receptors that may be occupied after exercise, effectively reducing noradrenaline release (26). Although systemic opioid blockade with naloxone has reversed post-exercise hypotension in animals, the role of opioids in humans remains controversial (27, 28). Pre-synaptic inhibition can also be caused by noradrenaline via a2-adrenergic receptor activation or by neuropeptide Y, which is co-released with noradrenaline during exercise (29). After exercise, neuropeptide Y may remain bound to pre-synaptic receptors, reducing noradrenaline release. None of these observations provide a complete and unequivocal explanation of the phenomenon.

The autonomic nervous system may provide useful information about the functional adaptations of the body. The heart rate adaption to exercise training is the result of changes in autonomic tone. The heart rate of trained persons at rest is lower than that of untrained due to the dominance of the parasympathetic tone. During exercise, trained individuals can achieve appropriate SBP values with a lower heart rate due to a higher stroke volume. Diastolic pressure values do not differ significantly. Trained athletes have a higher relative maximum oxygen consumption during physical effort, a lower resting heart rate and a faster short-term and long-term heart rate recovery than untrained people. Rapid recovery after exercise involves a coordinated interaction of parasympathetic reactivation and sympathetic withdrawal. Delayed heart rate recovery has been shown to be a strong predictor of mortality (30).

Evaluation of blood pressure response to exercise

During submaximal and maximal intensity exercise, a moderate increase in BP is expected among children and adolescents. However, there are very little specific data on BP changes depending on the duration and intensity of physical activity. Standardized load testing involving cycle ergometers or treadmills is used to evaluate the CV system. These exercise tests are done in specially equipped laboratories and are meaningful for certain clinical conditions, but are also used as part of the assessment of athletes. **Table 1** gives an overview of the publications that provide reference data for BP response toward different exercise protocols.

Cycle ergometers are most frequently used in pediatric practice since they are cheaper, take up less space, and are easier to use, especially in the case of individuals with weight-bearing limitations (31). The downside of using a cycle ergometer is that muscle fatigue of the lower extremities can lead to the test ending prior to obtaining values, which are caused by central factors. In addition, for some children maintaining a constant rhythm of pedaling (cadence) can be a problem. Two relatively recent studies reported the BP readings of

TABLE 1 Overview of studies reporting reference values for blood pressure during exercise testing in childhood.

Author	Age	N (m/f)	Country	Selection	Device	Protocol	Termination	Normalization	Adjustment	Limitations
Clarke et al., 2021 (31)	6–18 y	648 (314/334)	Australia	Single center routine examination, normal cardiac anatomy, BMI < P95, BP < P95	Treadmill	Bruce protocol	Exhaustion	P5, P10, P50, P90, P95 of SBP change	Age, sex, height	Reports only change of SBP from baseline
Sasaki et al., 2021 (34)	7–17 y	1085 (642/397)	USA	Single center routine examination, normal cardiac anatomy	Treadmill	Modified Bruce protocol	Exhaustion	Table for P5, P10, P50, P90, P95 of SBP/DBP Formula by linear regression for P50, P90, P95 of SBP	Age, sex	No adjustment for height
Burstein et al., 2021 (59)	6–18 y	1829 (951/878)	USA	Single center routine examination, BMI P5-P95, normal cardiac anatomy	Cycle	Ramp (10–25 W/min)	Exhaustion	Trajectories and formula (fractional polynomial regression)	Age, sex, BMI, race	Not readily usable in practice
Szmigielska et al., 2016 (32)	10–18 y	711 (457/254)	Poland	Athletes, single center, resting BP < P90	Cycle	Individual (multi stage 30/60 W every 3 min)	Exhaustion	Diagram (multivariate linear regression) depicting 2 SEE	Age, sex, workload	No adjustment for height
Hacke and Weisser, 2016 (33)	12–17 y	492 (251/241)	Germany	6 public schools no diagnosis of hypertension or CV disease	Cycle	Individual (multi-stage 0.5 W/kg every 3 min)	Submaximal 1.5 W/kg	P95 and P90 of SBP	Age, sex	No adjustment for height
Wanne and Haapoja, 1988 (60)	9–18 y	497 (260/237)	Finland	Random sample from multi-center study (n = 14.487) corrected for age and social class	Cycle	Ramp (HR controlled, increment of 8 bpm)	HR of 170 bpm	Trajectories with 2SD adjusted	Sex, HR, puberty (9–12 y/14–18 y)	Age group 12–14 y not reported

BMI, body mass index; bpm, beats per minute; CV, cardiovascular; DBP, diastolic blood pressure; f, female; HR, heart rate; m, male; N, number; P, percentile; SBP, systolic blood pressure; SD, standard deviation; SEE, standard error of estimate; W, watt; y, years.

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adolescents during laboratory testing conditions that involved a cycle ergometer (32, 33). Hacke and Weisser used a standardized graded submaximal exercise test at a Physical Working Capacity 170 (PWC 170) with a load of 1.5 W/kg body mass, while for participants who were overweight/obese corrections were made based on the average weight values for sex and age (33). The authors provided systolic resting BP and BP after exercise in sex- and age-related percentiles for the ages of 12–17 years. Szmigielska et al. presented data on BP during submaximal cycle ergometer testing among individuals aged 10–18 years, who were involved in some form of sports activity. Unfortunately, without any data on duration and intensity of the sports training and without determination of maximum oxygen uptake (32).

Laboratory treadmill testing is the method of choice for all functional testing as it relies on the well-known mechanics of walking and enables longer activity due to the smaller impact of local fatigue factors. However, data on BP for children and adolescents using this kind of testing are even more infrequent. Still, two new studies offer some normative values (31, 34). Sasaki et al. (34) measured BP and maximum oxygen uptake during a standardized test following the Bruce protocol (35). Systolic BP under load was presented in sex- and age-related percentiles for the ages of 7–17 years. A limitation of their study is that height of the participants and the values of resting BP were not taken into consideration. Clarke et al. (31) took matters a step further as they reported normative values for systolic BP during standardized testing under the Bruce protocol among children and adolescents aged 6–18 years by taking into consideration the participants' height and resting BP (31). Their study explicitly excluded obese individuals because of anticipated differences in BP changes during physical activity in this specific group.

All of the studies on reference values have their limits as summarized in **Table 1**. In the absence of more complete reference values, the percentiles proposed by Sasaki et al. (34) (treadmill) and Hacke and Weisser (33) (cycle) may be considered the most practical. An overview of the respective 95th percentile as a cut off for clinical use is provided in **Supplementary Table 1**.

Exaggerated blood pressure response

Some individuals present with abnormally exaggerated rise in systolic BP during exercise. This phenomenon is known as an exaggerated blood pressure response to exercise (EBPR). It can be observed in individuals without known CV diseases. EBPR can be explained by impairment of endothelial function with an impairment of exercise induced endothelial vasodilation, especially in younger individuals. Other possible mechanisms of EBPR could be an augmented rise of angiotensin II during exercise found in individuals with EBPR (36). EBPR is generally considered to be a pathological response, however, its clinical significance is not entirely clear.

Exaggerated blood pressure response is defined as an increase in BP (with or without a correlation to heart rate) that is too high for the individual undergoing (sub)maximal stress test. In adults, classically cut off points of >210 mm Hg in men and >190 mm Hg in women are proposed based on the CARDIA study (37). However, even in adults, the definition of EBPR is hampered by differences in methodology and criteria used during testing, e.g., whether the exercise is performed on a treadmill or bicycle, and the BP is measured at a moderate or a maximum level of exercise (38).

As indicated in the previous section, the definition of exaggerated blood pressure in the pediatric population is related to sex- and age-specific reference values and not to fixed cut-off points. It does not come as a surprise that the differences in methodology and criteria as described for adults result in different reference values for the pediatric population, which makes the interpretation of stress testing difficult. Only a limited number of studies examined the levels of post-exercise SBP in the general population. Data from the above-mentioned German population-based study on 531 healthy adolescents aged 12–17 years showed that 13.6% of the adolescents had at least high normal exercise SBP values and 5.9% displayed both, increases in resting as well as end exercise BP. Moreover, in this study 7.7% of children had increased resting but normal exercise BP (33). The retrospective study from Michigan, USA, based on 1,085 children aged 7–17 years showed that up to 14.1% of children presented with an exaggerated BP after treadmill exercise (34). As indicated, the strength and limitation of those studies is using centiles—relative measure in contrary to fixed mmHg values. This will finally need to be reconsidered as using this cut-off point will always give the risk of about 5% of inappropriate results. Contrary, using fixed cut-off points (ex. adult) can give both, over- or underestimating the true number of affected children.

Exaggerated blood pressure response indicating future hypertension development

High BP is a leading risk factor for CV disease (CVD). The identification of high BP is conventionally based on in-clinic (resting) BP measures, performed within primary health care settings. However, many cases of high BP go unrecognized or remain inadequately controlled. Thus, there is a need for complementary settings and methods for BP assessment to identify and control high BP more effectively. Since the early 1980s, numerous studies made on adults, have shown a relationship between the presence of exaggerated BP response to exercise and the future risk of developing HTN. However,

many of these studies were conducted on small samples and were not representative of the general population (39). The two main population-based studies in which it was identified that exaggerated blood pressure response to exercise could be a predictor of the development of hypertension were the CARDIA study (687 subjects followed for 5 years) and a Framingham study sample of 2,310 participants who were followed for 8 years (37, 40).

Keller et al. recently published a systematic review of 18 original studies of retrospective and prospective design including 35,151 healthy normotensive adult subjects (41). The follow-up period varied between 2 and 14 years. Most studies showed an association between EBPR (systolic, diastolic, or both) and incident HTN regardless of the heterogeneity of the criteria used to define the hypertensive response. Therefore, in adults, it could be concluded that EBPR is able to identify a subgroup of patients at high risk for developing resting HTN.

Forty years ago, some small studies made on adolescents found that SBP during exercise was significantly higher in subjects with a parental history of HTN compared with those without (42, 43). These results suggest that the exaggerated BP responses to exercise, characteristic of hypertensive patients, may be present in normotensive adolescents with an increased risk of developing the disorder, and may reflect pathophysiological changes that precede sustained BP elevation. A sub-study of the European Youth Heart Study aimed to analyze whether SBP, heart rate, and rate pressure product (RPP) measured during exercise in childhood could predict resting SBP levels in adolescence independent of resting SBP and conventional CV risk factors (44). This was studied in a sample of 226 randomly selected children followed longitudinally for 6 years and re-assessed during adolescence. SBP and rate pressure product during exercise in stage two of the test were positively associated with future resting SBP, independent of resting SBP in childhood. After additional adjustment for conventional CV risk factors, the associations with SBP and rate pressure product during stage two on future resting SBP changed only slightly with rate pressure product remaining significant (P = 0.059 and P = 0.012, respectively). Rate pressure product expressed as the product of SBP and heart rate during exercise was associated with future BP levels. Based on these results, it could be inferred that measuring BP during exercise might be of diagnostic value in some children at risk for developing hypertension. This is not only the case in children with a family history of HTN, but also for certain clinical conditions such as obesity, heart and kidney disease, for which an association to exercise-induced increases in BP have been proposed (45–48). As EBPR increases the risk of developing future HTN, these children would benefit from an early detection of EBPR resulting in a closer BP control. This would be of specific importance during adolescence and just before transitioning to adulthood, a time of life when systematic health check-ups end. Nevertheless, there are no prospective data available on the real impact of EBPR in childhood and the risk of developing HTN in adulthood (33). The European Society of Hypertension guidelines for the management of high BP in children and adolescents, therefore, do not recommend exercise testing in this specific setting (49). On the other hand, the same guidelines recommend ambulatory BP measurement (ABPM) in those subjects with an EBPR.

This later recommendation is based on studies such as the one by Kavey et al. (50). They evaluated 119 children aged 6–18 years with confirmed office HTN. Office BP, ABPM, and BP response to treadmill exercise were measured. They observed an exaggerated SBP response to exercise not only in 61% of the boys and 64% of the girls in the HTN group (HTN based on office BP and ABPM), but also in 39% of boys and 36% of girls from the group of white-coat hypertensive subjects (office HTN, but normal ABPM) (50). Moreover, an exaggerated SBP exercise response predicted HTN on ABPM in 63%, while a normal SBP response to exercise had a negative predictive value of 72%. This association between EBPR and elevated ABPM was confirmed in the Avon Longitudinal Study of Parents and Children (ALSPAC) (51). In the ALSPAC, a total of 657 adolescents (mean age: 17.7 $\pm$ 0.3 years; 42% male) completed a step-exercise test with pre-, post-, and recovery-exercise BP, office BP and ABPM. Fifty participants (7.8%) were classified with masked hypertension. Office BP, pre-, post-, and recovery-exercise systolic BP were associated with masked hypertension (AUC $\geq$ 0.69 for all, respectively), with the office systolic BP threshold of 115 mm Hg having high sensitivity and specificity and exercise BP thresholds of 126, 150, and 130 mm Hg, respectively, having high specificity and negative predictive value (individually or when combined) for ruling out the presence of masked hypertension. Based on these results, the authors concluded that "systolic BP responses to step-exercise testing, not being definitive in terms of "diagnosing" masked hypertension (which should be confirmed with out-of-clinic BP monitoring), the high negative predictive values indicate that the presence of masked hypertension could be effectively ruled out by exercise testing. This observation is important as individuals found to have normal office BP have no indication for an out-of-clinic BP monitoring. Thereby, the presence of masked hypertension may be overlooked and the associated CV risk missed. The measurement of BP during exercise could be therefore a good screening tool.

Exaggerated blood pressure response and its association with cardiovascular risk factors

Other studies have found children with high LDL-cholesterol levels to have significantly higher SBP and DBP

immediately before and after a treadmill exercise, as well as at the end of post-exercise recovery (52). These findings were observed in children with severely elevated levels of LDL-cholesterol suggesting that severely unfavorable levels of blood lipids are necessary to impair the regulation of BP during exercise. The association between conventional CVD risk factors and BP response during acute exercise was studied in 439 Danish third-grade children and 364 ninth-grade adolescents who participated in the European Youth Heart Study (53). Researchers found that HOMA-IR score was positively associated with SBP response during exercise in boys. This relationship remained significant after controlling for resting SBP, exercise heart rate, body height, school grade, test protocol, and workload. In boys, they also found a significant positive relationship between BMI and SBP response.

While various studies suggested an EBPR in obese children (47), a small but very elegant study Dipla et al. (54) showed that after handgrip exercise obese children without a family history of hypertension did not show an exaggerated blood pressure response. Notably, the obese and non-obese children in this study had equal blood pressure levels at baseline. In this study, obese and lean children showed different adaptions to exercise: the obese children increased stroke volume whereas the lean children increased systemic vascular resistance.

Exaggerated blood pressure response and its association with target organ damage and cardiovascular disease

An exaggerated SBP during exercise has also been reported in children at risk for early damage in vascular structure and functioning. This was observed in the study by Kavey et al. (50), in which LV mass correlated significantly with office SBP, maximal exercise SBP (SBP max), ABPM awake and asleep SBP. Using multiple regression, maximum correlation was achieved with inclusion of height, weight, ABPM awake SBP, and treadmill exercise (TE) maximal SBP. Previously similar results have been observed in a bigger cohort of 274 subjects (6–15 years) based on the Muscatine study (55). Anthropometrical variables, office BP, BP response to exercise in an ergometer, and echocardiographic left ventricular mass (LVM) were assessed at baseline and after a mean of 3.4 years. At baseline, LVM correlated with maximum SBP during exercise and also with SBP increase during exercise. The final SBP was best predicted from the initial variables of office SBP, SBP max, and LVM; and the final LVM was best predicted from the initial variables of LVM and DBP max. Assessment of left-ventricular mass index (LVMI) and carotid-femoral pulse wave velocity (aortic

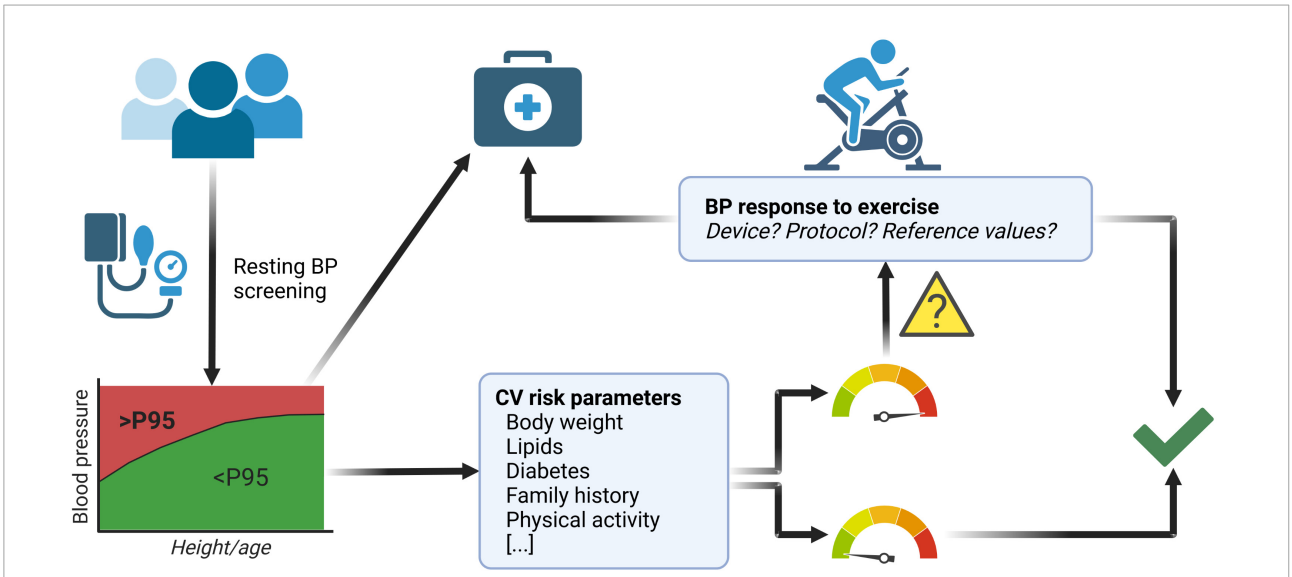

FIGURE 2
Possible implementation of exercise stress testing to improve cardiovascular (CV) health screening in children and adolescents. Measurement of resting blood pressure (BP) identifies children and adolescents with elevated BP [i.e., pathologic reading above the 95th percentile according to guidelines (49)], who can be subsequently referred to medical follow up and potential treatment. However, subjects with a normal resting BP (i.e., below the 95th percentile) but presenting with additional CV risk factors (e.g., obesity/adiposity, abnormal lipid status, abnormal glucose tolerance or overt diabetes, a family history of CV disease and/or a severe lack of physical activity) may profit from further evaluation by undergoing exercise stress testing. An exaggerated BP response during exercise stress testing would warrant closer medical follow up. Children and adolescents with normal BP response to exercise as well as those with no other CV risk factors do not need increased medical attention. When performing exercise stress testing one must be aware of the limitations described in this article with regard to device, protocol and reference values. Figure created with BioRender.com.

PWV) was also undertaken in the ALSPAC cohort (51). The proposed cut-off points for pre-, post-, and recovery-exercise systolic BP were associated with greater LVMI and aortic PWV. These results indicate that detecting EBPR could identify children and adolescents at risk for the development of target organ damage (TOD).

There is evidence that EBPR predicts CV events and CV mortality in otherwise normotensive adults (56, 57). On the other hand, post-exercise hypotension, defined as a drop of SBP below pre-exercise values, is often indicative of significantly increased risk for cardiac events, especially when associated with prior myocardial infarction or exercise-induced ischemia (58). There is no information on the prognostic value of these measurements in children and adolescents, but a hypotensive response to exercise is a criterion to end exercise testing in children (48).

Conclusion

In this review, we discuss the potential usefulness of stress testing to unmask EBPR, especially in children presenting with certain risk factors this diagnostic procedure might be useful (**Figure 2**). In adulthood the link between EBPR and CV events and mortality has been demonstrated. The situation during childhood is less clear due to a lack of studies showing that EBPR is preceding HTN and CV morbidity. In addition, studies performing stress testing are hampered by methodical limitations inherent to the currently available reference values. Still, it might be reasonable to have children undergo exercise stress testing as a rather non-invasive procedure to add additional information with regard to their CV risk profile. But at the moment there is not enough data to make the general recommendation of introducing BP measurement during exercise in the cardiovascular risk disease evaluation in children and adolescents. Future studies are needed that use similar methodology to extend our current knowledge on possible links between the presence of certain clinical conditions, the detectability of an EBPR and the risk of developing CV morbidity and mortality in later life.

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Conflict of interest

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Supplementary material

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Adults remember their birth weight, an important anamnestic item for cardiovascular and renal disease risk stratification

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To assess how many adults remember their own birth weight, an important anamnestic item for cardiovascular and renal disease risk stratification, we conducted an inquiry among all employees of public hospitals of Ente Ospedaliero Cantonale (EOC) in Ticino region (Southern Switzerland). The results show that the vast majority of adults remember their own birth weight. Hence, it is reasonable to include this information in the stratification of risk for cardiovascular and renal diseases.

KEYWORDS

birth weight, cardiovascular risk, Barker's hypothesis, renal disease, low birth weight

Introduction

Low birth weight confers an increased risk for cardiovascular and renal diseases (1). Consequently, it has been recommended that infants with growth-restricted, preterm, or low birth weight should undergo annual blood pressure measurement and urinalysis from the age of 3 years (2).

Like hypertension, physical inactivity, excessive body weight, smoking, diabetes, abnormal lipids and a positive family history of premature cardiovascular disease, low birth weight is a also relevant cardiovascular risk factor in adulthood (1, 3). Nevertheless, low birth weight is neglected in everyday clinical practice, at least partly because physicians assume that it is a feature that is unlikely to be remembered in adulthood.

Materials and methods

To assess how many adults remember their own birth weight, all (about 5,000; 70% women) employees of public hospitals of Ente Ospedaliero Cantonale (EOC) in Ticino region (Southern Switzerland) were invited to fill in a close-ended web-based questionnaire addressing, among others, own weight at birth. Since the analysis was completely anonymous, the institutional review board waived the necessity to have approval for this type of study. In an effort to get as much information as possible, we analyzed the responses to 12 questions: 6 questions about demographic data of the participants, 3 questions about knowledge of birth weight, birth length, and duration of pregnancy, 2 questions about cardiovascular risk factors and diseases and their pharmacotherapy, and one question to assess how the participants get the birth information.

Low birth weight was defined as weight of less than 2,500 g. Continuous data are presented as median values with interquartile range or minimum and maximum range, and categorical data are presented as frequencies and percentages calculated from single answers. A comparison of prevalence between groups was performed by Fisher exact test. Mann-Whitney *U*-test was conducted to compare the two groups. All statistical analyses were performed using the GraphPad Prism® software version 8.0 (GraphPad Software, San Diego, CA, United States). Significance was defined at $p < 0.05$.

Results

A total of 1,369 (27%) employees answered the questionnaire, 1,054 (77%) were female and 315 (23%) were male. They ranged in the ages of 17 to 67 years (median 40 years), 677 (49%) were younger than 40 years, and 692 (51%) were 40 years of age or older. Twenty-one (1%) had an educational level of secondary school or less, 682 (54%) had higher professional education, and 567 (45%) had an university degree. but for 99 participants the educational level was not known. The profile of the employees who answered was similar to that of all employees (i.e., sex and educational level). A total of 1164 (85%) declared to remember their own birth weight, the majority (70%) of them knew this fact by heart, 24% asked their parents, and 6% searched this information on birth documents at home. The knowledge of birth weight was slightly but significantly lower in the subjects 40 years of age or older [572 out of 692 (83%) vs. 593 out of 677 (88%); $p < 0.01$]. Median declared birth weight was 3,300 g (interquartile range between 2,850 and 3,600 g). Low birth weight was present in 8.2% of the subjects, and 13% of the subjects presented at least one cardiovascular risk factor or disease. A trend toward an association between low birth weight and higher body mass index or cardiovascular diseases was found in this cohort ($p = 0.16$).

Discussion

The majority of the adults remember their own birth weight, but the knowledge of it seems to be slightly lower in the elderly subjects. These conclusions might be flawed by some limitations. Given the rather low response rate (27%), our results should be considered preliminary and further confirmation is needed. Nevertheless, the educational level of the employees who answered is similar to that of all employees. Also, the high percentage of women who answered is in line to the high percentage of women working in public hospitals of Ente Ospedaliero Cantonale (EOC) in Ticino, Switzerland.

A possible bias of the results is the fact that the survey was carried out among hospital workers, and many of them are health professionals who generally have more knowledge of health history than the general population and that it is impossible to know the veracity of the data given in the survey by the participants since the answers for birth weight knowledge could not be confirmed with data from healthcare records. However, the birth weight distribution and mean values are in line with the reference birth weight percentiles (4).

Although further studies conducted on the general population are needed to confirm the preliminary results, we can assume that in developed countries such as Switzerland birth weight is correctly remembered, as a good agreement between birth record and self-reported birth weight is normally observed (5). Hence, it seems reasonable to include this information in the history for stratification of risk for cardiovascular and renal diseases not only in young patients but also in patients older than 40 years of age.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Canton of Ticino.

Author contributions

AC-M: study design, collection of data, analysis of data, and first draft of the manuscript. OG: study design, analysis of data, and final draft of the manuscript. MB: study design and final draft of the manuscript. GS: study design, collection of data, analysis of data, and final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Knowledge gaps and future directions in cognitive functions in children and adolescents with primary arterial hypertension: A systematic review

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Arterial hypertension (AH) among adults is known to be associated with worse cognitive outcomes. Similarly, children and adolescents with AH could be expected to underperform during neuropsychological evaluations when compared with healthy peers. Our aims were to review the existing literature on cognitive functioning among children and adolescents with primary AH and to identify what additional evidence may be needed to substantiate the impact of hypertension on poor cognitive outcomes in this population. We conducted a systematic review of articles in PubMed and Web of Science published before 17 January 2022, reporting on cognitive testing among children and adolescents with primary AH. From 1,316 records, 13 were included in the review—7 used battery-testing while other employed indirect measures of cognitive functions. Most of the studies reported worse results among individuals with AH. Results of two prospective trials suggested that cognitive functioning may improve after starting antihypertensive treatment.

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Ambulatory blood pressure monitoring was shown to be more strongly related to cognitive testing results than office measures of blood pressure. Significant confounders, namely obesity and sleep apnea, were identified throughout the studies. Our review indicates that evidence relating AH with poor cognitive functioning among youth is usually based on indirect measures of executive functions (e.g., questionnaires) rather than objective neuropsychological tests. Future prospective trials set to test different cognitive domains in children and adolescents undergoing treatment for AH are endorsed and should consider using standardized neuropsychological batteries as well as adjust the assessing results for obesity and sleep disorders.

KEYWORDS

blood pressure, primary arterial hypertension, executive functions, neuropsychology, pediatrics, childhood, adolescence, HyperChildNET

Introduction

Executive functions are high order cognitive processes that are necessary when an automatic response to a situation is insufficient. This typically occurs when the brain needs to involve additional resources to adapt its response to complex demands (1). These cognitive processes are involved in planning or reasoning, and are important abilities that have been shown to be related to critical development of the brain during childhood and adolescence (2, 3). Executive functions can be evaluated with standardized neuropsychological tasks that assess different types of functions, such as cognitive flexibility, working memory, or response inhibition. These complex cognitive processes are strongly related to the prefrontal structures of the brain (4), and require a large amount of resources; thus, the activations associated with these processes imply high oxygen demands (5, 6). Therefore, good brain vascularization and the adequate perfusion are essential to achieve a good performance in these high order cognitive processes. Consequently, a healthy development of the prefrontal cortex (PFC) remains critical for the optimal development of an individual's executive functions (7). As the PFC reaches its maturity later than the rest of the brain structures, both gray and the white matter of the PFC present significant changes during childhood and adolescence (2, 8, 9).

Arterial hypertension (AH) during childhood and adolescence could imply vascular disruptions in the brain, and more precisely, in the PFC. This would be associated with vascular cognitive impairment, presenting deficits in highly demanding mental processes (10). The brain is susceptible to damage by high blood pressure (BP), which may cause microinfarctions, white matter lesions, promote atrophy, and disrupt the neurovascular unit as well as the perivascular space (11, 12). It has been shown that AH is associated with worse cognitive outcomes among adults and new findings suggest that such a relationship also exists in children and adolescents (13, 14). It is important to highlight that AH without a known secondary cause (i.e., primary hypertension) is becoming more and more frequent among children and adolescents (15).

The topic is of great interest as early-onset AH could potentially determine cognitive health later in life (16). It could be expected that if the AH in children is not treated correctly, these subjects would be at higher risk of presenting cognitive decline at older ages, as well as neurological brain disorders, including Alzheimer's disease (10, 17). AH may cause both acute-severe neurological complications as it is in case of hypertensive crisis, and chronic, subclinical impairment of neurocognitive function (18, 19). Thus, at a neurological level, their BP levels remain important not only for future cognitive development, but are also affecting their health and quality of life from an early age.

Consequently, early detection and treatment of primary AH in children and adolescents may be a relatively easy measure to decrease the risk of future cognitive impairment. However, it remains unclear which cognitive domains are most susceptible to being damaged in children with AH and which are merely consequences of cofounders associated to AH such as obesity or sleep disturbances (20, 21). Additionally, there is not much information about the possible positive effects of antihypertensive treatment on cognitive impairment in children with AH. Therefore, the main aim was to review the literature on cognitive impairment in children and adolescents with primary AH, highlighting current evidence and identifying potential gaps in the literature. Thus, our first specific objective was to summarize the results of anti-AH intervention on the executive functioning of children with AH. Secondly, to gather evidence about what type of AH and what BP measurements are more associated to cognitive impairments (e.g., primary/secondary hypertension, central/peripheral measures, ambulatory, etc.).

And finally, to summarize the evidence on the possible association with cofounders.

Methods

Literature information sources and search terms

The review process was conducted according to the PRISMA guidelines (22). Two databases (PubMed and Web of Science) were used to obtain literature search of articles published up to 17 January 2022. The following search string was used, without any filters in PubMed: "[(hypertension[Title/Abstract]) OR (blood pressure[Title/Abstract])] AND [(child*[Title/Abstract]) OR (pediat*[Title/Abstract]) OR (young[Title/Abstract] OR (adolescent*[Title/Abstract])] AND [(cogn*[Title/Abstract]) OR (executive[Title/Abstract]) OR (memory[Title/Abstract])]" and Web of Science: "AB = [(hypertension OR "blood pressure") AND (child* OR pediat* OR young OR adolescent*) AND (cogn* OR executive OR memory)]."

Inclusion and exclusion criteria

The inclusion criteria were: (1) pediatric studies (only individuals aged <18 years), (2) studies containing a group with primary AH (studies that did not explicitly rule out secondary hypertension among their sample were also considered for inclusion) and (3) using any instrument to assess cognitive functions. The exclusion criteria were: (1) records in other languages than English, (2) studies including no identifiable group with hypertension (e.g., blood pressure measures used only as continuous variables), (3) undefined methodology of BP measurement, (4) studies of secondary AH and (5) the relationship between hypertension and cognitive outcomes is not reported.

Study selection and data extraction

The articles were first screened by title, selected for inclusion and reviewed in full by I.L. and K.P. Data extracted were: sample, age, method of BP measurement, type of hypertension, method of cognitive assessment, type of analysis, major results. Discrepancies were dealt with by mutual agreement between the reviewers.

Quality appraisal

Quality of reviewed literature was assessed by two independent reviewers using the Downs and Black checklist (23). Cross-sectional and longitudinal studies were assessed. This scale has been broadly used to assess the methodological quality of health studies. Any discrepancies between the two reviewers were mediated by a third reviewer (**Supplementary Table 1**). The evaluation found that the studies were largely based on valid and reliable methods with good outcome reports.

Results

Study selection

The search yielded 1,316 individual results from the two databases, of which 13 met the eligibility criteria (**Figure 1**). Additionally, six articles provided data on the relationship between BP and cognitive domains in the pediatric population but made no distinction of AH groups (24–29).

Study results

A summary of available studies is presented in **Table 1**.

Executive functions assessment

Neurocognitive assessment was heterogeneous, with seven studies reporting results of battery-testing, while indirect measures of executive functioning were evaluated in ten studies. Some of the validated tasks for direct assessment of the executive functions reported deficits in executive functioning in children with AH. Children with AH showed lower digit span in the verbal scale of the WISC-R, a measure of short-term memory, attention and concentration (30). Children with AH also reported worse performance than normotensive ones in the Rey Auditory Verbal Learning Test (RAVLT) and in the CogState Groton Maze Learning Test delayed recall, measures of short term and working memory (31). Additionally, AH was also related to worse performance in the Grooved Pegboard dominant hand subtest, showing less fine motor dexterity, and lower scores in the vocabulary subscale of the Wechsler Abbreviated Scales of Intelligence (31).

Six studies included in this review only assessed cognitive performance by indirect measures of executive functions and behaviors. The BRIEF questionnaire (Behavior Rating Inventory of Executive Function), a subjective proxy-reported measure for evaluating behaviors related to the executive functioning of these children, reported association between AH and higher scores in the Metacognition Index (MI), Behavioral Regulation Index (BRI) and Global Executive Composite (GEC) scales (32). High scores in the BRIEF scales suggest that there could be difficulties in their executive functions (32–37). Moreover, child behaviors have also been assessed using the Child Behavior Checklist (CBCL), a tool aimed at evaluating their internalizing and externalizing behaviors. AH in children was associated with

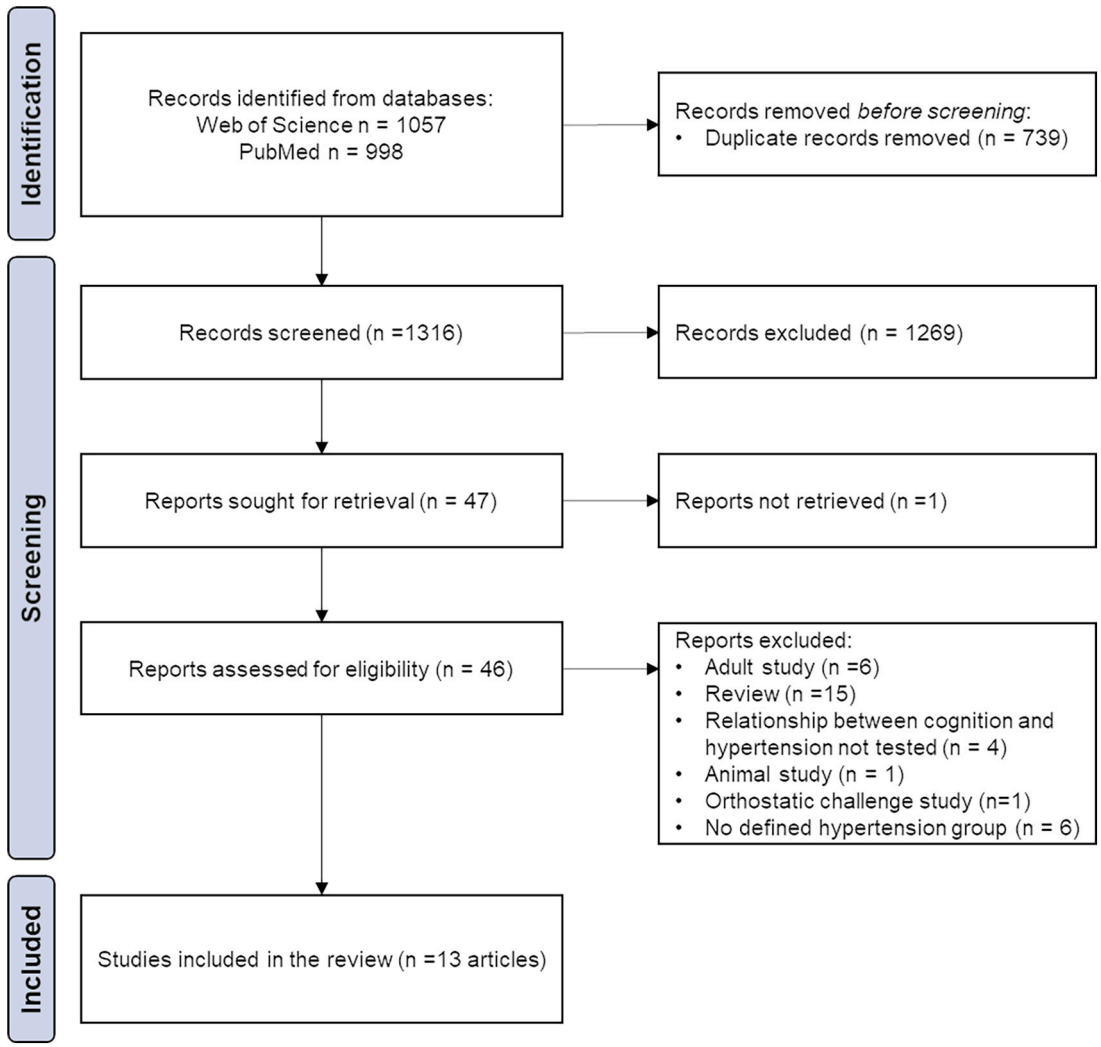

FIGURE 1
The article selection procedure, according to the PRISMA flowchart.

both clinically significant higher internalizing and externalizing behaviors (32, 34). Also, in one of the studies, parents were asked about the presence of learning difficulties and children with AH were more likely to present learning difficulties than normotensive children (38).

Effect of anti-arterial hypertension treatment

Except for two trials of prospective design and one collecting retrospective data (38), the reports were cross-sectional. Prospective designs evaluated the effect of anti-AH therapy on the neurocognitive performance of children with AH. The results of one of the prospective studies reported that children with AH showed improvement in the BRIEF scale after 12 months of anti-hypertensive treatment (33). However, in the other prospective study, a year of anti-AH therapy did not improve neurocognitive test performance, but complementary analysis showed that it may have enabled children with AH to benefit from task learning at the same level as normotensive children (39).

Arterial hypertension etiology and measurements

Two studies used solely office BP measures to define AH and control groups, others sought confirmation by performing 24-h ambulatory blood pressure monitoring (ABPM). ABPM was found to be more precise in distinguishing hypertensive children with executive dysfunctions (37, 40). Ten of the studies excluded the participants with secondary hypertension from the study, only two studies did not make the distinction between primary and secondary hypertension and one study compared a group of children with primary AH to children with renal AH. This study observed that children with renal AH presented lower executive

TABLE 1 Studies that evaluated cognitive impairment in children and adolescents with primary AH.

References	Study design	Sample size	n(AH)/n(HC)	Age (mean, SD or range)	Definition of hypertension	Type of arterial hypertension	Psychological assessment	Type of analysis	Main findings
Lande et al. (30)	Cross-sectional	5,077	288/4,789	6–16	Office BP, three measurements, ≥ 90th percentile	No distinction	WISC-R: block design (constructional skills) and digit span (short-term memory, attention, and concentration) subtests. WRAT-R: reading and arithmetic sections	Group comparisons and multiple linear regression	AH associated with lower Digit span after adjustment
Lande et al. (32)	Cross-sectional	64	32/32	16 (14–17)	History of office BP, three occasions, ≥ 95th percentile confirmed by 24 h-ABPM. WCH excluded	Only primary	IQ WISC (10–15) or WAIS (>15), CBCL, BRIEF	Group comparisons and multiple linear regression	CBCL: AH and BMI interaction on Internalizing behaviors BRIEF: Higher BRI, MI, and GEC scores in AH
Adams et al. (38)	Retrospective	201	100/101	15 (13–17)	Initial office BP ≥ 95th percentile, confirmation by 24 h-ABPM or three measurements	Only primary	Learning disabilities (defined as having a current individualized education plan or section 504 plan, both formal indicators of a student's need for services to address an educational problem) or treated for ADHD	Categorical chi-square and multivariate analysis	AH associated with ADHD and LDs after adjustment
Lande et al. (33)	Prospective. 12-month follow-up of (32)	47	22/25	15 (13–16)	Repeated 24 h-ABPM at follow-up	Only primary	CBCL, BRIEF	Repeated measures ANCOVA	BRIEF: BRI, MI, GEC score improvement in AH
Ostrovskaya et al. (35)	Cross-sectional	14	n/a	14.5 (3.3)	24 h-ABPM	Only primary	BRIEF	Correlation analysis	Lower cerebrovascular reactivity slopes among AH, inversely associated with BRIEF scores
Lande et al. (34)	Cross-sectional	72	38/34	15.0 (2.1) [AH]	History of office BP, three occasions, ≥ 95th percentile confirmed by 24 h-ABPM	Only primary	SRBD-PSQ, CDI, BRIEF, RAVLT (attention, learning and memory), CPT-II (Attention and vigilance, Response inhibition, Attention), WASI: Vocabulary Matrix, Reasoning FSIQ (general intelligence), WISC-IV: Digit Span F and B, Spatial Span F and B (working memory, attention), DKEFS (Planning/Problem Solving), Tower test, Grooved Pegboard, CogState GMLT (Planning/Problem Solving, Memory), CogState Set Shifting	Group comparisons, correlation analysis	Higher SRBD-PSQ score associated with worse executive function (BRIEF), internalizing and externalizing behavior (CBCL), and worse ratings of depression (CDI)

(Continued)

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TABLE 1 (Continued)

References	Study design	Sample size	n(AH)/n(HC)	Age (mean, SD or range)	Definition of hypertension	Type of arterial hypertension	Psychological assessment	Type of analysis	Main findings
Madaeva et al. (42)	Cross-sectional	38	n/a	14–17	Office BP, three occasions, ≥ 95th percentile	No distinction	Lichko's Pathocharacterologic Diagnostic Questionnaire, "attention processes with Schulte tables, audio verbal features and visual-spatial memory by memorizing ten words and icons, peculiarities of speech and thinking with "60 words" and "classification of objects" techniques, making the story on the subject"	Group comparison within the hypertension group (with OSA or without)	Poorer cognitive outcome among adolescents with both AH and OSA
Lande et al. (31)	Cross-sectional	150	75/75	15.1 (2.2)	History of office BP, three occasions, ≥ 95th percentile confirmed by 24 h-ABPM	Only primary	BRIEF, RAVLT (attention, learning and memory), CPT-II (Attention and vigilance, Response inhibition, Attention), WASI: Vocabulary Matrix, Reasoning FSIQ (general intelligence), WISC-IV: Digit Span F and B, Spatial Span F and B (working memory, attention), DKEFS (Planning/Problem Solving), Tower test, Grooved Pegboard, CogState GMLT (Planning/Problem Solving, Memory), CogState Set Shifting	Group comparisons, correlation analysis, multivariate analysis	AH associated with worse verbal (RAVLT) and visual (CogState GMLT) learning and recall, verbal and visual reasoning (WASI). AH not impaired on tasks of vigilance and visuomotor reaction time, auditory and visual attention, working memory, problem solving, planning, set shifting
Kupferman et al. (40)	Cross-sectional, extension of (31)	150	75/75	15.1 (2.2)	History of office BP, three occasions, ≥ 95th percentile confirmed by 24 h-ABPM	Only primary	RAVLT (attention, learning and memory), WASI-Vocabulary Matrix (vocabulary), Grooved Pegboard (manual speed and dexterity), CogState GMLT (Planning/Problem Solving, Visual Memory)	Group comparisons, correlation analysis, multiple logistic regression	24 h-ABPM superior to office BP in distinguishing AH youth with lower neurocognitive test performance
Lande et al. (39)	Prospective. 12-month follow-up of (31)	121	55/66	n/a	History of office BP, three occasions, ≥ 95th percentile confirmed by 24 h-ABPM	Only primary	BRIEF, RAVLT (attention, learning and memory), CPT-II (Attention and vigilance, Response inhibition, Attention), WASI: Vocabulary Matrix, Reasoning FSIQ (general intelligence), WISC-IV: Digit Span F and B, Spatial Span F and B (working memory, attention), DKEFS (Planning/Problem Solving), Tower test, Grooved Pegboard, CogState GMLT (Planning/Problem Solving, Memory), CogState Set Shifting	Repeated measures ANCOVA	A year of anti-AH therapy did not improve neurocognitive test performance beyond improvement in control subjects. Anti-AH therapy may influence test performance by enabling strategic learning

(Continued)

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TABLE 1 (Continued)

References	Study design	Sample size	n(AH)/n(HC)	Age (mean, SD or range)	Definition of hypertension	Type of arterial hypertension	Psychological assessment	Type of analysis	Main findings
Chrysaidou et al. (37)	Cross-sectional	116	38/78	11.20 (3.08)	Office BP, three measurements, ≥ 95th percentile + 24 h-ABPM	Only primary	BRIEF	Group comparisons, correlation analysis, multiple linear regression	Executive function lower in night-time AH, mediated by SBP despite obesity. Office-BP parameters inferior to 24 h-ABPM
Stabouli et al. (41)	Cross-sectional	92	46 (primary AH)/46 (secondary AH)	11.4 (2.9) [AH]	Office BP, three measurements, ≥ 95th percentile + 24 h-ABPM + cBP scores ≥ 95th	Compared primary vs. secondary hypertensive groups	BRIEF	Group comparisons, multiple linear regression	cSBP the only significant predictor of the parent MI. cSBP and BMI associated with parent BRI, but with an interaction between AH group and anti-AH treatment. Ambulatory AH group not predictive of BRIEF
Stabouli et al. (36)	Cross-sectional	99	30/69	11.1 (3.1)	Office BP, three measurements, ≥ 95th percentile + 24 h-ABPM	Only primary	BRIEF	Group comparisons, correlation analysis, ANCOVA, mediation analysis	Serum uric acid concentration associated with worse executive function, association partly mediated by night time SBP

ABPM, Ambulatory blood pressure monitoring; ADHD, attention deficit hyperactivity disorder; AH, arterial hypertension; ANCOVA, Analysis of covariance; BMI, body mass index; BRI, Behavior Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; cBP, central blood pressure; CBCL, Child Behavior Checklist; cSBP, central systolic blood pressure CogState; CDI, Child Depression Inventory; FSIQ, Full Scale Intelligence Quotient; GEC, Global Executive Composite; GMLT, CogState Groton Maze Learning Test; CPT-II, Conners' Continuous Performance Test II; DKEFS, Delis-Kaplan Executive Function System; HC, healthy control; LD, learning disability; MI, Metacognition Index; OSA, obstructive sleep apnea; RAVLT, Rey Auditory Verbal Learning Task; SBP, systolic blood pressure; SRBD-PSQ, Pediatric Sleep Questionnaire: Sleep-Related Breathing Disorder scale; WASI, Wechsler Abbreviated Scales of Intelligence; WCH, white coat hypertension; WISC, Wechsler Intelligence Scale; WRAT, Wide Range Achievement Test.

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function performance but also higher levels of central SBP, and, after adjustment by their central SBP levels, no significant differences were found in parents' cognitive and behavioral assessments (41). Besides, effects of systolic vs. diastolic AH was assessed in one study, which reported closer association of cognitive deficits with systolic AH (30).

Potential cofounders

The reviewed literature also analyzed the possible effect of cofounders associated to AH. One study found that the executive impairments were independent of obesity levels in children with AH (37). While others found that body mass index (BMI) was associated to the BRI scale of the BRIEF inventory (41) and internalizing behaviors of the CBCL (32). Also, one study found a positive association between higher levels of serum uric acid and worse executive performance (36). Furthermore, children with AH were more prone to sleep disordered breathing (34) and children with AH who also presented obstructive sleep apnea showed poorer cognitive performances (42). Interaction between disordered sleep and poorer executive functioning was also observed in children with AH (31). Additionally, one study showed that learning difficulties were independent from the presence of attention deficit hyperactivity disorder (ADHD) symptomatology (38).

Assessment instruments

After reviewing the literature on cognitive functions in children and adolescents with AH, we found that the used instruments were heterogeneous. Therefore, in **Supplementary Table 2** we suggest a battery of instruments for evaluating cognitive functions in children and adolescents with AH. This battery includes a series of validated instruments (some of them used in the reviewed studies) that assess different cognitive domains and would allow easier comparison of the results.

Discussion and future directions

The current review outlines the scarcity of studies that assess a wide spectrum of cognitive domains in children and adolescents with AH. There is a broader literature on the association of AH mediated cognitive impairments in adults, but fewer studies on children and adolescents (13, 16). Alongside reports relating global IQ and BP measurements, the few studies that employed neuropsychological batteries provide evidence that AH-associated cognitive damage may be generalized and reflected by deficits in verbal and visual reasoning, learning and recall, working memory and semantic/letter fluency. As impaired executive functions are known among adults with AH, this association could also be expected among children and adolescents as well (16, 43). However, a direct assessment of executive function (e.g., the CogState GMLT) has only rarely been used in children with AH (31). Identification of domain-specific damage could lead to better understanding on how neurovascular beds differ in their susceptibility to AH among pediatric and adult patients, and define the possible reversibility of these effects. For instance, it has been shown by Lande et al. that poor BP control limits the ability to use previous learning techniques for better performance during subsequent cognitive testing (39). The authors associate this finding with cognitive deficits that may remain present in adulthood. Thus, it is essential to further investigate: (1) which cognitive domains are most susceptible to damage by high BP in early life and (2) whether good BP control suffices for patients with AH to match controls in cognitive outcomes (otherwise, what other treatment, rehabilitation or learning techniques could improve their cognitive functions).

Globally, the reviewed studies report that children and adolescents with AH perform worse than their normotensive peers following a wide-range of neurocognitive domains. However, the investigations were very heterogeneous in their approach toward neurocognitive testing and therefore hamper the general extrapolating from the studies. Overall, the neurocognitive assessment using validated batteries reported deficits in executive functions in children and adolescents with AH compared to normotensive controls. According to the reviewed literature, young individuals with AH might have deficits in short-term memory, working memory, attention, concentration, fine motor dexterity and vocabulary (30, 31). However, the literature using valid direct assessment of executive functions in children and young people with AH is limited. Furthermore, several studies relied solely on subjective measures such as BRIEF and/or CBCL questionnaires to measure cognitive functions (namely executive domains, externalizing and internalizing behaviors). While BRIEF has good psychometric properties and ecological validity, it remains an indirect measure of executive functions that relies on patient or parent reporting of the child's behavior in different environments (44). This may be especially problematic if subtle subclinical deficits are sought to be assessed, for which specialized tests of executive function are needed. Also, results obtained from BRIEF differ from recent studies showing that AH-related executive dysfunctions are either absent following adjustment for confounders (especially disordered sleep) or related only to measures of central but not brachial BP (31, 41). Finally, as BRIEF relies on parent reporting, it is also prone to additional bias if treatment groups are not blinded (as parents expect treatment to have effect on their child's performance) (33).

As has been observed in this review, the literature that analyzed the possible effects of anti-AH treatment on the executive functions of children with AH is scarce. The few evidence measuring the effect of an anti-AH treatment seems to indicate that it could improve cognitive outcomes, but further research is needed. One of the few studies that analyzed the effect of the treatment found improvements in the executive

functions of children with AH after 12 months of anti-AH therapy (33). However, the same research group was not able to replicate the findings in another study (39), although further analysis of the data of this second study showed that treatment could have led to improvements in children with AH similar to those of normotensive children. Moreover, most of the studies included in this review present cross-sectional designs that assess AH and executive functioning at a specific point of time. Therefore, it would be necessary to perform further longitudinal studies to evaluate if the cognitive deficits observed in children with AH in comparison to normotensive controls could be reduced following specific treatment or and/or reduction of BP levels.

The observation that the influence of higher BP on executive functions may be better detected through testing of central hemodynamics is in line with current pathophysiological theories suggesting that the latter are more relevant for AH mediated organ damage (45). Furthermore, the reviewed literature emphasizes that ABPM is the best method for detecting AH associated with possible cognitive deficits, and should therefore be the preferred measure to use in this clinical domain dysfunctions (37, 40). In this line, the measure of systolic AH was also more related to cognitive deficits than diastolic hypertension (30). Although neurological complications, both acute, clinically symptomatic and chronic, and subclinical are well described in children with secondary AH, from a public health point of view the important problem is the recognition of neurocognitive impairment in children and adolescents with primary AH. The cognitive differences between primary and secondary AH could be influenced by the general higher levels of BP of patients with secondary AH (41). Therefore, the analyzed publications emphasize the importance of a precise definition of the etiology of the AH and the employed measurement method.

Furthermore, pediatric studies investigating cognitive functions in AH face great methodological challenges in addressing confounders that may refute the hypothesis of a direct association between AH and worse performance during neuropsychological testing. While multiple regression and mediation analyses can help to partly distinguish the role of high BP in cognitive dysfunction, factors like comorbid sleep and mood disorders, ADHD symptomatology, as well as widespread obesity remain major reasons to question the direct relationship between cardiovascular and cognitive variables (34). Besides, studies treating learning difficulties and ADHD as end-points may miss mild early-onset cognitive decline that does not produce significant learning difficulties (38). The executive deficits can be associated with attentional problems in children with AH, however, children with ADHD seem to present lower levels of BP (46), so the deficits related to AH could be independent from the ADHD symptomatology. Recently, it has also been shown that uric acid levels alongside high BP are associated with worse executive functions (36). Such findings highlight the need for a complex approach toward studies of cognitive function in children with AH that would include biological as well as imaging biomarkers as part of the investigation process (13).

Conclusion

Studies assessing cognitive function in children and adolescents with AH remain scarce and are highly heterogeneous in methodology. Most of the studies that assessed executive functions in this population widely relied on indirect parent-reported measures, with the limitations and possible biases that this entails. While several studies report deficits of executive functions among patients with AH, the improvement of cognition after treatment remains undetermined. Given the mixed findings, future studies should prospectively employ comprehensive neuropsychological batteries that directly assess different cognitive domains, including verbal/visual memory, working memory, attention, reaction speed and global intellect. The heterogeneity of the evaluation methods found in this review highlights the necessity of establishing a standardized protocol for evaluating the cognitive functioning of children with primary AH.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Author contributions

IL and KP conducted the review of the studies and wrote the first draft of the manuscript. IL, KP, EL, SJ-M, AJ, and FF-A contributed to the idea and conceptualization of the review. AJ and FF-A supervised the preparation of the review and the interpretation of the results. MS, ML, KM, KA, RR, MP, LO, TB, JŚ-K, ES, EL, and SJ-M revised the manuscript and provided substantial comments. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.973793/full#supplementary-material

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Prevalence of left ventricular hypertrophy in children and young people with primary hypertension: Meta-analysis and meta-regression

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Background: Left ventricular hypertrophy (LVH) is the main marker of HMOD in children and young people (CYP). We aimed to assess the prevalence of LVH and its determinants in CYP with primary hypertension (PH).

Methods: A meta-analysis of prevalence was performed. A literature search of articles reporting LVH in CYP with PH was conducted in Medline, Embase, and Cochrane databases. Studies with a primary focus on CYP (up to 21 years) with PH were included. Meta-regression was used to analyze factors explaining observed heterogeneity.

Results: The search yielded a total of 2,200 articles, 153 of those underwent full-text review, and 47 reports were included. The reports evaluated 51 study cohorts including 5,622 individuals, 73% male subjects, and a mean age of 13.6 years. LVH was defined as left ventricle mass index (LVMI) ≥ 95th percentile in 22 (47%), fixed cut-off ≥38.6 g/m$^{2.7}$ in eight (17%), sex-specific fixed cut-off values in six (13%), and miscellaneously in others. The overall prevalence of LVH was 30.5% (95% CI 27.2–33.9), while heterogeneity was high ($I^2 = 84\%$). Subgroup analysis including 1,393 individuals (76% male subjects, mean age 14.7 years) from pediatric hypertension specialty clinics and LVH defined as LVMI ≥95th percentile only (19 study cohorts from 18 studies), reported prevalence of LVH at 29.9% (95% CI 23.9 to 36.3), and high heterogeneity ($I^2 = 84\%$). Two studies involving patients identified

through community screening (n = 1,234) reported lower LVH prevalence (21.5%). In the meta-regression, only body mass index (BMI) z-score was significantly associated with LVH prevalence (estimate 0.23, 95% CI 0.08–0.39, p = 0.004) and accounted for 41% of observed heterogeneity, but not age, male percentage, BMI, or waist circumference z-score. The predominant LVH phenotype was eccentric LVH in patients from specialty clinics (prevalence of 22% in seven studies with 779 participants) and one community screening study reported the predominance of concentric LVH (12%).

Conclusion: Left ventricular hypertrophy is evident in at least one-fifth of children and young adults with PH and in nearly a third of those referred to specialty clinics with a predominant eccentric LVH pattern in the latter. Increased BMI is the most significant risk association for LVH in hypertensive youth.

KEYWORDS

left ventricular hypertrophy, primary hypertension, children, adolescents, left ventricular mass index

Introduction

Arterial hypertension (HT) is considered one of the most important global health problems and represents a potentially reversible risk factor for cardiovascular disease (CVD) development (1, 2). HT affects 4–5% of children and adolescents in general, and the prevalence increases with age (3). Importantly, childhood blood pressure (BP) has been shown to track into adulthood and is associated with subsequent cardiovascular (CV) outcomes (4). The increasing prevalence of childhood HT observed over the last decades associated with the global childhood obesity epidemic is likely to have significant implications for the development of adult CVD (5).

The heart and blood vessels are the primary organs adversely affected as a result of HT as they are directly exposed to the elevated BP, with secondary involvement of the kidneys and the central nervous system. In most cases, hypertension-mediated organ damage (HMOD) occurs in several stages. The development of diagnostic techniques makes it possible to detect early changes, which are often clinically silent and potentially reversible before established CVD (6). Persistent HT results in adaptive changes to reduce wall stress in the blood vessels and heart and include increasing thickness of blood vessels and left ventricular remodeling (7). Thus, cardiomyocyte hypertrophy and thickening of the artery wall are observed. With disease progression, the deposition of the extracellular matrix develops with an increase in the stiffness of the arterial wall and impaired function of the left ventricle and arteries (8). The development of HMOD is complex and depends on several factors including the level and duration of HT, individually variable response of tissues and organs to increased BP, and accompanying metabolic abnormalities (8–11).

Left ventricular hypertrophy (LVH) is the primary marker evaluated for HMOD. Its presence is a therapeutic indication in individuals with primary hypertension (PH) (12). Numerous studies have reported that in a substantial proportion of children and adolescents with PH, LVH is present already at diagnosis, but the extent of its prevalence has not yet been evaluated systematically. Furthermore, there are few data regarding the remodeling of the left ventricle and its determinants. The aim of our study was to estimate the prevalence of LVH and its determinants in children and young people with confirmed PH by meta-analysis and meta-regression using clearly defined inclusion and exclusion criteria and focusing on studies with PH in CYP.

Materials and methods

A systematic review and meta-analysis to determine the prevalence of LVH and different remodeling patterns in children and young people with PH was performed. Meta-regression was used to analyze between-study factors explaining observed heterogeneity in reported prevalence.

This systematic review and meta-analysis were carried out and the data are presented according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13).

Eligibility criteria

The following eligibility criteria were used to select studies for the analysis:

Inclusion criteria

- Original research published since 1990.
- Studies that include children and young people (up to 21 years) with PH (or reports subgroup data for patients with PH).
- Prevalence and definition of LVH are reported.

Exclusion criteria

- Other languages than English.
- Reviews, case reports, case series, and animal studies.
- Studies including <20 patients.
- Studies analyzing the data from the same or overlapping cohort.
- Studies primarily including patients with obesity or diabetes mellitus.
- Community studies where the exclusion of secondary causes of HT was not stated.
- Studies that include data from patients receiving antihypertensive treatment or when the treatment status of patients was not explicitly stated.

Literature search and articles selection

A literature search was performed in MEDLINE, Embase, and Cochrane Library databases on 25 April 2022 by an academic librarian (ISKS). The search was peer-reviewed by a second academic librarian. The search included relevant synonyms and MeSH/Emtree subject headings, as well as an adapted broad search filter for children from Ovid Expert Searches to best include all pediatric and young adult studies. The literature search strategy is described in detail in the Supplementary Methods. After the removal of duplicates, all articles underwent title and abstract screening by two authors (TB and JSK). Shortlisted articles that were screened as potentially meeting eligibility criteria were independently evaluated by full-text review by at least two authors (KA, KM, TB, JSK, and MDS) and selected for final analysis. In cases where repeated data were identified between two or more studies, the study with the highest sample size or most accurate cohort description (i.e., BP phenotypes reporting) was selected.

Definitions and data extraction

Definitions of HT, pre-hypertension (preHT), high-normal BP, and white-coat hypertension (WCH), both by office BP and by ambulatory BP monitoring (ABPM), that were proposed as per relevant international or national clinical practice guidelines were considered for the analyses. No restrictions on the method to estimate left ventricular mass index (LVMI), to define LVH and left ventricular remodeling patterns were applied.

All data extraction was performed independently by two authors and compared. The following data were extracted into pre-specified data extraction forms: first author; year of publication; description of study population based on recruitment: (i) community sample or (ii) specialty clinic; sample size and number of patients with different BP phenotypes; sex, ethnicity, mean age, and age range; mean body mass index (BMI) and waist circumference (WC) with their respective z-scores (BMIz and WCz, when available); and the number of obese individuals. For LVMI and definition of LVH, we analyzed the LVMI calculation method, definition of LVH, number of patients with LVH, severe LVH, concentric remodeling, concentric LVH, and eccentric LVH (if such data were reported). Data were extracted for the whole group of individuals with PH and per each BP phenotype (if such data were reported). In case of longitudinal studies, the data from the baseline visit were included.

If the study reported data on subgroups of different phenotypes of PH (e.g., WCH and preHT) and data were not reported for the overall/combined group or pooling was impossible, data were extracted and analyzed separately for each subgroup that were treated as independent (further referred as "study cohorts"). If a study compared several definitions of BP status and/or LVH, European Society of Hypertension (ESH) 2016 guidelines and LVH definition based on the 95th percentile cut-off were selected for primary analysis (12, 14). If absolute numbers were not indicated but could be determined by transforming data (percentage to absolute number) or confidently identified from graphs—these estimates were used.

Critical appraisal

All studies selected for the final analysis underwent risk of bias assessment by two authors independently (JSK, TB, KM, KA) using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (15). Domain regarding the sufficient coverage of the sample in the analysis (number five) was not evaluated as not being relevant based on the instrument's manual. Studies scoring low risk of bias (answer "Yes") in more than half of the evaluated domains were considered as low risk of bias. Details on the provisional guidance to use the critical appraisal tool for the present analysis are shown in Supplementary Table S1.

In cases of any discrepancies in the process of study selection, data extraction, or critical appraisal, discussions with a third reviewer led to the resolution and final decision.

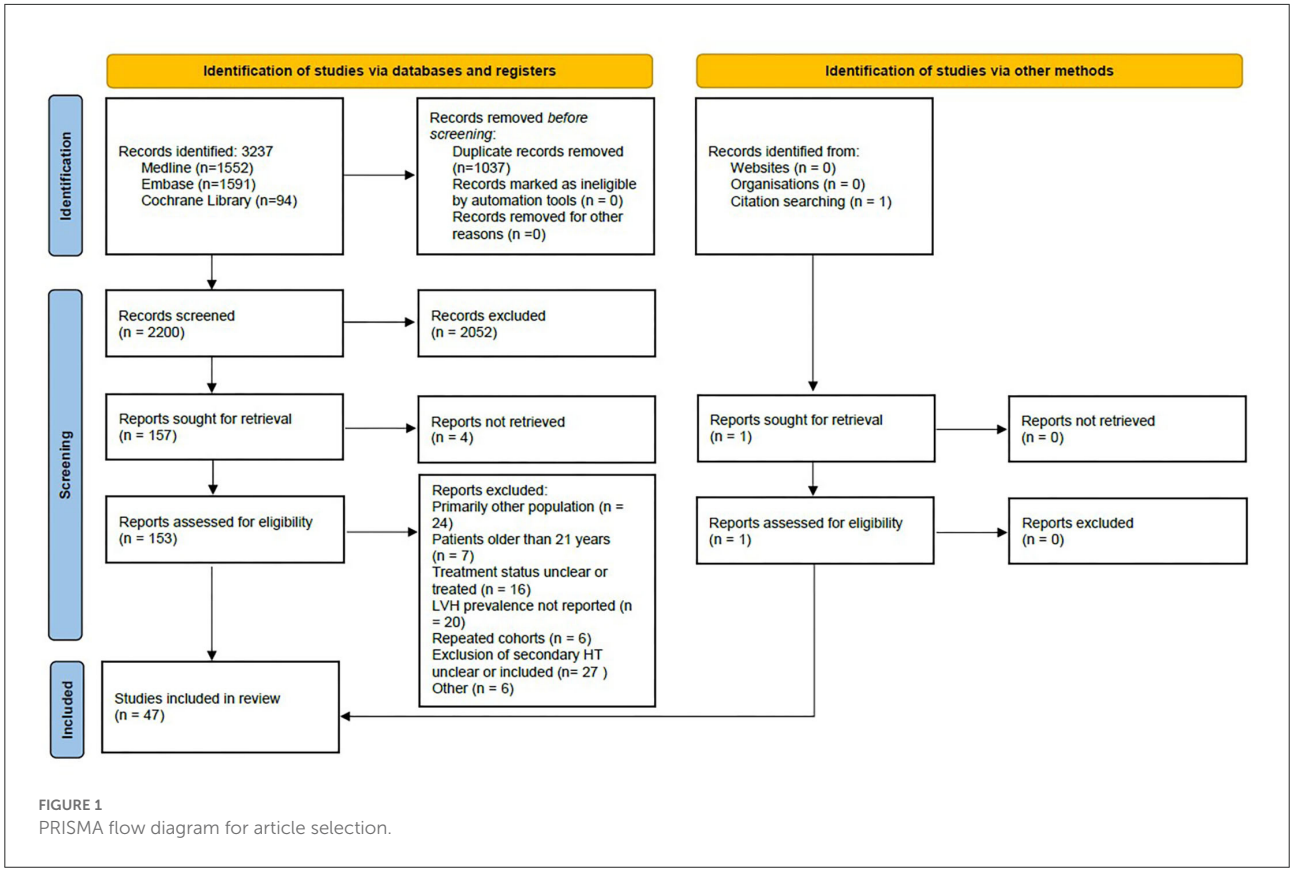

FIGURE 1
PRISMA flow diagram for article selection.

Meta-analysis and meta-regression

Descriptive characteristics of selected studies were summarized by calculating weighted means for continuous data and weighted proportions for categorical data. A meta-analysis of proportions was performed to calculate weighted pooled prevalence using a random effects model to account for expected heterogeneity. Prevalence estimates first underwent Freeman–Tukey double arcsine transformation to stabilize variance and the data were then back-transformed to provide a pooled estimate. Heterogeneity was assessed by Higgins I^2 and Cochrane Q-tests. Mixed effects meta-regression was performed to determine between-study factors leading to observed heterogeneity. Funnel plots were created and visually inspected, as well as Egger's test was used to identify potential publication bias. All statistical analyses were performed using RStudio version 1.4.1106 and packages meta and metafor.

Results

The article selection process is summarized in the PRISMA flow diagram (Figure 1). Briefly, out of 2,200 records identified through a literature search, 153 underwent full-text review (studies excluded from the analysis are shown in Supplementary Table S2) and 47 were selected for the analysis (16–62). These studies with 51 study cohorts included a total of 5,622 subjects (73% male subjects), mean age of 13.6 years (reported in 41 study cohorts), mean BMI of 25.4 kg/m^2 (reported in 33 study cohorts), and BMIz 1.43 (21 study cohorts). The proportion of obese children (23 study cohorts) was 37%, while the mean WCz was 1.30 (8 study cohorts). Three were community screening-based cohorts (17, 30, 50), 41 reported data from pediatric HT specialty clinics, and four reported mixed data from both (31, 42, 45, 56). LVH was defined as LVMI above 95th percentile in 22 (47%) studies (17, 18, 21, 23, 25–28, 32–34, 37, 44, 46, 47, 50–53, 57, 60, 61), fixed cut-off ≥38.6 g/m$^{2.7}$ in eight (17%) (19, 24, 36, 40, 43, 45, 49, 55), sex-specific fixed cut-offs (≥36.88 g/m$^{2.7}$ and ≥39.36 g/m$^{2.7}$ for female and male subjects, respectively) in six (13%) (29, 35, 38, 39, 41, 48), one used magnetic resonance imaging (MRI) (58), while the remaining were heterogeneous. Ethnicity was reported in 27 (61%) studies. Fourteen studies included subjects with WCH (28, 35, 36, 38, 45, 46, 57, 58) and/or preHT (24, 28, 37, 39, 46, 54, 57, 61). Detailed characteristics of all studies are shown in Supplementary Table S3.

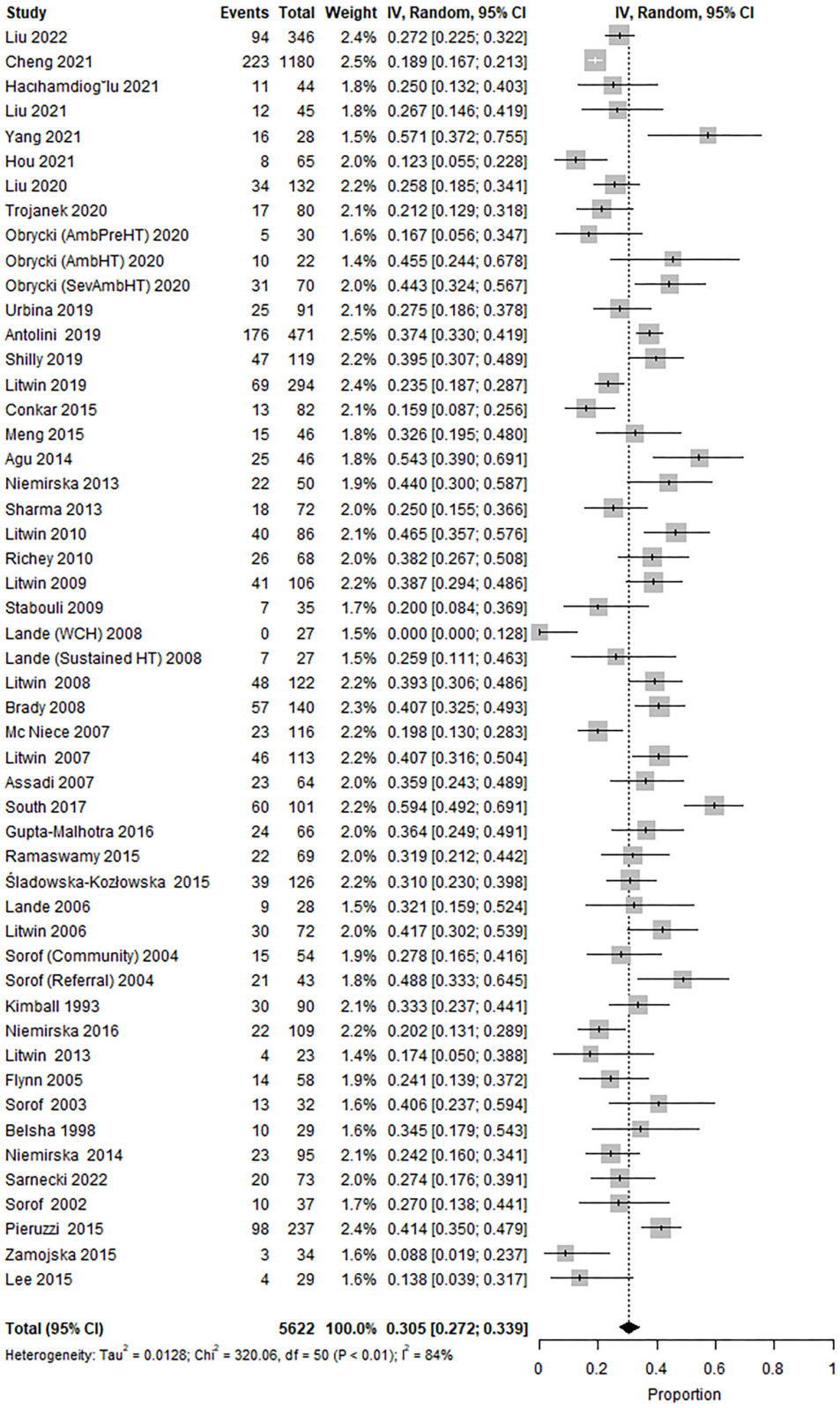

FIGURE 2
Forest plot showing the prevalence of LVH in all identified studies (47 studies, 51 study cohorts).

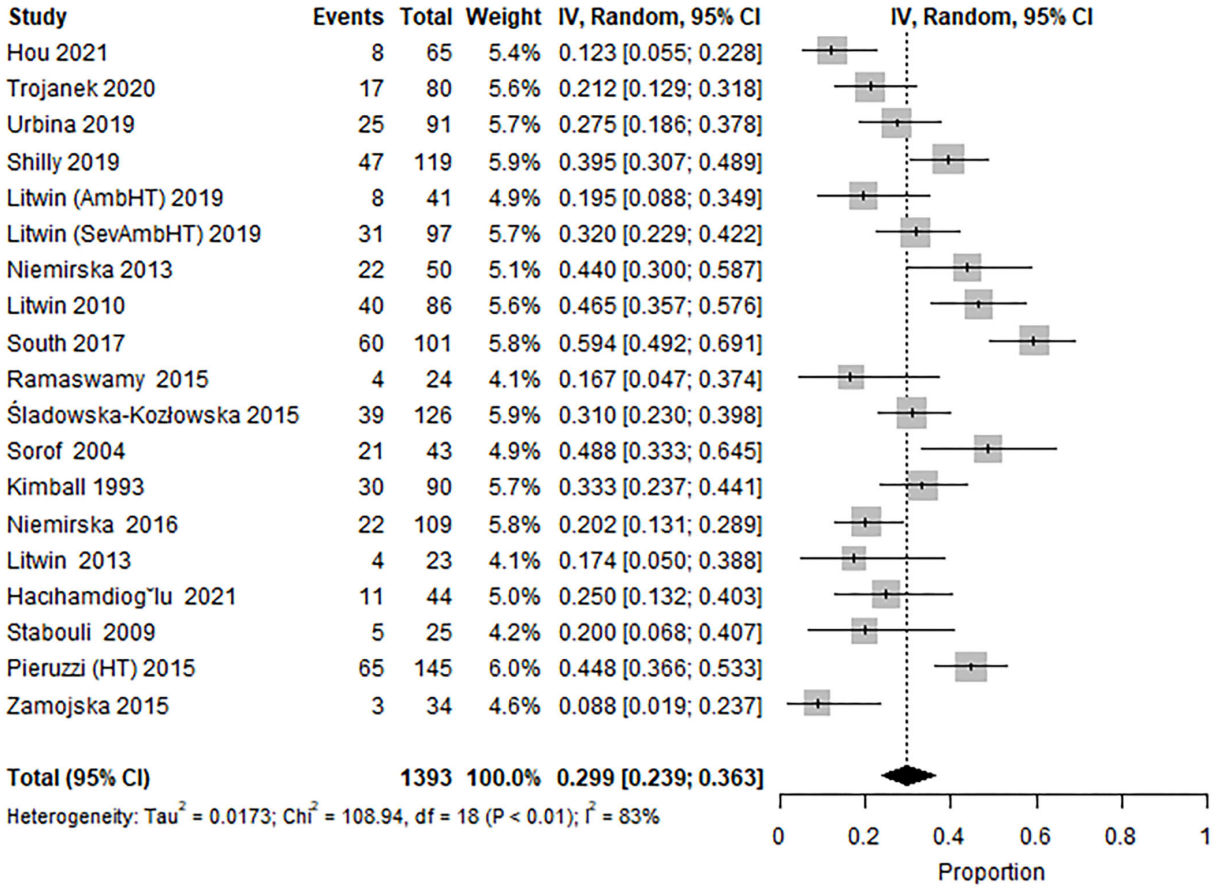

FIGURE 3
Forest plot showing the prevalence of LVH in the subset of studies from specialty clinics, LVH defined by ultrasound estimated LVMI ≥95th percentile and excluding subjects with WCH and/or preHT (18 studies, 19 study cohorts).

Prevalence of LVH

The overall prevalence of LVH was 30.5% (95% CI 27.2 to 33.9; Figure 2), while the heterogeneity was high ($I^2 = 84\%$).

Two sub-group analysis studies were performed. (i) Subgroup 1: including studies reporting data from pediatric HT specialty clinics only (19 study cohorts from 18 studies) (18, 21, 23, 25, 27, 28, 32, 34, 37, 44, 46, 47, 50–53, 60, 61), reported prevalence of LVH at 29.9% (95% CI 23.9–36.3; Figure 3), and high heterogeneity ($I^2 = 84\%$). LVH in them was defined as LVMI ≥95th percentile; and excluded subjects with WCH and/or preHT and included 1,393 patients (76% male subjects) with a mean age of 14.7 years, mean BMI of 25.9 kg/m^2 (17 study cohorts), and mean BMIz of 1.40 (14 study cohorts). Six study cohorts reported a 29% obesity rate in children, and six reported WCz (mean 1.28). The characteristics of these studies are shown in Table 1. Hypertension was defined exclusively by only office BP in six study cohorts.

(ii) Subgroup 2: additionally including study cohorts reporting data from pediatric HT specialty clinics only that defined LVH by a fixed cut-off of 38.6 g/m$^{2.7}$. Twenty-nine study cohorts (25 studies) (18, 19, 21, 23–25, 27, 28, 32, 34, 36, 37, 40, 43, 44, 46, 47, 49–53, 55, 60, 61) were included with a total of 1,940 subjects. The estimated pooled prevalence of LVH was 31.4% and heterogeneity was similarly high ($I^2 = 79\%$) (Supplementary Figure S1). Mean age in this subset was 14.7 years, 75% were male subjects, mean BMI was 25.8 kg/m^2 (22 study cohorts), and mean BMIz 1.38 (20 samples). The proportion of obese children and WCz was reported in 11 study cohorts and was 27% and 1.22, respectively. HT was defined by only office BP in nine study cohorts.

Severe LVH defined as LVMI >51 g/m$^{2.7}$ was reported in 12 included studies (15 study cohorts) with 873 individuals (mean age 14.9 years, 79% male subjects), and the pooled prevalence of severe LVH was 11% ($I^2 = 72\%$) (Supplementary Figure S2) (20, 23, 24, 32, 34, 36, 39, 43, 48, 49, 59, 62).

Left ventricle geometry

Left ventricle geometry was reported in eight studies from specialty clinics that included 996 participants (mean age 13 years, 72% male subjects) with an overall prevalence of LVH at 34.2% ($I^2 = 70\%$). The prevalence of concentric remodeling was 9.0% ($I^2 = 88\%$), concentric LVH was 11.2% ($I^2 = 94\%$), and that of eccentric LVH was 21.6% ($I^2 = 0\%$) (Figure 4) (16, 19, 22, 27, 35, 46, 49, 61). In addition, one study with an overall prevalence of LVH of 18.9% reported LV geometry data for children identified by community screening (17). In this study, the predominant LV geometry pattern was concentric LVH (12%), followed by concentric remodeling (8.7%) and eccentric LVH (6.9%).

Meta-regression

Meta-regression for LVH prevalence was performed in Subgroup 1 with the following variables: age, proportion male, BMI, BMIz, and WCz. BMIz alone was significantly associated with LVH prevalence (estimate 0.23, 95% CI 0.08–0.39, $P = 0.004$; Figure 5A) and accounted for 41% of the observed heterogeneity. The other variables were not associated with LVH prevalence including age and sex (Supplementary Table S4; Figures 5B,C).

Repeating the analysis in Subgroup 2 revealed similar results (BMIz as explanatory variable, estimate 0.23, 95% CI 0.09–0.36, $P = 0.001$; 34.7% heterogeneity accounted for).

Other subgroups

Community samples

Left ventricular hypertrophy prevalence in two community screening-based study cohorts (17, 50) was 21.5% ($I^2 = 60\%$) (Supplementary Figure S3). The studies included 1,234 participants (mean age 11.9 years, 61% male subjects).

White-coat and pre-hypertension

A total of 222 participants with WCH from four study cohorts were included (mean age 15.0 years, 80% male subjects) and the prevalence of LVH was 20.2% ($I^2 = 88\%$) (Supplementary Figure S4) (28, 36, 38, 46).

Three studies with preHT included 151 patients (mean age 15.2 years, 74% male subjects; ABPM used to define preHT in two studies) and the prevalence of LVH was 21.2% ($I^2 = 79\%$) (Supplementary Figure S5) (24, 28, 61).

Risk of bias assessment

Only 19% of the studies were evaluated as low risk of bias (Supplementary Figure S6). More than half of the studies received a high risk of bias or unclear judgment on five evaluated domains: participant sampling, sample size, subject description, methods to define LVH, and reliability of LVMI measurements. Due to a small number of studies assessed as low risk of bias, the subgroup meta-analysis based on the assessed quality of the studies was not performed.

Visual inspection of Funnel plots and Egger's test suggested the risk of publication bias in Subgroups 1 and 2 (intercept 0.827, $p = 0.07$ and intercept 0.803, $p = 0.04$, respectively) with a tendency of smaller studies to report lower LVH prevalence (Supplementary Figures 7, 8).

Discussion

The mean prevalence of LVH was estimated to be 30.5% in this systematic review and meta-analysis of 5,622 children and young people with untreated PH and 47 studies reported over the last two decades. Even with the exclusion of studies from community-based populations, studies with WCH and pre-hypertension phenotypes, and variable definitions of LVH from the analysis, the same figure of 29.9% LVH from 1,393 individuals was found. The prevalence of LVH was lower in studies at 21.5% when including children identified through community screening only.

The left ventricle is one of the primary targets for HMOD but has also been shown in hypertensive adults to be an independent risk factor for cardiovascular morbidity and mortality (63–65). Moreover, both worsening LV geometry and increasing severity of LVH are known to be associated with adverse outcomes (66–69). Although similar data associating LVH in childhood PH with subsequent CV morbidity and mortality do not exist currently, data from the Bogalusa study highlight that persistently elevated blood pressure, particularly through adolescence, is associated with a significantly higher risk for adult LVH when compared with normotensive adolescents (70). It is, therefore, widely accepted that LVH in childhood PH is an adverse surrogate marker of CV morbidity, and an important target to ameliorate future CV morbidity and mortality seen in hypertensive heart disease (12, 71).

The pathophysiology of LVH in PH is complex and not fully understood, and includes both modifiable and non-modifiable risk factors, including age, sex, ethnicity, genetic factors, and co-morbidities like obesity and metabolic syndrome (72). These observations are reflected in our study findings, which show that 76% of those with hypertension were male subjects, with a mean age of 14.6 years. Despite this, no significant relationship between age or male sex and the prevalence of LVH was found in individual studies.

TABLE 1 Characteristics of samples included in the main analysis (Subgroup 1).

References	Sample population (*n*) and PH phenotype (*n*, %)	Ethnicity, *n* (%)	Age (years) Male, *n* (%)	BMI z-score WC z-score Obese patients, *n* (%)	Patients with LVH (%)
Hacihamdioglu et al. (18)	44	NA	14.0 ± 3.19	1.33 (0.66–1.87)[c]	11 (25%)
				NA	
	NA		34 (77.3%)	26[&&] (59.1%)	
Hou et al. (21)	65	Asian	12.4 ± 2.3	NA	8 (12.3%)
	NA		48 (73.8%)		
Trojanek et al. (23)	80	NA	15.1 ± 2	1.3 ± 0.74	17 (21.2%)
				1.5 ± 0.7	
	NA		67 (83.7%)	NA	
Urbina et al. (25)	91	White 53 (58.2%), Hispanic 15 (16.5%), Other 23 (25.3%)	15.3 ± 1.7	1.094 ± −0.81	25 (27.5%)
				NA	
	NA		54 (59.3%)	NA	
Shilly et al. (27)	119	Black 35 (29.4%), Other 84 (70.6%)	14 ± 3.3	1.2 ± 1.0	47 (39.5%)
	NA			NA	
			84 (70.6%)	33 (27.7%)	
Litwin et al. (AmbHT) (28)	41	NA	15 ± 3	0.9 ± 1.1	8 (19.5%)
	AmbHT (41, 100%)			1.1 ± 1.1	
			35 (85.4%)	NA	
Litwin et al. (SevAmbHT) (28)	97	NA	15.3 ± 2.3	1.1 ± 0.8	31 (31.9%)
	SevAmbHT (97, 100%)			0.9 ± 0.8	
			72 (74.2%)	NA	
South et al. (44)	102	White 26 (25.5%), Black 29 (28.4%), Hispanic 44 (43.1%), Other 3 (3%)	14.9* (13.1–16.3)[b]	NA	60! (59.4%)
	HT1 (48, 47%), HT2 (14, 14%)			NA	
				76[&] (74.5%)	
			78 (76.5%)		
Niemirska et al. (52)	109	NA	15.6 ± 1.5	1.35 ± 0.83	22 (20.2%)
				1.2 ± 0.9	
	HT1 (63, 58%), HT2 (46, 42%)		90 (82.6%)	NA	
Ramaswamy et al. (46)	24	Hispanic 7 (29.2%), Caucasian 10 (41.7%), Other 7 (29.2%)	14.7 ± 3.3	1.2 ± 1.1	4 (16.7%)
				NA	
			17 (70.8%)	NA	
	NA				
Sladowska-Kozłowska et al. (47)	126	Caucasian	15*	1.75 ± 1.7	39 (30.9%)
	AmbHT (92, 73%), SevAmbHT (34, 27%)		95 (75.4%)	1.62* (−2.03 to 6.12)[a]	
	NA				
Niemirska et al. (32)	50	NA	15* (8.5–17)[a]	2.0 ± 1.5	22 (44%)
	AmbHT (21, 42%), SevAmbHT (29, 58%)				
			50 (100%)	NA	
				28 (56%)	

(Continued)

TABLE 1 (Continued)

References	Sample population (*n*) and PH phenotype (*n*, %)	Ethnicity, *n* (%)	Age (years) Male, *n* (%)	BMI z-score WC z-score Obese patients, *n* (%)	Patients with LVH (%)
Litwin et al. (53)	23	NA	15.0 ± 2.1	1.16 ± 0.8	4 (17.4%)
				0.93 ± 0.9	
	NA		19 (82.6%)	NA	
Litwin et al. (34)	86	Caucasian	14.1 ± 2.4	1.8 ± 1.8	40 (46.5%)
	AmbHT (50, 58%), SevAmbHT (36, 42%)			1.8* (−1.1 to 6.1)[a]	
			66 (76.7%)	21 (24.4%)	
Stabouli et al. (37)	25	Caucasian	14.8 ± 4.2	1.28 ± 1.03	5 (20%)
	NA		13 (52%)	NA	
				NA	
Sorof et al. (50)	43	White 13 (30.2%), Hispanic 10 (23.25%), Black 18 (41.9%), Other 2 (4.65%)	13.9 ± 2.0	1.76 ± 0.76	21 (48.8%)
	NA				
				NA	
			33 (76.7%)	25^ (58.1%)	
Kimball et al. (51)	90	White 46 (51.1%), Black 44 (48.9%)	14 ± 4.0	NA	30 (33.3%)
				NA[$]	
	NA		54 (60%)		
Pieruzzi et al. (61)	145	NA	NA	NA	65 (44.8%)
				NA	
	NA		84 (57.9%)	71 (48.97%)	
Zamojska et al. (60)	34	NA	15.3 ± 2.1	NA	3 (8.8%)
				NA	
	NA		27 (79.4%)		
				0	

Continuous data are represented as mean values with standard deviation, unless specified otherwise.
* Median.
[a] Data range; [b] Interquartile range; [c] 95% confidence interval.
[&] Overweight/obesity defined as ≥85th percentile and reported together.
[&&] Obese or overweight.
[!] n = 101.
^ In the article, the term "Overweight" was defined as BMI ≥95th percentile.
[$] Patients with obesity were excluded in this particular study.
AmbHT, Ambulatory hypertension; BMI, body mass index; n, number of patients; HT1, hypertension stage 1; HT2, hypertension stage 2 defined according to the fourth Report (ref.). LVH, left ventricular hypertrophy. LVMI, left ventricular mass index. NA, not available or not applicable. SevAmbHT, severe ambulatory hypertension. WC, waist circumference.

In healthy children, changes in LV dimensions and mass associate with age, sex, and growth throughout childhood (14, 73–75). Increasing body size and adiposity have the highest correlation with LV mass, highlighting the increasing demands on LV (32, 39, 76–78). We observed that BMIz had a significant positive relationship with the prevalence of LVH. Other adiposity characteristics, such as the proportion of obese children or WCz were reported in fewer studies with no relationship with the prevalence of LVH following meta-analysis. The exclusion of studies primarily evaluating those with obesity, metabolic syndrome, and diabetes mellitus may also have contributed to our findings. Unfortunately, individual patient data were not available to investigate the complex interactions between BP and adiposity for the development of LVH further. BMI is the most important determinant of BP in childhood. Thus, our finding that BMI was the main determinant of LVH may be caused by the fact that increased BMI mediates the effects of other cardiovascular risk factors, such as birth weight, socioeconomic status, and metabolic abnormalities (79).

Overall, these issues highlight that the relationships among age, body size, and LVM are complex, especially during

the process of growth as seen during adolescence. These complexities result in difficulties when defining LVH across the childhood age range for both sexes and are reflected in the diverse definitions for LVH by age and sex in Clinical Practice Guidelines from learned societies (12, 71). We observed that despite using different definitions of LVH reported in the literature, the prevalence of LVH remained at ∼30%. These findings are in keeping with recent reports that have highlighted no differences in the prevalence of LVH when 2017 AAP vs. 2016 ESH clinical practice guidelines LVH criteria have been applied (26, 80).

One of the major criticisms of individual studies reporting the prevalence of LVH in PH is that they might reflect highly selected populations, derived from children referred to specialist centers. In keeping with this, we observed that there was a lower prevalence of LVH in studies representing a community-based population, with an estimated mean prevalence of LVH at 21.5% from 1,234 individuals. Although only two studies have reported data for children identified through community screening, this may reflect lesser severity of BP elevation or clinical presentation as opposed to those referred to specialty centers. The lower prevalence of LVH in this group highlights the importance of early identification of elevated BP to prevent HMOD development and may be in support of screening programs within the pediatric population.

As expected, those with lower levels of BP including preHT category and less severe hypertension phenotype, e.g., WCH, also had lower estimated prevalence of LVH at 21.2 and 20.2%, respectively. Although smaller in numbers, these findings are in keeping with similar observations in adults and the significant pathophysiological association of BP level with LVH (81–83).

In adult hypertensives, it has been suggested that LVH develops following a complex interaction of hemodynamic and non-hemodynamic variables (72). It has been a common view that LVH develops due to chronic pressure overload from hypertension and results in LV remodeling to reduce myocardial wall stress with the development of concentric LVH (84). Despite this traditional view, concentric LVH is not always the most common LV geometry in hypertensive adults and this may reflect other significant pathophysiological pathways and variables (85). These observations were confirmed in our study with sub-analyses with LVH prevalence of 34.2%, in whom concentric and eccentric LVH was seen in one- and two-thirds, respectively. This is perhaps unsurprising, given that LV remodeling in hypertensive adolescents reflects adaptations to increased demand on the ventricle as a result of an increase in body size, BP, but also interactions as a result of ventricular-vascular coupling at rest and after increased physical activity (86, 87). Eccentric hypertrophy is associated with obesity (88, 89), which was reflected in our study population with a mean of 25.4 kg/m^2 and BMIz 1.43, despite the fact that these data were not reported uniformly in the studies reporting LV geometry.

In addition to cardiac remodeling, PH during childhood is associated with arterial stiffening including both structural (as assessed by carotid intima medial thickness and carotid wall cross-sectional area) and functional (as assessed by carotid-femoral pulse wave velocity) impairment of the arterial tree (24, 90). Further, although studies have previously reported LVH in the absence of other signs of arterial stiffening in childhood PH, and few investigators have performed a comprehensive evaluation of cardiac and vascular HMOD (86). We did not systematically assess arterial stiffening in subjects with LVH, but we highlight it because a better understanding of cardiac and vascular interactions during childhood in PH is required.

Based on our study findings several recommendations can be made. Despite 24-h ABPM being recommended as vital for the diagnosis of HT in this population in current guidelines (12, 71), five studies defined HT exclusively following office BP measurement. There was a large heterogeneity in the reporting of BP levels, with most studies only reporting mean values for raw data limiting the ability to analyze associations between standardized BP levels and LVH. Few studies reported ethnicity, which is a well-known predictor for BP levels (70, 77, 91, 92). Differences in the definition of LVH were common as discussed previously and can lead to significant misclassification and few studies reported LV geometry. Future studies should aim to report adjusted BP levels, BP phenotypes by ABPM, the method of indexation of LVM and its level, and the severity of LVH and LV geometry as a minimum. Future clinical practice guidelines should provide a preferred method of reporting BP levels and LVM indexation, with improved harmonization of current guidelines across ESH and AAP.

There are several limitations to this analysis, the most prominent being that none of the 47 included studies had the primary aim of reporting the prevalence of LVH in children with PH. Thus, they are unlikely to be of adequate size or optimal design to precisely estimate the prevalence of LVH in children with PH. This is in part reflected by publication bias analysis indicating lower prevalences in studies with lower sample sizes. Furthermore, other sources of biases could not have been accounted for in the original study designs. Importantly, only a few studies qualified as low risk of bias following critical appraisal, probably resulting in the observed high degree of heterogeneity between reported studies. This was mainly related to the lack of random probabilistic sampling, small sample sizes, lack of BP phenotypes descriptions, unclear duration of PH, heterogeneous LVH definitions, and lack of reporting sufficient details to confirm the reliability of LVMI measurements. In addition, different definitions of hypertension may contribute to heterogeneity in LVH prevalence, despite a recent meta-analysis finding similar predictive value between AAP and ESH guidelines (93). Finally, we were limited when evaluating by the level of BP as this was only reported in a small number of studies.

In conclusion, this systematic review and meta-analysis

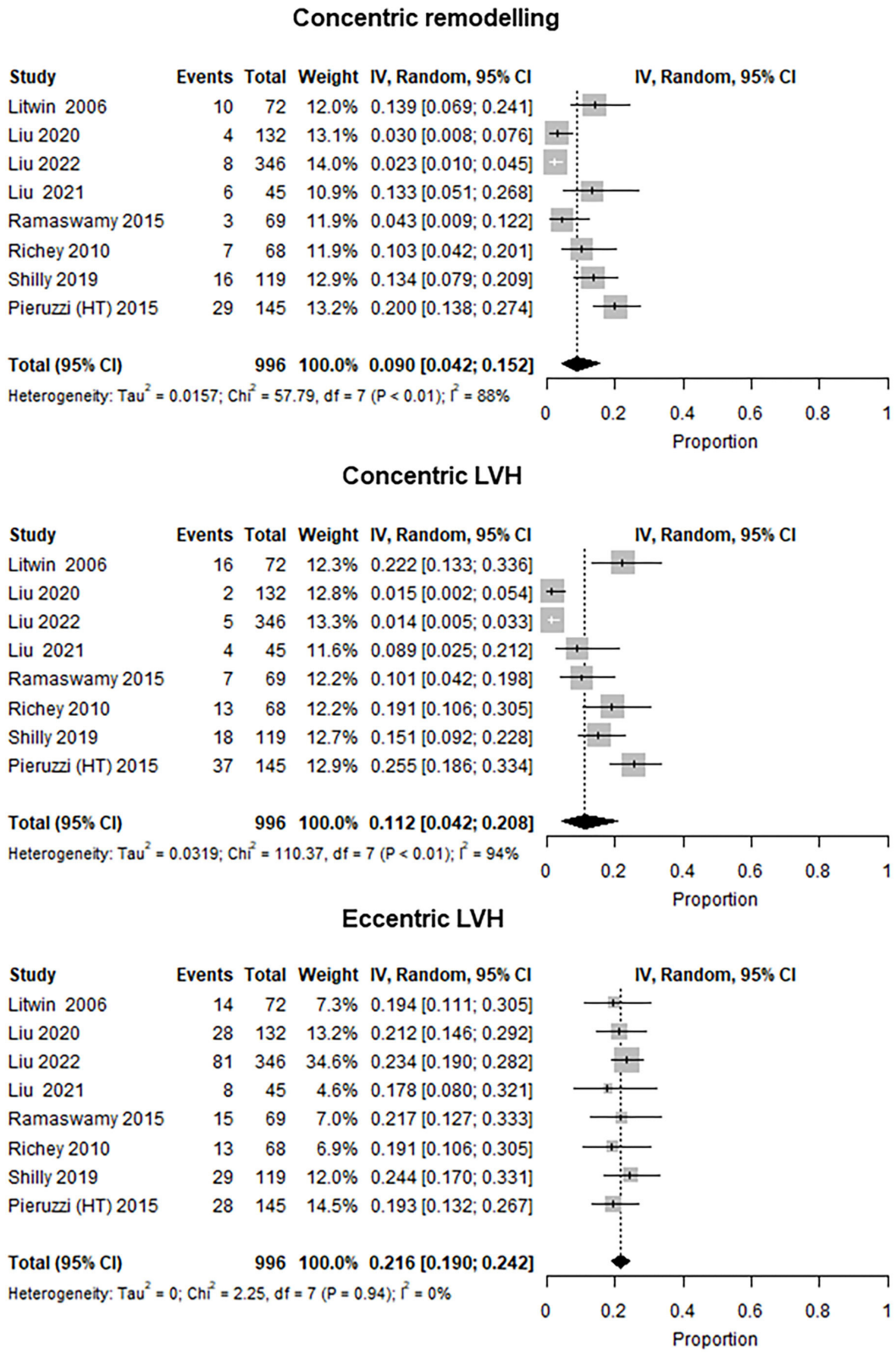

FIGURE 4
Forest plot showing the prevalence of LV geometry patterns (concentric remodeling, concentric LVH, and eccentric LVH) in studies with available data (eight studies). Three studies were excluded as being mixed [included community and specialty clinic patients: Agu et al. (31) and Gupta-Malhotra et al. (45)] or community samples (17).

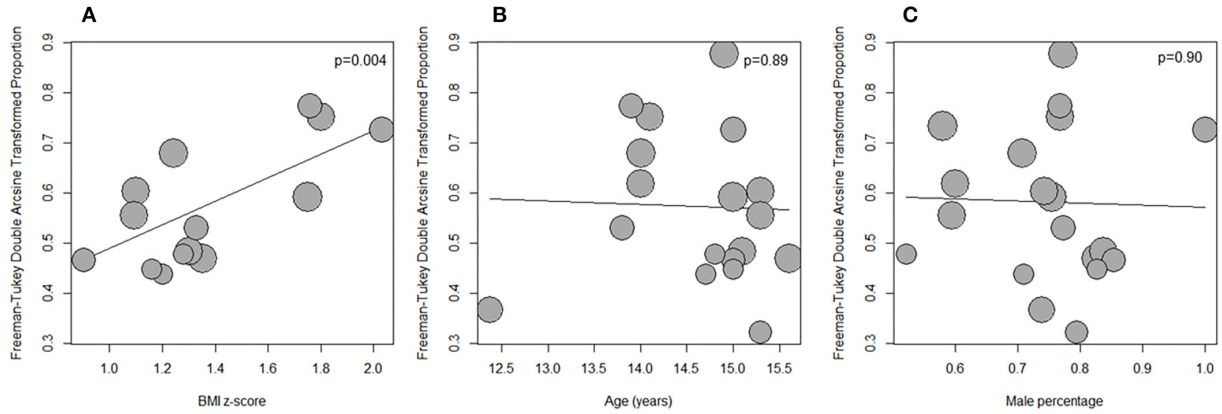

FIGURE 5
Bubble plot showing the relationship between LVH prevalence and BMI z-score **(A)**, age **(B)**, and male proportion **(C)** in the subset of studies from specialtyclinics, LVH defined by ultrasound estimated LVMI 95th percentile and excluding subjects with WCH and/or preHT.

estimate a 30% prevalence of LVH in children and young persons with PH, highlighting the significance of childhood hypertension but also providing a treatment target for optimizing management. A large body of literature on hypertensive adults has established that LVH improves following increased physical exercise, weight loss, and anti-hypertensive therapy (94). Although similar data in hypertensive children are few and less robust, similar interventions are likely to be effective, with improved BP control following anti-hypertensive therapy and the reduction of abdominal obesity being most impactful (32, 34, 88, 95, 96). Further prospective research is required to more carefully evaluate LVH in children with PH, to understand the progression of LVH in different hypertension phenotypes and through increasing levels of BP. HMOD including cardiac and vascular assessments is needed to detect both early complications but also improve our understanding of pediatric PH.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

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Author contributions

JS-K, TB, KM, MS, KA, AJ, FF-A, and ML contributed to conception and design of the study. IS performed literature search. JS-K and TB performed title and abstract screening. JS-K, TB, KM, MS, and KA performed full-text reviews, risk of bias assessment and data extraction. JS-K, KM, and TB performed data checking. KA conducted statistical analysis. MS and KA prepared the first draft of the manuscript. MS, KA, ML, TB, and JS-K wrote sections of the manuscript. JS-K, TB, KM, MS, KA, IS, AJ, BB, LO, MP, and ML contributed to critical manuscript revision, read, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.993513/full#supplementary-material

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The enigma of primary hypertension in childhood

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Beginning in the 1970s, hypertension in children and adolescents has been defined as systolic and/or diastolic blood pressure (BP) that is equal to or greater than the 95th percentile of the normal BP distribution in healthy children. The definition of hypertension in adults is based on longitudinal data that links a BP level with an increased risk for subsequent adverse outcomes related to hypertension including heart failure, kidney failure, stroke, or death. The statistical definition of hypertension continues to be used in childhood because there have been no data that link a BP level in childhood with a heightened risk for adverse outcomes in adulthood. Findings from clinical and epidemiologic research have advanced understanding of high BP in childhood. While hypertension in some children can be secondary to underlying kidney, cardiovascular, or endocrine disorder, it is now known that primary (essential) hypertension can be present in childhood. The prevalence of hypertension in childhood is approximately 2–5% and another 13–18% of children and adolescents have elevated BP and are at heightened risk for developing hypertension. The leading cause of childhood hypertension is primary hypertension, especially in adolescents. For children and adolescents with secondary hypertension, the treatment can focus on managing the underlying cause of hypertension. Less is known about managing primary hypertension in childhood, including diagnosis, evaluation, treatment, and possibilities for prevention. The phenotype of primary hypertension in childhood and recent findings will be discussed.

KEYWORDS

blood pressure, hypertension, children, adolescents, obesity

Introduction

Hypertension in adults is based on longitudinal data that defines a BP level that increases the risk for subsequent adverse outcomes including heart failure, kidney failure, stroke, or death. No such data have been available for children or adolescents. In the 1970s, reference BP data became available on the normal distribution of BP levels in children and adolescents according to age and sex (1, 2), and later, height was added in the distribution (3). Based on that data, the definition of hypertension in childhood became a systolic and/or diastolic BP $\geq$ 95th percentile according to age, sex, and height. Therefore, unlike the outcome-based definition

in adult hypertension, the pediatric definition of hypertension in childhood has remained a statistical definition.

With available tables to identify abnormal BP in children and adolescents, early pediatric guidelines on childhood hypertension focused on diagnostic testing to identify a secondary cause for the hypertension in a child or adolescent including renal, cardiovascular, or endocrine disorder; and primary (essential) hypertension was considered a disorder limited to adulthood. The childhood obesity epidemic has changed this perspective.

The primary hypertension phenotype in childhood

An analysis of the two separate National Health and Nutrition Survey (NHANES) periods in 2004 reported a population increase in BP levels among children and adolescents that was largely related to an increase in overweight/obesity (4). A subsequent analysis of sequential NHANES periods demonstrated that independent predictors of increasing BP levels in children and adolescents were body mass index, waist circumference, and dietary sodium intake (5). Clinical reports on hypertensive adolescents noted a strong association of obesity with hypertension (6). Other cross-sectional clinical studies on adolescents with hypertension described a strong association with obesity and also noted a substantial prevalence of the left ventricular hypertrophy (LVH) in the adolescents with hypertension (7–9). Based on these clinical findings, the Fourth Report on childhood hypertension (10) recommended an echocardiogram as part of the clinical evaluation in hypertensive children to determine the presence of hypertension-associated LVH as a measure of target organ damage (TOD); screening for other risk factors including lipids and glucose was also recommended. Subsequently, dyslipidemia was also reported in children with obesity-associated hypertension (11). Therefore, it was becoming apparent that childhood hypertension characterized by obesity and cardiometabolic risk factors is a phenotype very similar to primary hypertension in adults.

Blood pressure tracking in childhood

Identifying primary hypertension in asymptomatic healthy children and adolescents can be challenging. The BP reference tables developed from cross-sectional data on BP measurements in large samples of healthy children demonstrate a normal progressive increase in BP level from early childhood through adolescence consistent with normal childhood growth. Clinically, it known that BP measurements tend to be variable, especially in early childhood and it was not known whether a BP level at a given BP percentile consistently follows the same percentile with growth. To determine whether BP at a high BP percentile tracked from childhood through adolescence, Chen and Wang (12) performed a systematic review and meta-regression analysis that included 50 published reports of longitudinal childhood studies that included BP measurements in asymptomatic healthy children. Overall, the tracking correlation coefficient varied considerably. With further analysis, it was determined that the tracking coefficient varied according to baseline age and length of follow-up. For children <5 years at baseline measurement, the tracking coefficient was insignificant at 0.18. However, by baseline age 8–9 years, the systolic BP tracking coefficient was significant and consistent at 0.40–0.43 up to age 18 years. These findings indicate that by mid-childhood, systolic BP levels at the higher BP percentiles tend to track and indicate a heightened risk for primary hypertension.

Blood pressure trajectories from childhood to adulthood

Analysis of longitudinal data on BP and risk factors associated with abnormal BP in prospective studies that began in childhood and extended into early adulthood provide a life-course perspective on childhood origins of primary hypertension (13–15). Theodore et al. (13) analyzed data on 975 children who were enrolled at age 7 years and followed with repeated measurements to age 38 years. At age 38 years, participants were stratified based on BP status to hypertension, pre-hypertension, high normal BP, and normotensive. Using group-based trajectory modeling on BP curves for each BP status group at age 38 years, there were four systolic BP curves identified. According to BP classification at age 38 years, there was a clear separation of the systolic BP trajectory groups by 11 years of age. Significant risk factors identified for the hypertensive and pre-hypertensive groups were low birth weight, family history of hypertension, male sex, higher body mass index (BMI), and cigarette smoking. BP trajectory analysis was also performed by Hao et al. (14) in a cohort of 546 participants enrolled in early childhood and followed prospectively to adult age 30 years. Their data included measures of the left ventricular mass index (LVMI) and carotid intimal medial thickness (cIMT) as intermediate measures of cardiovascular injury. The authors identified three separate BP trajectory curves, designated as low-increasing, moderate-increasing, and high-increasing. By age 10 years, there was a separation of the systolic BP trajectory curves. Systolic BP was above 120 mmHg by age 15 years in the high-increasing group. At age 30 years, LVMI and cIMT were highest in the high-increasing systolic BP group. These reports demonstrate that higher systolic BP levels in childhood can progress to

hypertension and pre-hypertension by early adulthood with markers of cardiovascular injury.

Subsequent analysis of data in longitudinal cohorts examined associations of higher BP status in childhood with intermediate markers of cardiovascular disease (CVD) in adulthood, and Yang et al. (16) conducted a systematic review of childhood to adulthood longitudinal cohort studies. The meta-analysis determined that BP levels ≥90th percentile in childhood or adolescence were significantly associated with risk for LVH, with a pooled odds ratio (OR) 1.40 (95% CI = 1.20–1.64); vascular stiffness ascertained by pulse wave velocity (PWV) OR 1.83 (95% CI = 1.39–2.40); and high cIMT, OR 1.60 (95% CI = 1.29–2.00). This systematic review also identified some associations of abnormal BP in adolescence with clinical CVD and mortality in adulthood. More recently, investigators in the International Childhood Cardiovascular Cohorts (i3C) Consortium reported an analysis on longitudinal data in the childhood to adulthood cohorts to determine whether there was an association of risk factors in childhood with CVD events in adulthood. Childhood risk factors considered were systolic BP, BMI, total cholesterol level, triglyceride level, and youth smoking. For each risk factor, age- and sex-specific z-scores were determined and a combined-risk z-score was calculated. There were 319 fatal cardiovascular events among 38,589 participants. The hazard ratio for the combined-risk z-score was 2.71 (95% CL, 2.23 to 3.29) per unit increase. A similar finding was found in the analysis of 779 fatal and non-fatal cardiovascular events that occurred in 20,656 participants (17). The results in this publication provide evidence that high BP and other cardiovascular risk factors in childhood are associated with adverse CVD outcomes in mid-adulthood.

Markers of cardiovascular injury in youth

The above describes associations of abnormal BP in youth with intermediate markers of cardiovascular disease, commonly termed target organ damage (TOD), in early adulthood. Moreover, LVH is frequently found in adolescents with confirmed primary hypertension, having systolic BP consistently ≥95th percentile (7–9). In adolescents with hypertension, confirmed by ambulatory blood pressure monitoring, subclinical, alterations in cognitive function have also been demonstrated. Compared to normotensive adolescents, adolescents with hypertension had scores significantly lower on tests of memory, attention, and executive function (18, 19).

Additional clinical studies also reported LVH in overweight/obese adolescents with pre-hypertension and hypertension (20, 21). These reports found that elevated BP and obesity were both independently associated with LVH in youth and led to questions on what BP level was linked with TOD in youth. The Study of Hypertension in Pediatrics, Adult Hypertension Onset in Youth (Ship Ahoy) project was designed to address this issue. Investigators sought to determine if the BP threshold for LVH in youth was below the 95th percentile and whether there were other cardiometabolic factors that raised the risk for TOD in adolescents. Healthy adolescents, aged 11–19 years, were enrolled, including participants with an average BP level >95th, and stratified into three groups according to office systolic BP measurements (average of six measurements from two separate visits): low risk = BP < 80th percentile; mid risk = 80th to <90th percentile; and high risk ≥ 90th percentile. The groups were matched by age and demographics with a slight difference in body mass index (BMI). Mean BP, LVMI, and prevalence of LVH increased across groups: For LVH, the low BP group prevalence = 13%, mid group = 21%, and high group = 27%. Systolic BP percentile was found to be a significant determinant of LVMI, and the 90th percentile for systolic BP resulted in the best balance between sensitivity and specificity in predicting LVH (LVMI > 38.8 gm/m$^{2.7}$). These results demonstrate that abnormal cardiac mass can be found at BP levels below the 95th percentile in adolescents (22). Advancements in echocardiology enable the measurement of cardiac function. In adults, cardiac function changes in left ventricular strain and diastolic function are found to precede decreases in left ventricular ejection fraction and CVD events. Further analysis of echocardiographic data in the Ship Ahoy cohort examined the effect of systolic BP level, across the three BP groups, on left ventricular strain and diastolic function. The mid-risk and high-risk participants had significantly lower left ventricular ejection fraction and peak global longitudinal strain than the low-risk group. The high-risk group had greater left ventricular strain and lower diastolic function compared to the mid-risk and low-risk groups. BP and adiposity were both statistically significant determinants of impaired left ventricular systolic and diastolic function (22). These novel findings indicate that even subclinical changes in cardiac function can be detected in adolescents with primary hypertension.

As noted above, increases in PWV, a measure of vascular stiffness, are commonly associated with hypertension in adults. Analysis of PWV data in the Ship Ahoy cohort was conducted to determine whether BP-related increases in arterial stiffness were present in adolescents with elevated BP. Carotid-femoral PWV increased across the BP groups from low-risk group to the high-risk groups. Aortic distensibility and compliance were greater in the low-risk group than the mid-risk and high-risk groups. Significant determinants of arterial stiffness were sex, age, adiposity, BP, and low-density lipoprotein (LDL). PWV and aortic compliance were significantly associated with measures of TOD (systolic and diastolic cardiac function and urine albumin/creatinine ratio) after controlling for BP level. These results indicate that BP-related vascular stiffness can also be detected at BP levels below the 95th percentile (23). Moreover, in this analysis, low-density lipoprotein (LDL) level

was significantly associated with vascular stiffness. The Ship Ahoy investigators conducted additional analysis to determine whether there is a metabolic phenotype associated with TOD in adolescents with elevated BP or hypertension. A cardiovascular disease risk score was developed using the number of CVD risk conditions including hypertension, dyslipidemia, obesity, and insulin resistance present in each participant. Generalized linear models indicated that dyslipidemia and insulin resistance were independently associated with markers of diastolic dysfunction, and increased systolic BP was associated with all markers of TOD (24). These publications from the Ship Ahoy project describe a high-risk phenotype in adolescence for subsequent cardiovascular disease that includes evidence of TOD as well as multiple risk factors even at BP levels below the 95th percentile.

Prevalence and diagnosis of primary hypertension in childhood

Reports on the prevalence of primary hypertension in childhood vary based on the population studied, location of the population, how the BP is measured, the number of BP measurements, the definition of hypertension, and the reference data on normative BP levels for age and sex. The overall estimated prevalence of hypertension in childhood is approximately 2–5% and the prevalence of elevated BP is 13–18% (25, 26), with higher rates in adolescence compared to childhood. The prevalence of secondary hypertension is approximately 1% and is generally identified in early childhood or in children with markedly elevated BP (27, 28). It is now established that primary hypertension is the most common type of hypertension in the young, especially in adolescence.

Some children are at greater risk for primary hypertension including children with overweight or obesity and children with a history of low birthweight. A sub-optimal diet can be a target for intervention in childhood and adulthood. Dietary salt intake is high in childhood with most children and adolescents exceeding recommended limits in sodium intake, largely due to the consumption of processed foods (29).

In clinical practice, it is challenging to recognize abnormal BP levels in asymptomatic otherwise healthy children and adolescents. Although BP measurement in children, beginning at age 3 years, is now standard practice in primary care settings, examinations of electronic health records have demonstrated under-recognition and underdiagnosis of hypertension in children and adolescents (30, 31). Evidence-based guidelines are available to facilitate diagnosis, evaluation, and management of hypertension including both primary and secondary hypertension (27, 28, 32). However, recognizing abnormal BP levels and taking appropriate steps in follow-up continue to be difficult to achieve in primary care settings (33). Electronic medical record alerts (34) and clinical decision support systems (35) improve recognition of abnormal BP in children somewhat but documentation of diagnosis and appropriate follow-up remains sub-optimal. A necessary step in identifying and managing abnormal BP is the accurate measurement of BP. A flawed technique used in the measurement of BP in both children and adults results in inaccurate readings. Staff who measure BP in children and adolescents in a primary care setting should be trained in a standard BP measurement protocol (27, 28, 36). It is also important to use a BP monitor that is validated for accuracy in children (37, 38).

Strategies and tools are still needed to help primary care clinicians overcome the barriers to appropriate screening, recognition, and confirming abnormal BP in children and adolescents (39). This is especially important because the rates of childhood obesity, the major risk factor for pediatric primary hypertension, are increasing (40). Moreover, an analysis of data in the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study found that young adults, with stage 1, stage 2 hypertension, and even elevated BP, had a significantly higher risk for subsequent CVD events compared to those who had normal BP before age 40 years (41). With the increasing prevalence of hypertension in adolescents, it is expected that the prevalence in young adults will also increase. In the United States, CVD projections estimate significant increases in CVD among adults in future decades, including hypertension (42). Detection and effective management of hypertension and elevated BP in adolescence, as well as primordial prevention beginning in early childhood, would have a substantial impact on stemming the rising tide of CVD in adults. Adolescents should be able to enter adulthood with a normal BP.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Narrative update of clinical trials with antihypertensive drugs in children and adolescents

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Introduction: To date, our knowledge on antihypertensive pharmacological treatment in children and adolescents is still limited because there are few randomized clinical trials (CTs), hampering appropriate management. The objective was to perform a narrative review of the most relevant aspects of clinical trials carried out in primary and secondary hypertension.

Methods: Studies published in PubMed with the following descriptors: clinical trial, antihypertensive drug, children, adolescents were selected. A previous Cochrane review of 21 randomized CTs pointed out the difficulty that statistical analysis could not assess heterogeneity because there were not enough data. A more recent meta-analysis, that applied more stringent inclusion criteria and selected 13 CTs, also concluded that heterogeneity, small sample size, and short follow-up time, as well as the absence of studies comparing drugs of different classes, limit the utility.

Results: In the presented narrative review, including 30 studies, there is a paucity of CTs focusing only on children with primary or secondary, mainly renoparenchymal, hypertension. In trials on angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and diuretics, a significant reduction of both SBP and DBP in mixed cohorts of children with primary and secondary hypertension was achieved. However, few studies assessed the effect of antihypertensive drugs on hypertensive organ damage.

Conclusions: Given the increasing prevalence and undertreatment of hypertension in this age group, innovative solutions including new design, such as *'n-of-1'*, and optimizing the use of digital health technologies could provide more precise and faster information about the efficacy of each antihypertensive drug class and the potential benefits according to patient characteristics.

KEYWORDS

clinical trial (2.172), children, adolescents, antihypertensive drug, pharmacological treatment

Introduction

Globally, and particularly in developing countries, hypertension (HTN) is the most common disease of adulthood (1) and low rates of antihypertensive treatment and blood pressure (BP) control are the most important cause of the high cardiovascular morbidity and mortality worldwide (2). Even though its prevalence is much lower in children and adolescents than in adults, HTN has a great clinical importance also at a young age because BP elevation in young people makes the development of sustained HTN in adulthood more likely (3). Furthermore, in recent decades the number of young patients with a diagnosis of hypertension has been found to increase. This is in part because of the wider use of BP measurements (4) but unquestionably also to the increase of overweight and obesity in younger populations (5). Because HTN in adulthood has its roots in childhood, it is important to measure BP appropriately and diagnose pediatric HTN in a timely manner (6). Diagnostic criteria for elevated BP in children and adolescents are based on the concept that BP increases with age and body size, making it impossible to utilize a single BP level to define HTN, as done in adults. Hypertension is defined as systolic and/or diastolic BP persistently ≥95th percentile of the normative BP distribution, adjusted by age, sex and height measured on at least three separate occasions. Consistent with the physiological body growth adult cut-points 140/90 mmHg are applied for adolescents 16 years and older (Table 1) (4).

Currently primary HTN is the most frequent cause of high BP in children and adolescents with a close association with overweight and obesity (7). As in adulthood, the first therapeutic step to adopt under these circumstances should be non-pharmacological treatment, i.e., modifications of incorrect lifestyles that may contribute to BP elevation (8, 9). However, in children where such a strategy fails, pharmacological treatment is indicated (4) and in young people with symptomatic HTN, secondary HTN, target organ damage, chronic kidney disease or diabetes mellitus, pharmacological treatment should be considered as first line therapy. Unfortunately, however, knowledge of what should be the optimal first step drug or drugs in children and adolescents is much more limited than in adults (4, 8). In addition, no or few good-quality long-term outcome data are available to guide pediatricians in selecting medication to treat HTN, which means, that treatment is often based on experience rather than on evidence. In the absence of evidence, use of "off-label" drugs is also common (10), further complicating the appropriate management of pediatric HTN and making it a challenging task for pediatricians. Many of whom feel uncomfortable treating a hypertensive child, also because recognition of a HTN state is more difficult than in adults. Nevertheless, during the last decades, childhood HTN has been studied more rigorously, to optimize BP measurements, collect normative data and establish diagnostic work-up guidelines. To-date the development of worldwide adopted recommendations has improved our ability to diagnose pediatric HTN to an extent superior to that of HTN management, which has made much less progress (4).

Clinical trials of antihypertensive drugs in the adult population have yielded in-depth information about their pharmacokinetics and pharmacodynamics, including BP lowering efficacy, effects on hypertension-related outcomes and safety for all major classes of antihypertensive medication. Data on optimal drug doses, best combinations, and differences in efficacy among the different drug classes have also been obtained. In contrast, in the pediatric population, paucity of studies is the rule, which is a major shortcoming because what works in adults does not necessarily work in children and adolescents. Furthermore, most drug formulations are not adapted for use in the pediatric age.

The present review focuses on CTs of antihypertensive drugs in primary and secondary HTN of children and adolescents, with emphasis on future research needed in this age population. PRISMA system have been used (11) to select the studies to be included with descriptors: clinical trials, antihypertensive drugs and children and adolescents, in PubMed. The flow diagram is in Figure 1.

Regulatory agencies and hypertension drug treatment

During the last three decades, Regulatory Agencies have effectively acted to provide better information about the use of drugs for pediatric treatment and to promote their availability. In the US, incentives were first authorized by the Food and Drug Modernization Act of 1997 such as the 6 month prolongation of the market patent for drugs which were tested by clinical trials in children, as well as the possibility to perform clinical trials with off-patent drugs. This was reauthorized in 2002 by the *Best Pharmaceuticals for Children Act (BPCA)* (12), and permanently reauthorized by FDA in 2012 under the *FDA Safety and Innovation Act* (13).

Similar actions were taken in Europe by the *Regulation of Medical Products for Pediatric Use* (14). The *Pediatric Committee of the European Medicines Agency (PDCO)* is the scientific committee responsible for activities connected with medicines to be used in pediatrics and for their development in the European Union *via* scientific support and help to data analysis in the area of pediatrics. The PDCO was created by the pediatric regulations that came into force in 2007, with the aim of improving the health of the European Union's pediatric population *via* development and increasing the availability of *ad hoc* medicines. A *Pediatric Investigation Plan (PIP)* promoting research activities has also been launched, including PIPs for treatment of cardiovascular disease, HTN in particular (15),

TABLE 1 Criteria for the methods to establish dosing recommendation and safety of antihypertensives from EMA (15).

Criteria of efficacy	
Blood pressure values	
Reduction of BP	X
Absolute or percent change in systolic or diastolic blood pressure	X
Trial design A/B–change from baseline to the end of the treatment period + inter-dosing interval (trough)	
Trial design C/D–change in blood pressure from the last on-treatment visit to the end of withdrawal period	
Morbidity and mortality	X
Establishing an effect on morbidity and mortality endpoints is not required in pediatric licensing trials of antihypertensive medicinal products	
Post-authorization long-term follow up and observational research are encouraged	X
End organ damage	X
Albuminuria	
Left ventricular hypertrophy and/or dilatation	X
Assessment of presence and progression of other types of organ damage is advisable in longer-term studies	X
Methods to assess efficacy	
Reduction in blood pressure values	
Office BP systolic or diastolic	X
Home BP and ABPM is encouraged	X
Changes in end organ damage	
Kidney: GFR and albuminuria/proteinuria	X
Left ventricular mass or dilatation by height	X
Arterial wall (thickening in the intima-media complex)	X
Patients	X
Hypertensive diagnosed	
Youngest age groups after the safety have been established in the older patients, especially in studies involving infants <6 months	X
Differentiated between essential and secondary forms of HTN	X
Unnecessary studies in children should be avoided. This is not the case for products with new mechanism of action and in younger age groups where dedicated dose-ranging and safety studies are always necessary.	X
The use of placebo or fixed low dose of the product require ethical acceptability and safety aspects when evaluating the feasibility of studies in the most severe forms of HTN	X
Stratification of randomization according to the etiology or patient characteristics needs to be discussed when has been identified as potentially useful	X
Design	X
Pharmacology studies	
PK data for all relevant pediatric age groups should be provided	
Bioavailability half-life, C_{max} and T_{max} in the various age groups and for parent and metabolites	
A reasonably precise estimate of which range of doses provides sufficient exposure, equivalent to the doses determined to be efficacious in adults with hypertension, is needed.	X
PD considerations to be addressed by the applicant include, but are not limited to, possible differences in pharmacology, metabolism and PK/PD relationship/dose-response slope according to age	X
For children 1 to <6 years of age, a formulation that allows adequate dosing flexibility is a must to assure reliable administration and accurate weight- adjusted dosing	X
Therapeutic studies	X
The main aim of the pediatric development is to establish the therapeutic dose as well as tolerability, palatability (where appropriate), short- and long- term safety.	
Double blind randomized study design with or without a placebo arm (no in youngest, <6 years) and more severe HTN	X
Rescues treatments in case of insufficient response should be predefined	X
Dose ranges enough wide	X

(Continued)

TABLE 1 (Continued)

Dose ranges will also depend on age-specific differences suggested by PBPK-modeling and/or pediatric PK data	X
Doses providing exposure from slightly lower than the lowest approved adult dose up to somewhat higher than the highest approved dose in adults (unless restricted by safety concerns) could be considered	X
Safety	X
Short-term tolerability and safety data should be collected in the controlled studies and compared with the known safety profile in adults.	
The trial program is expected to have a total of no <300 pediatric patients for safety reasons to identify adverse reactions occurring with a 1% frequency.	X
Extension studies with individual dose titration after completion of the short-term studies or dedicated safety studies are needed for collection of longer-term safety data.	X
At least 12 month extension studies are necessary to allow investigation of long-term safety in terms of growth (head circumference, weight and height) and development, including neurocognitive development	X
Younger age groups (infants, children under 6 years of age) have to be adequately represented and may need to be followed up longer (e.g., 24 months).	X
Identified safety concerns from adult or non-clinical studies may necessitate further data collection,	X

PK, pharmacokinetics; Cmax, highest concentration; Tmax, time it takes for a drug to reach the maximum concentration; PD, pharmacodynamics.

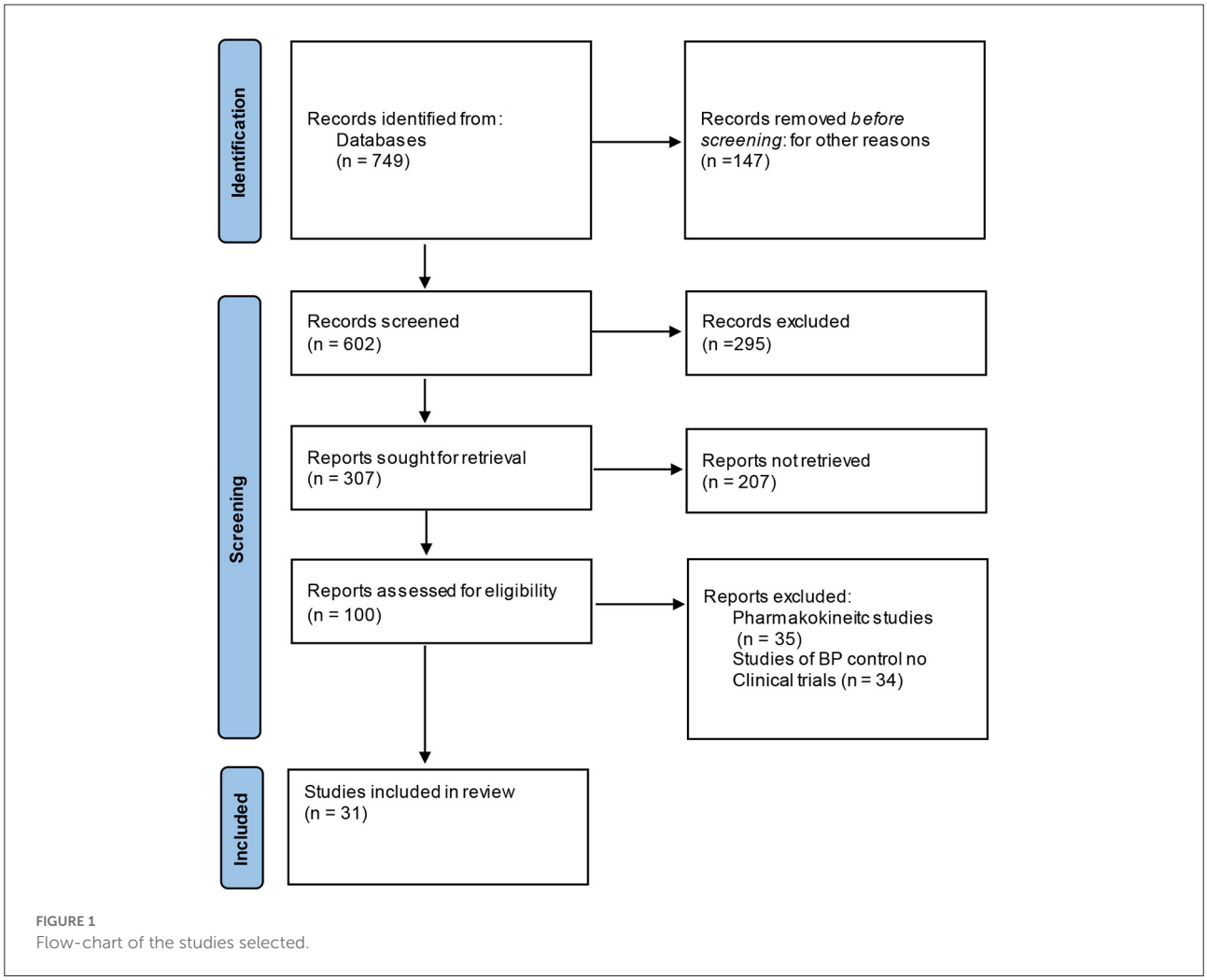

FIGURE 1
Flow-chart of the studies selected.

although at present the numbers of PIPs in this area lags behind other therapeutic areas.

As shown in Tables 1, 2 the two Regulatory Agencies have also established the requirements for the approval and conduction of CTs. Although some requirements are in agreement, others differ between the two Agencies (16, 17), with the main differences involving methods of measuring BP, assessment of organ damage, range of drug dose to be used, and time for extended observation after completion of a trial.

Clinical trial challenges

Barriers

Research on children in CTs faces ethical, epidemiological, and economic difficulties or barriers, which have some special characteristics in the case of antihypertensive drugs. Research failures may occur because the results do not reach statistical significance and thus the efficacy of a tested drug cannot be proven. Other reasons are inconsistent results, controversial results or project failure because the budget has been overspent, the project targets have not been achieved or deadlines haven't been met (18).

In a review of CTs on failure rates and causes of the use of drugs for hypertension care in children and adolescents since 2000 (search keywords "pediatric drug therapy," "hypertension," "clinical trials" and "fail of trials") nine of the sixteen pediatric antihypertensive drug trials failed to show a dose response (19) due to unskilled project manager, unproductive team, complexity of protocol, the dilemma of "*Project Completion Targets" vs. "Eligibility of the Volunteers*," poor training and poor verification, ethical issues and data quality (20, 21).

Finally, early discontinuation and lack of publication of study findings are common in registered pediatric CTs. Targeted efforts are needed to support trial completion and timely result dissemination to strengthen evidence-based pediatric medicine (22).

Previous analysis assessing BP lowering effect and safety

As in adults, in children and adolescents the BP-lowering effect of drug treatment may be influenced by several factors, including age, sex, weight, and severity of baseline hypertension, which makes achievement of conclusive information on between-drug differences in efficacy far from simple.

In a Cochrane review article (23) including 21 randomized CTs, a total of 3,454 hypertensive children and adolescents were enrolled when at least a 2 week comparison was made between (a) monotherapy or combination therapy with either placebo or another medication or (b) different doses of the same drug. Despite use of random effect models the authors emphasized that safe conclusions could not be made due to lack of sufficient data. Nevertheless, they stated that the agents tested, i.e., ACEIs, ARBs and CCBs did not exhibit a consistent dose-response relationship, although all of them appeared to be safe, at least within the short-term context of the studies.

A more recent meta-analysis (24) tried to assess more uniform and higher clinical quality CTs by selecting 13 trials with a randomized placebo-controlled design, more than 50 patients enrolled, and a follow-up of at least 4 weeks. Patients affected by secondary forms of hypertension, which may benefit from specific and targeted therapies, were not systematically excluded. The results were rather inconclusive because, despite the more demanding selection of the studies, the results remined heterogeneous and the follow-up time short. The authors highlighted that the observations nevertheless increased the available experience with drugs that block the renin angiotensin system (i.e., ACEIs and ARBs), because these drugs accounted for the greater proportion of treatment in the patients recruited.

Update of present knowledge

A total of 31 (25–55) CTs have been summarized in the present review, the majority ($n = 20$), (26, 29–38, 40, 41, 45, 47–53) (Table 3) including children with both primary and secondary HTN. Fewer CTs investigated antihypertensive drugs focusing only on children with primary HTN and taking into account concomitant obesity (48) or race (46). The majority children participating in CTs on secondary HTN had renal disease as the first cause of HTN (27, 31, 34–40, 42, 43, 47, 49–55). Some of the CTs in renal disease assessed changes in albuminuria or proteinuria (35, 36, 52, 53).

Among the CTs specifically addressing primary HTN, one study analyzed the antihypertensive efficacy of Valsartan (48) in obese and non-obese hypertensives, and found that BP reduction was similar in the two groups. In another specific CT on primary HTN, Olmesartan, an angiotensin receptor blocker, was less effective in reducing BP in African American children compared to Caucasians (46), a result in line with data available in the adult population.

Regarding secondary vs. primary HTN, most CTs did not perform a separate analysis of the BP lowering effect of study medication in children with primary and secondary HTN.

In the mixed cohorts, in which ACEI, ARBs or diuretics were used a significant reduction of both systolic (SBP) and diastolic BP (DBP) was observed. This was the case also in the only study in which amlodipine was used. In this study however, a separate analysis of children with primary and secondary HTN was made. The results showed that there was no effect of the underlying cause of HTN on BP response (34). Thus, the authors concluded that, at least with regard to amlodipine, the BP lowering effect of drug treatment in children with secondary HTN is not different

TABLE 2 Criteria for the methods to establish dosing recommendation and safety of antihypertensives from FDA agencies (16).

Criteria of efficacy	
Blood pressure values	
Reduction of BP	
Absolute or percent change in systolic or diastolic blood pressure	X
Trial design A/B–hange from baseline to the end of the treatment period + inter-dosing interval (trough)	
Trial design C/D–change in blood pressure from the last on-treatment visit to the end of withdrawal period	
Morbidity and mortality	
Post-authorization long-term follow up and observational research are encouraged	X
Methods to assess efficacy	
Patients	
Hypertensive diagnosed	X
$>90^{th}$ percentile if concurrent conditions present	X
Demographic criteria: >50% pre-adolescents subjects; 40–60 black subjects, both sexes	X
Design	
Pharmacology studies	
PK data for all relevant pediatric age groups should be provided	X
Bioavailability half-life, C_{max} and T_{max} in the various age groups and for parent and metabolites	X
Blood levels should range from less than those achieved with the lowest approved adult dose to more than those achieved with the highest generally used adult dose	X
For children 1 to < 6 years of age, a formulation that allows adequate dosing flexibility is a must to assure reliable administration and accurate weight- adjusted dosing	X
Therapeutic studies	
Trial duration typically 2 weeks but longer if a period of dose titration is needed	X
For statistical consideration ≥80% power to detect a 3 mmHg change in blood pressure of conventional ($p < 0.05$, two-sided) statistical significance	X
Safety	
At least 12-month extension studies are necessary to allow investigation of long-term safety in terms of growth (head circumference, weight, and height) and development, including neurocognitive development	X
Specific safety concerns during the studies in infants may need to be addressed by stepwise recruitment to the trials (interim safety data analysis before the inclusion of the youngest patients)	X
Trials should include a 1 year open-label treatment period to evaluate adverse events, growth (change in head circumference, weight, length, or height) and development (milestones, school performance, neurocognitive testing)	X

PK, pharmacokinetics; Cmax, highest concentration; Tmax, time it takes for a drug to reach the maximum concentration; PD, pharmacodynamics.

from that in children with primary HTN. Taken together, the data suggest that in children with primary vs. secondary HTN there may be no significantly different BP lowering effect of a variety of antihypertensive drugs, a conclusion supported by data in adults.

Four studies analyzed the impact of antihypertensive drug treatment only in secondary HTN. In renal posttransplant patients one study compared three CCBs, i.e., amlodipine, nifedipine and felodipine, and found no difference in the BP-lowering effect among them (32). In the second study losartan and amlodipine both resulted in a significant decrease of SBP but not of diastolic BP compared to placebo in children with Alport syndrome (51). In the last two studies, esmolol and atenolol, beta-blockers, effectively reduced BP in the post-operative phase of surgery for aortic coarctation (30, 31).

From the above review it is clear that data on antihypertensive drugs in the young age are scarce. Beside the limited information on the BP lowering effect of different drugs and the probable similarity of antihypertensive drug treatment effects in primary and secondary HTN, no adequate data are available on the effect of different timing of drug administration, the relationship with food intake, the effect on BP reduction during sleep and the comparison of different agents within the same drug class. Data about the effect of antihypertensive drugs on hypertensive target organ damage are also very limited and the safety profile of the antihypertensive drug administration, although addressed by some CTs, almost entirely lacks of longer-term information as well as of information in children with other health problems such as lung disease, cardiac disease, and others.

TABLE 3 Main characteristics of clinical trials in blood pressure reduction.

Drug/s Reference (__)	Age range (Sample size)	Low dose* (daily)	Maximal dose (daily)	Dosing interval	Baseline BP SBP/DBP	BP (mmHg)** SBP*** DBP	Population additional comments
Diuretics							
HCTZ vs. Clonidine (Cl) Falkner et al. (25)	13–19 (28)	25 mg/day vs. 0.1 mg/kg/day	50 mg/day vs. 0.2 mg/kg/day	oid	Hczt 146/96 Cl 145/97	Hctz 10 Cl 10-10*** Hctz 4 Cl 7-7	
Chlortalidone vs. Propanolol Bachman (26)	(9)	0.3 mg/kg	2 mg/kg up to 50 mg	oid		15 to 22,3	
Eplerenone vs. placebo Li et al. (27)	4–16 (304)	25 mg/day	50 mg/bid	oid/bid	128/70	7.6/7.9*** 2.7/2.8	Primary + secondary
Beta-blockers							
Bisoprolol/HCTZ vs. placebo Sorof et al. (28)	6–17 (94)	2.5 mg/day 6.25 mg/day	10 mg/day 6.25 mg/day	oid	133/82	4.9/9.3*** 2.9/7.2	
Metoprolol vs. placebo Batisky et al. (29)	6–17 (138)	0.2 mg/kg	2 mg/kg	oid	128/95	7.7*** 4.9	
Esmolol Tabbutt et al. (30)	1–6 (116)	0.1 mg/kg iv	5 mg/kgv iv	Ibolus and iv infusion	No reported^	9.6*** –	After repair aortic coarctation
Atenolol vs. Enalapril Di Salvo et al. (31)	6–20 (49)					A 9.0 E 8.0***	After repair aortic coarctation
Calcium channel blockers							
Amlodipin, Nifedipin, Felodipin Rogan et al. (32)	9–17 (9)	0.1 mg/kg	5 mg	oid	No reported^	No reported	Renal transplants No differences between the drugs
Felodipine vs. placebo Tractman et al. (33)	6–12 (128)	2.5 mg/day	10 mg/day	oid	No reported^	0.1*** 4.9	
Amlodipine vs. placebo Flynn et al. (34)	6–16 (352)	2.5 mg/day	5 mg/day	oid	137/74	7.3/9.1*** 3.7/4.4	Primary + secondary
Angiotensin converning enzyme inhibitors							
Ramipril vs. placebo Soergel et al. (35)	5–18 (12)	1.5 mg/m^2	10 mg	oid	No reported^	5 (24 h)*** –	Only renal disease
Ramipril vs. placebo Seeman et al. (36)	2–19 (29)	1.5 mg/m^2	10 mg	oid	No reported^	11 (day) 8 (night)*** –	Only renal disease
Ramipril Wühl et al. (37)	3–8 (385)	6 mg/m^2	10 mg	oid	Mean BP 89.5 (24 h)	Mean BP 11.6 (24 h)	Renal disease hypertensive and normotensive
Enalapril vs. placebo Wells et al. (38)	6–16 (110)	0.625 to 5 mg/day	20–40 mg	oid	129/86	6.8/11.0*** 7.1/10.2	>50% renal disease
Lisinopril Soffer et al. (39)	6–16 (115)	2.5–5	50–100 mg	oid	129/90	5.0/15.0*** 7/16	>50% renal disease
Fosinopril vs. placebo Li et al. (40)	6–16 (255)	0.1 mg/kg/day	6 mg/kg/day	oid	134/71	11/11*** 4.5/5.1	21% renal disease

(Continued)

TABLE 3 (Continued)

Drug/s Reference (__)	Age range (Sample size)	Low dose* (daily)	Maximal dose (daily)	Dosing interval	Baseline BP SBP/DBP	BP (mmHg)** SBP*** DBP	Population additional comments
Enalapril (E) vs. Valsartan (V) Schaffer et al. (41)	6–16 (281)	0.1 mg/kg/day	6 mg/kg/day	oid	134/79 133/78	E 11 V 11*** E 4.5 V 5.1	
Angiotensin-AT1-receptor blockers							
Losartan vs. placebo Shahinfar et al. (42)	6–16 (175)	2.5–5	50–100 mg	oid	129/89	4.4/10.0*** 6.0/12.2	>50% renal disease
Valsartan vs. placebo Flynn et al. (43)	1–5 (90)	5 mg/day	89 mg/day	oid	118/71	8.5*** 5.7	63% renal disease
Candesartan vs. placebo Trachtman et al. (44)	6–17 (233)	2–4 mg/day	16–32 mg/day	oid	133/78	4.9-7.5*** 3.0/6.2	
Telmisartan vs. placebo Wells et al. (45)	6–18 (77)	1 mg/kg/day	2 mg/kg/day	oid	131/79	9.0/14.0***	
Olmesartan vs. placebo Hazan et al. (46)	6–16 (302)	2.5–5 mg/day	20–40 mg/day	oid	130/78	7.8/12.6*** 5.5/9.5	Lower response in black
Candesartan Schaefer et al. (47)	1–5 (93)	0.05 mg/kg	0.4 mg/kg	oid	112/70	12*** 11	80% renal disease
Valsartan vs. placebo Meyers et al. (48)	6–16 (261)	10–20/day	80–160 mg/day	oid	No reported^	7.0/13.0*** 4.0/9.0	Obese and non-obese
Valsartan vs. placebo Wells et al. (49)	6–16 (261)	10–20/day	80–160 mg/day	oid	**133/77**	7.9/11.5*** 4.6/7.4	18% renal disease
Losartan vs. Amlodipino Webb et al. (50)	1–17 (28)	L0.7 mg/kg A0.1 mg/kg	L1.4 mg/kg A1 mg/kg	oid	No reported^	1.9*** +3.9	Alport syndrome Hypertensive and normotensive No significant BP reduction
Valsartan vs. placebo Schaefer et al. (51)	1–5 (75)	0.25 mg/kg	4 mg/kg	oid	No reported^	8.3/14.4*** –	61% renal disease
Losartan Webb et al. (52)	6 mo–6 (101)	0.1 mg/kg	100 mg	oid	111/69	7.9*** –	66% renal disease
Valsartan open label Lou-Meda et al. (53)	6–17 (150)	40 mg/day	160–320 mg/day	oid	135/82	11.0/19.0*** 9.6/12.0	With and without CKD
Valsartan vs. placebo Jankauskiene et al. (54)	1–5 (127)	0.25 mg/kg	4 mg/kg	oid	No reported^	4.4*** –	53% renal disease
Azilsartan open label Ito et al. (55)	6–15 (55)	2.5–5 mg/day	20–40 mg/day	oid	123/72 136/71	8.8/15.4*** 10.3/13.6	Secondary HTN

+oid, once a day; bid, twice a day. *Body weight dependent. **Lowest to highest placebo subtracted. ***Indicated separation between reductions in SBP (upper) or in DBP (down). ^No reported the baseline values was in some studies no presented and only reduction of BP values are reported. In other studies, the baseline was reported for different categories of body weight and the lowest to highest reduction were reported. Gray shaded lines: studies with secondary hypertension.

Overall, the available evidence appears to allow a relatively safe choice of at least the class of antihypertensive drugs in children with secondary HTN. Most other clinical considerations, however, are still largely depending on the underlying pathophysiology and the presence of concurrent disorders such as diabetes mellitus, chronic kidney disease, proteinuria, overweight and more.

The studies available in the ClinicalTrials.gov Search Results (56) (consulted 07/05/2022) include only six studies in different stages of conduction but not published yet (Table 4). The design does not seem to cover the previously mentioned issues.

TABLE 4 ClinicalTrials.gov search results 07/05/2022 (56).

A study of the effectiveness and safety of ramipril in the treatment of hypertension in children and adolescents	Terminated	Has results	HTN	Ramipril Placebo
Evaluation of the safety, efficacy and pharmacokinetics of MICARDIS® (Telmisartan) in children and adolescents with hypertension	Completed	No results available	HTN	Telmisartan Placebo
Assessment of efficacy and safety of olmesartan medoxomil in children and adolescent patients with high blood pressure	Completed	Has results	HTN	Olmesartan medoximil Placebo
Safety study of lisinopril in children and adolescents with a kidney transplant	Completed	Has results	HTN	Lisinopril
Treatment of pediatric hypertension with altace trial	Completed	No results available	HTN	Ramipril
A study of valsartan used to treat hypertension for up to 13 months in hypertensive children ages 6–16 years of age	Completed	No results available	HTN	Valsartan

n-of-1 trials

Given the limitations of the CTs performed in the last 20 years, new research approaches are needed to provide evidence on how to select appropriate antihypertensive medications in children, in terms of efficacy and tolerance as well as persistence of the effect over prolonged time periods.

The ***n-of-1 trial*** (a.k.a. single-patient trials) is a promising approach to identify the most successful treatment for diseases that require treatment during prolonged periods of time. Based on a document released in 2014 by the Agency for the Health Care Research and Qualities (57), *n-of-1* trials, is a form of prospective research in which different treatments are evaluated in an individual patient over time.

The approach has been applied to HTN using ambulatory blood pressure monitoring (ABPM). In a randomized trial (58), three drugs from different classes were selected and started in patients in whom HTN had been confirmed by ABPM. The first drug was given during the first 2 weeks, the second drug during weeks 3 and 4 and the third drug during weeks 5 and 6. At the end of each 2 week period a 24 h ABPM was performed. Once the first circle (6 weeks) was finished, the drug with unacceptable side effect profile or minimal BP reduction was discarded and the procedure was repeated for the remaining two drugs. In the end the drug with the best treatment adherence, patient satisfaction, and BP control was selected. It should be noted that the above design does not meet with universal agreement because compliance can be challenging for both patients and physicians, although the results can be useful in patients who require long-term BP control.

Future perspectives

Innovative solutions are needed to optimize the traditional testing of drugs. The application of rapidly evolving digital health technologies and artificial intelligence in HTN healthcare and research (digital hypertension) holds promise to provide further insights into the understanding of pathophysiology as well as the identification of therapeutic targets and efficacy of antihypertensive drugs.

The stringent isolation measures adopted during the pandemic have strongly promoted telemedicine practices that provide information *via* communication technologies that use several distinct methods (59).

A prospective study evaluating 263 interviews between health care professionals and children with chronic diseases suggests that telemedicine applications are useful tools not only during pandemics but also in daily practice (60). One application now frequently used in managing HTN is BP telemonitoring (BPT) (61). Although patients' compliance might be a potential limitation, a systematic review article points out that all current studies regarding the efficacy of BPT exhibit several benefits for long-term follow-ups, including reduction of health care costs and improvement of outcomes in the pediatric population (62). This opens also opportunities to improve drugs.

Artificial intelligence (AI) is another promising tool for the management of patients with high blood pressure and can also improve the assessment of drug efficacy (63). Machine learning methods differ significantly from traditional statistical methods. While conventional statistics focuses mainly on the conclusions, AI-derived statistics generally concentrates on

prediction and decision-making. Therefore, they are commonly used as risk-stratifying and scoring tools (64, 65). However, the role of AI techniques in the management of HTN remains unclear and controversial due to several limitations, such as requiring large amounts of data, lack of data quality, lack of standardized models that can be reliably used for different populations, dependence mostly on laboratory findings without adequate environmental factor assessments, necessity to retrain the neural network whenever a significant change is made in the target population, and insufficient training of clinicians in bioinformatics and data science (63, 66, 67).

Conclusions

Despite the traditional belief that HTN is a rare condition in children, there is accumulating evidence that elevated BP is increasingly common in both children and adolescence. Despite the abundance of different pharmacological agents designed to treat HTN these are mostly studied in adults and only over the last years industry and authorities have identified the need of well conducted randomized trials of pharmacological treatment in childhood HTN.

Legislation changes have pushed for pediatric studies, but we are still far from establishing a confident level of knowledge in HTN management for children. CTs available today lack hard evidence to recommend any class of antihypertensive medication over the others as first line in children. Furthermore, the impact of pharmacological therapy on cognitive development and growth is not sufficiently studied.

Overall, it is beyond any doubt that we lack important knowledge when it comes to pharmacological antihypertensive treatment in children. The increasing number of children to be treated rises the need for large multicenter randomized trials to investigate the best treatment strategies for each child, to identify optimal dosage regimes and improve the long-term safety of antihypertensive medication in children. In addition to classical CTs, new approaches will contribute to get more grounded information.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JR, GM, and SE contributed to conception and design of the study. JR wrote the first draft of the manuscript. JR, SE, EW, GM, DP, TS, LS, and KK wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Comparison of validation protocols for blood pressure measuring devices in children and adolescents

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Accuracy of blood pressure (BP) measurement is important for the evaluation of hypertension in children and adolescents, and it is critically dependent upon the accuracy of the BP measuring device. A device that could pass validated protocols with reliable accuracy would be desirable in clinical and research settings. Several scientific organizations have published recommendations on the validation of different BP measuring devices. Most of them focus on adults but separate recommendations and validation criteria for BP devices intended for use in children and adolescents are included in some validation protocols. In this review, we compare the validation criteria for BP measuring devices among consensus documents from different scientific organizations focusing on the pediatric population and we discuss the evidence gaps targeting the needs for validated BP measuring devices in children and adolescents. We also highlight common pitfalls in the validation studies of BP measuring devices in children and adolescents using the example of office BP devices.

KEYWORDS

blood pressure, device, validation, children, adolescents

Introduction

Accuracy of blood pressure (BP) measurement is important for the evaluation of hypertension in children and adolescents, and it is critically dependent upon the accuracy of the BP measuring device. The need for evaluation of the accuracy of automated BP measuring devices available in the market, both for use in clinical settings, as well as out-of-office environment, using validation procedures has been well-recognized by the scientific community and the manufacturers (1). A device that can pass validated protocols with reliable accuracy would be desirable in clinical and research settings.

Several scientific organizations have published consensus documents on the validation of BP measuring devices. First, in 1987, the American Association for the Advancement of Medical Instrumentation (AAMI) published a monograph on clinical validation procedures for automated BP monitors, which was recognized as a national standard in the United States (2). This protocol was subsequently revised in 1992 and 2002. In 1990, the British Hypertension Society (BHS) published another validation protocol for BP monitors, which was revised in 1993 (3, 4). The German Hypertension League (DHL) developed its own Quality Seal Protocol in 1999 (5), and in 2002, the European Society of Hypertension (ESH) introduced the ESH-International Protocol (ESH-IP) that was revised in 2010 (ESH-IP2) (6, 7). In 2009, the International Organization for Standardization (ISO) published its own protocol (8) and in 2013 the American National Standards Institute (ANSI), the AAMI, and the ISO collaboratively released a revised protocol (9). Finally, in 2018, the AAMI/ESH/ISO released the most recent validation protocol in an effort to develop a single universal protocol for the validation of BP monitors (10).

Most of the validation protocols are developed only for adults and children are regarded as a special population requiring separate validation studies. The main objective of these consensus statements was to provide practical guidance for validation studies of BP measuring devices and to ensure that conditions are fulfilled, and data are reported in detail. Still, despite previous and current recommendations performing and reporting on validation studies present significant limitations. The pitfalls are more pronounced when the validation studies are performed in children and adolescents (11).

In this review, we compared the validation criteria for BP measuring devices among the consensus documents from scientific organizations focusing on the pediatric population and we discuss the gaps in evidence targeting the needs for validated BP devices in children and adolescents. We also highlight common pitfalls in the validation studies of BP measuring devices in children and adolescents using the example of office BP devices.

Differences between validation protocols

The basic differences between the validation protocols are summarized in **Table 1** and include the following key features:

Sample size

A major difference between protocols is that the ESH-IP2 is the only one that requires a smaller sample size of 33 individuals instead of 85 and 96 individuals that the other protocols require.

Age of participants

Most of the protocols are designed for adults, whereas the ANSI/AAMI/ISO and the AAMI/ESH/ISO include children older than 12 years.

Distribution of participants

In all protocols, the inclusion criteria for the participants vary in regard to their age, sex, arm circumference, and entry BP distribution. The sample is distributed based on age only in DHL, whereas in the others the distribution is random. Most of the protocols, except from the BHS, include participants selected with sex criteria. Only the ANSI/AAMI/ISO and AAMI/ESH/ISO protocols use sample that is selected according to the arm circumference. Finally, all protocols use BP range as a criterion for the selection of the subjects.

Measurement method

All protocols endorse the same-arm sequential measurement as the most accurate method except for the ANSI/AAMI/ISO, which suggest alternatively the same or the opposite arm simultaneous BP measurement procedure.

Reference blood pressure measuring device

In the BHS, DHL, and ESH protocols, the recommended reference BP measurement device is a mercury sphygmomanometer, whereas the protocols of ANSI/AAMI/ISO and AAMI/ESH/ISO suggest alternatively the use of other non-mercury devices with a maximum error of 1 mmHg.

TABLE 1 Comparison of validation protocols for blood pressure (BP) measuring devices.

	BHS (3)	Quality seal protocol -DHL (4)	ESH IP2 (5)	ANSI/AAMI/ISO (7)	AAMI/ESH/ISO (8)
Organization	British Hypertension Society	German Hypertension League	European Society of Hypertension	American National Standards Institute/Association for the Advancement of Medical Instrumentation/ International Organization for Standardization Collaboration	Association for the Advancement of Medical Instrumentation/ European Society of Hypertension/ International Organization for Standardization Collaboration
Last revision	1993	1999	2010	2013	2018
Sample size	85	96	33	≥85	≥85
Participants' age	15–80 years	>20 years	≥25 years	>12 years	> 12 years
Age distribution	By chance	3 age groups Distribution based on age and SBP and DBP levels	By chance	By chance	By chance
Sex distribution	By chance	Equally represented	≥10 subjects of each sex	≥30% of each sex	≥30% of each sex
Arm circumference distribution	By chance	By chance	By chance	Single cuff: ≥40% in the upper/lower half of the specified cuff-range ≥20% in the upper/lower quarter. Multiple (n) cuffs: each cuff at least 1/(2 × n) of the subjects	Single cuff: ≥40% in the upper/lower half of the specified cuff-range ≥20% in the upper/lower quarter, ≥10% within the upper/lower octile Multiple (n) cuffs: each cuff at least 1/(2 × n) of the subjects
BP range distribution	SBP (mmHg) <90: ≥8 subjects, 90–129: ≥20, 130–160: ≥20, 161–180: ≥20, >180: ≥8, DBP (mmHg) <60: ≥8 subjects, 60–79: ≥20, 80–100: ≥20, 101–110: ≥20, >110: ≥8	20–40 years SBP (mmHg): ≤140:12 subjects ≥141:12 DBP (mmHg): ≤90:12 ≥91:12 41–70 years: SBP: ≤120:8 121–140:16 141–160:16 ≥ 161:8 DBP: ≤80:8 81–90:16 91–100:16 ≥101:8 ≥71 years: SBP: ≤140:12 >141:12 DBP: ≤90:12 >91:12	SBP (mmHg) <130:10–12 subjects, 130–160:10–12, >160 mmHg: 10–12 DBP (mmHg) <80:10–12, 80–100:10–12, >100:10–12	SBP (mmHg) ≤100 mmHg: ≥5% of readings ≥140 mmHg: ≥20% ≥160: ≥5%, DBP (mmHg) ≤60 mmHg: ≥5% ≥85 mmHg: ≥20% ≥100 mmHg: ≥5%	SBP (mmHg) ≤100 mmHg: ≥5% of readings ≥140 mmHg: ≥20% ≥160: ≥5%, DBP (mmHg) ≤60 mmHg: ≥5% ≥85 mmHg: ≥20% ≥100 mmHg: ≥5%
Reference BP measurement	Mercury sphygmomanometer	Mercury sphygmomanometer	Mercury sphygmomanometer	Mercury sphygmomanometers or non-mercury auscultatory device with maximum error ± 1 mmHg	Mercury sphygmomanometers or accurate non-mercury devices with maximum error ± 1 mmHg
Measurement method	Same arm sequential BP measurement	Same arm sequential BP measurement	Same arm sequential BP measurement	Same-arm sequential or simultaneous (same or opposite arm) BP measurement	Same arm sequential BP measurement
Paired BP measurements	255	≥288	99 (22–44 in each BP range)	255	255
Specific guidelines for ABPM	Yes	No	No	Yes (separate validation protocols)	Yes (separate validation protocols)

(Continued)

TABLE 1 (Continued)

	BHS (3)	Quality seal protocol -DHL (4)	ESH IP2 (5)	ANSI/AAMI/ISO (7)	AAMI/ESH/ISO (8)
Pass criteria	Grading system (A, B, C, D) based on differences between paired readings by ≤ 5, 10, 15 mmHg separately for each observer and separately for SBP and DBP Additionally, mean differences ≤ 5 mmHg and SD ≤ 8 mmHg (AAMI recommendations)	Criteria based on mean difference and SD and point system for individual paired SBP and DBP readings Pass if the device fulfills all the following criteria: mean difference for SBP and DBP ≤ 5 mmHg and the SD ≤ 8 mmHg and point score ≥ 55% of the maximum attainable point score.	Criteria based on the number of readings with test-reference BP difference ≤ 5, 10, 15 mmHg Criteria for individual BP measurements (Part 1) individual subjects (Part 2) Part 1: Pass if 73.7% (73/99) of differences between readings: ≤ 5 mmHg, 87.9% (87/99) ≤ 10 mmHg, 97.6% (96/99) ≤ 15 mmHg Part 2 (Accuracy): number of subjects with 0, 2 or 3 of absolute difference ≤ 5 mmHg	Criteria based on mean BP differences and their SDs Criteria for individual BP readings and individual subjects. Criteria 1 and 2 should be applied for SBP and DBP Criterion 1 (for individual BP readings): The mean BP difference ≤ 5 mmHg and SD ≤ 8 mmHg Criterion 2 (for individual subjects): The mean difference and SD of BP readings within threshold defined by mean value of criterion 1	Criteria based on mean BP differences (test vs. reference) and their SDs Criteria for individual BP readings and individual subjects. Criteria 1 and 2 should be applied for SBP and DBP Criterion 1 (for individual BP readings): The mean BP difference ≤ 5 mmHg and SD ≤ 8 mmHg. Criterion 2 (for individual subjects): The mean difference and SD of averaged BP differences must be within a threshold defined by mean value of criterion 1 Additionally, the number of absolute BP differences within 5, 10, and 15 mmHg (ESH-IP2) and standardized Bland–Altman scatterplots will be presented The mean test-reference BP difference and SD per cuff subgroup must be reported without pass/fail criteria for the test device
Special groups	Pregnant women, elderly, and children Only if a device has successfully completed all phases of Part I and has achieved at least a B grading for accuracy for both SBP, DBP (Part II.I)	Pregnant women, diabetics, arm circumference > 33 cm	No specific guidelines Separate studies recommended for special populations	Pregnant women, neonates and children, heart irregularities/disease	Children < 3 years, pregnancy including preeclampsia, arm circumference > 42 cm, atrial fibrillation Possible special groups: individuals aged 12–21 or >80 years and those with end-stage kidney disease Special population studies with smaller sample sizes should be performed only after a full general population study has been successfully completed. If the device is intended only for a special population, then a full 85-subject study is required
Special occasions	During exercise and in various postures. Only if a device has successfully completed all phases of Part I and has achieved at least a B grading for accuracy for both SBP, DBP (Part II.II)	No specific guidelines	No specific guidelines	During exercise	No specific guidelines
Extra	Examines intradevice variability, accuracy of devices after long term period of performance				

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring; SD, standard deviation.

Pass/Fail criteria

Different pass criteria have been used in all the protocols. The DHL, AANSI/AAMI/ISO, and AAMI/ESH/ISO criteria are based on calculating the mean difference and the standard deviation (SD) between the test and the reference BP measuring devices. The DHL has used additionally a point system scoring. On the other hand, the BHS and the ESH-IP2 criteria are based on summing up the cumulative incidence of the difference between the test and the reference BP devices in the categories of less than 5, 10, and 15 mmHg.

Specific guidelines for ABPM

Only the BHS, ANSI/AAMI/ISO and the AAMI/ESH/ISO protocols highlight the need of separate validation studies for ABPM.

Special occasions (such as exercise)

The BHS includes specific guidelines for the validation of BP devices in special occasions, such as during exercise and in different postures, whereas the AAMI provides recommendations for the validation of BP monitors only during exercise.

Special populations (such as pregnant women, children, elderly, and patients with diabetes)

All the protocols recognize that BP devices should be validated in special populations and provided specific recommendations for these groups except for ESH-IP2 that recommends separate studies to be carried out.

Finally, the BHS protocol is the only one that tests the intradevice variability and the consistency in the performance of the BP monitor after prolonged use.

Validation protocols in children and adolescents

The recommendations for validation of BP measurement devices are mainly "tailor made" for adults. Although some organizations have addressed the validation in special populations including children, they mostly consider children as "small adults" and do not take into account several distinct characteristics of the pediatric population. Finally, most of the documents on the validation of BP measuring devices have included in the writing committees only adult hypertension specialists putting less emphasis on this special population. Given that the scientific evidence beyond the recommendations is limited and all organizations provide consensus documents the lack of statements on the validation of BP measuring devices specifically addressing to the unique characteristics and needs of children and adolescents by specialists and practitioners caring exclusively for pediatric patients gains extreme importance as a fundamental step for accurate and reliable BP measuring devices in the pediatric population.

The BHS, ANSI/AMI/ISO, and AAMI/ESH/ISO are the only protocols, which include specific recommendations for the validation of BP measuring devices in children (3, 9, 10) (**Table 2**). According to BHS, a sample of 30 children aged 5–15 years with specific inclusion criteria for their age, sex, and entry BP distribution is required (3). Afterwards, the mean BP difference and SD between test and reference device measurements should be reported without specified pass criteria. The ANSI/AMI/ISO and AAMI/ESH/ISO protocols share the same principles (9, 10). If the device is intended for use on both adults and children, the sample should consist of 35 children aged 3–12 years and 50 individuals aged older than 12 years. On the other hand, if the device is intended only for the use on children, a study with a sample of 85 children with specific criteria for sex and cuff size distribution should be carried out. According to the protocols, the studies should meet both two criteria for BP differences of individual readings and of individual subjects. The criterion 1 defines that the mean BP difference (test minus reference BP for all of the measurements) must be 5 mmHg or less, and its SD 8 mmHg or less for systolic and diastolic BP and the criterion 2 that the SD of averaged BP differences (test minus reference BP per subject) must be within a threshold defined by the mean of criterion 1 (9).

Considerations on validation protocols in children and adolescents

Population and sample size

The optimal sample size for a BP measuring device validation study varies among different organizations. As mentioned above the ESH validation protocol suggested a minimum of 33 subjects, while the BHS, the ANSI/AAMI/ISO as well as the AAMI/ESH/ISO required 85 participants (3, 10). The disagreement on ideal population sample sizes lies on the statistical power of the validation procedure against the cost and complexity (10, 12).

In the AAMI/ESH/ISO consensus statement, it was reported that that a validation study with a sample size of 35 subjects would be inadequate for a moderate accuracy device defined as a difference of 4 ± 5 mmHg compared to the test device, because of an unacceptably high at 28% chance to fail (10). However, according to a biostatistician report, a validation study with 35

TABLE 2 Comparison of validation protocols for BP measuring devices in children.

	BHS revised (1993) (3)		ANSI/AAMI/ISO (2013) (7)		AAMI/ESH/ISO (2018) (8)		
	After a successful study in general population		Device for children and adults or with pediatric mode:	Devices only for children:	Devices for both general population and children: (after a successful 85-subject study in general population)	Devices with a special pediatric mode: (after a successful 85-subject study in general population)	Devices only for children: (without previous study in general population)
Age range	0–5 years	5–15 years	3–12 years		3–12 years and ≥ 12 years	3–12 years	3–12 years
Sample	30 subjects	30 subjects	35 subjects	85 subjects	85 subjects	35 subjects	85 subjects
Age distribution	0–12 months: 15 subjects, 1–5 years: 15	Evenly distributed	Not specified		3–12 years: 35 subjects, > 12 years: 50	Not specified	Not specified
Sex distribution	≥10 each of sex	By chance	≥30% of each sex		≥30% of each sex		
BP range distribution	**SBP:** 5/30 > mean + 1 SD for population **DBP:** 5/30 < mean—1 SD for population	**SBP:** 5/30 > mean + 1 SD for population 5/30 < mean—1 SD for population **DBP:** 4/30 > mean + 1 SD for population 5/30 < mean—1 SD for population	Not specified		As the total 85-subject study	Without BP distribution requirements	
Arm circumference distribution	Not specified	5/30 > 70th centile for weight 5/30 < 30th centile for weight	Single cuff: 40% of subjects' circumference within upper half of range; 40% within lower half; 20% of subjects' circumference within upper quarter of range; 20% within lower quarter. N cuffs, test each in ≥ 1/(2 × n) subjects		Single cuff: 40% of subjects' circumference within upper half of range; 40% within lower half; 20% of subjects' circumference within upper quarter of range; 20% within lower quarter. N cuffs, test each in ≥ 1/(2 × n) subjects		

(Continued)

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TABLE 2 (Continued)

	BHS revised (1993) (3)	ANSI/AAMI/ISO (2013) (7)	AAMI/ESH/ISO (2018) (8)	
Reference BP measurement device	Conventional mercury sphygmomanometry	Mercury sphygmomanometer, or non-mercury auscultatory device with max permissible error ± 1 mmHg	Mercury sphygmomanometer, or non-mercury auscultatory device with max permissible error ± 1 mmHg	
Reference diastolic BP	K5	K4	K4	
Pass criteria	Mean difference and SD for test-reference BP differences to be reported No pass threshold is provided	Criterion 1: mean ± SD for test-reference BP differences ≤ 5 ± 8 mmHg Criterion 2: intersubject SD of BP differences within threshold defined by the mean of criterion 1	Mean difference and SD of SBP and DBP should be reported separately for subgroups aged 3–12 and > 12 years Pass criteria: validation criteria 1 and 2 Criterion 1: mean ± SD for test-reference BP differences ≤ 5 ± 8 mmHg Criterion 2: intersubject SD of BP differences within threshold defined by the mean of criterion 1	Validation criterion 1 Validation criteria 1 and 2

BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, SD: standard deviation.

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subjects would be adequate for high- or low-accuracy devices. Then, it was calculated that a population sample of 85 subjects as previously suggested by the ANSI/AAMI/ISO has an acceptable chance of failing (18%) supporting the previous consensus of at least 85 subjects and taking into account that most devices in the market probably have moderate accuracy.

Adolescents older than 12 years are considered as general population and are evaluated within an 85-population sample. Transfer functions and in-built algorithms for the calculation of systolic and diastolic BP are not usually available by the manufacturer (13). The algorithms differ between devices, are considered proprietary for the manufacturer, and are, therefore, confidential. Of note, these algorithms are developed for adults with higher BP levels, and automated initial cuff inflations to high pressures may cause discomfort or pain in the child precluding its cooperation (14). Oscillation may also be lower in the youngest with lower BPs. For example, for a 12-year-old-boy with short stature at the 5th centile, the median level (50th centile) of systolic and diastolic BP is at 101/65 mmHg, respectively. Then, it is well described that in adolescents, the pulse wave contour is different than in older individuals with stiffer arteries (15). Whether these algorithms could evaluate with the same accuracy, the BP level in an adolescent as young as 12 years old and in a 65-year-old individual remains unanswered and uninvestigated.

A low-accuracy device for adolescents with an in-built algorithm resulting in high accuracy in older subjects would result in a medium-accuracy device with the inclusion of subjects 12–18 years in general population study. While the impact of this result would be moderate for the adult population, it may have important implications for adolescents regarding misclassification of their BP status and possibly undiagnosed hypertension.

The ESH 2016 guidelines on the management of high BP in children and adolescents consider that only older adolescents (≥16 years) are evaluated for hypertension using the adult BP threshold (16). It may be prudent that this age limit of 16 years would also apply for the validation studies in the general population. Then, a separate validation study considering adolescents <16 years as a special population may offer the opportunity for more precise assessment of accuracy before a device is suggested in the adolescent age range.

Children are considered as a special population if younger than 12 years. According to the BHS, the number of pediatric patients 3–12 years needed for a BP measurement device validation study is 30, if the device has been successfully validated in the general population. The ANSI/AAMI/ISO and the AAMI/ESH/ISO recommend a sample size is of at least 85 subjects if the study includes only children, but in the case of an existent validation study for the general population, the required sample size is 35 children. For validation, studies including both children and adults' general population, a total sample size of at least 85 is required, with children consisting of 35 out of 85 participants. The same concerns about the transfer functions and in-built algorithms may apply for children 3–12 years. Again, given all the above considerations, it is unclear if the sample of 35 children would be adequate for this age range with low oscillation and different vascular functions for moderate accuracy devices (13).

Cuff size

Most monitors included two cuffs for the adult population. Special-size cuffs are not always available and in case of minors, children, and adolescents, this is an important issue. In the same concept as in the previous section, younger adolescents may erroneously be considered as general populations as they have different characteristics. It is recommended that the cuffs used for reference auscultatory BP measurement must have an inflatable bladder length that covers 75–100% of the upper arm circumference of each participant and a width that covers 37–50% of the arm circumference measured at the upper arm midpoint between acromion and olecranon (10). Many manufacturers include adult cuffs that are suitable for arm length >22 cm. For 12–15–years-old girls, the 5th–25th centile of midarm circumference is <20 cm and adult cuffs are not suitable for reliable BP measurement (17, 18). Similarly, the 25th centile of midarm circumference of a 12-year-old boy is <20 cm and for 14- and 15-years-old boys is at 22 and 23 cm, respectively. In the AAMI/ESH/ISO, it is recommended that inflatable bladder dimensions should be 12 cm for 12–15 years old and 15 cm for 15–18 years old.

If a device is considered for validation in children and adolescents, commercially available cuffs sizes both for the validation study but also for routine use should be a prerequisite criterion. Although not specifically reported in the consensus documents using cuffs from other manufacturers or from the test device, not designed for the device under evaluation, for the reference BP measurement during the validation study may result in significant measurement errors and significant bias of the validation study methodology.

Diastolic blood pressure

The latest ESH and American Academy Pediatrics (AAP) guidelines for the diagnosis of high BP in children and adolescents recommend the use of Korotkoff sound 5 (K5) during office BP measurement (16, 19). The most frequently used validation protocol, the ANSI/AAMI/ISO recommends the use of Korotkoff sound 4 (K4) during the validation procedure which constitutes a major inconsistency between validation and clinical use of a device (9). However, in line with the guidelines for diagnosis of the hypertension in children and adolescents, the BHS, as well as the universal AAMI/ESH/ISO 2018 protocol recommend the use of K5 (3, 20). The latter recommends that if K5 is not audible, the child should be excluded.

Validation criteria

In all consensus validation documents, two criteria as defined by the ANSI/AAMI/ISO are used to evaluate the

TABLE 3 Validated devices for office BP measurement in children and adolescents.

Device (References)	No. of patients/ age range	No. of pediatric patients/ age range	Validation protocol	Result	Test device	DBP definition (K4 or K5)	Cuff sizes used	Device commercially available cuff sizes	Funding
Successful validation including only children									
BpTru BPM-100 (BpTRU Medical Devices, Canada, USA) (21)	36/3–18 years	36/36 (3–18 years)	ANSI/AAMI, BHS	Pass, grade A	Auscultatory mercury sphygmomanometer	K5	na	Child 13–18 cm, Small adult 18–26 cm, Regular adult 26–34 cm, Large adult 32–43 cm, Extra—large adult 41–52 cm	nr
CasMed 740 (CAS Medical Systems, Branford, Connecticut, USA) (22)	29/ < 3 years	29/29 (29 days–1 year: 5, 1–3 years: 3)	ANSI/ AAMI/ISO	Pass	Invasive arterial measurement	na	Neonate cuffs: #1: 3–6 cm #2: 4–8 cm #5: 8–15 cm, Child cuff: 13–20 cm	Neonate: #1: 3–6 cm #2: 4–8 cm #3: 6–11 cm #4: 7–14 cm #5: 8–15 cm, Infant 8–14 cm, Child 13–20 cm, Small adult 18–26 cm, Adult 26–35 cm, Adult long 29–38 cm, Large adult 32–42 cm, Large adult long 35–44 cm, Adult thigh 42–50 cm,	CAS Medical Systems Inc.
Datascope Accutorr Plus (Datascope Corporation, Mahwah, New Jersey, USA) (23)	44/5–15 years	44/44 (5–15 years)	ESH	Pass	Auscultatory mercury sphygmomanometer	K5	na	9–14.8 cm orange, 13.8–21.5 cm green, 20.5–28.5 cm light blue, 27.5–36.5 cm navy blue, 35.5–46 cm burgundy, 45–56.5 cm brown	Hong Kong Paediatric Nephrology Society, Children's Kidney Trust Fund
Dinamap Procare-120 (Critikon, Tampa, Florida, USA) (23)	44/5–15 years	44/44 (5–15 years)	ESH	pass/fail	Auscultatory mercury sphygmomanometer	K5	na	Infant, Child, Small adult, Adult, Large adult, Adult thigh	Hong Kong Paediatric Nephrology Society, Children's Kidney Trust Fund
Dinamap Procare-200 (Critikon, Tampa, Florida, USA) (24)	45/(7–18 years)	45/45 (7–18 years)	BHS, ESH	pass, pass/fail	Baumanometer Mercury Gravity Sphygmomanometer (W.A. Baum Co., Copiague, NY, USA)	na	Child 17–22 cm, Small adult 22–30 cm, Large adult 30–38 cm	Neonate Neo #1 Neo #2 Neo #3 Neo #4 Neo #5, Infant, Child, Small adult, Adult, Large adult, Adult thigh, Adult long cuff *(Different assortment packs available)*	Korea Center for Disease and Prevention (KCDC)

(Continued)

TABLE 3 (Continued)

Device (References)	No. of patients/ age range	No. of pediatric patients/ age range	Validation protocol	Result	Test device	DBP definition (K4 or K5)	Cuff sizes used	Device commercially available cuff sizes	Funding
Successful validation including only children									
Raycome RBP-1200 (Shenzhen Raycome Health Technology, China) (25)	3–12 years	87/87 (3–12 years)	ANSI/AAMI/ ISO	Pass	Auscultatory mercury sphygmomanometer	K5	Extra small 15–18 cm, small 18–22 cm, standard 23–32 cm	Extra small (SS) 15–18 cm, Small (S) 18–22 cm	National Nature Science Foundation of China, Shenzhen Raycom Health Technology Company (Shenzhen, China)
Successful validation both adults and children									
CAS 9010 (CAS Medical Systems, Branford, Connecticut, USA) (27)	4–78 years	35/88	AAMI	Pass	Auscultatory mercury sphygmomanometer	na	na	na	nr
Colin BP8800MS (Colin Medical Instruments Corp., San Antonio, TX) (28)	170, 8 months–80 years	85/170 (8 months–16 years)	ANSI/AAMI	Pass	Mercury manometer (model Marshall Deluxe, Omron Healthcare, Inc., Vermon Hills, IL)	K5	Infant 8–12.5 cm, Child 12.5–18 cm, Small adult 18–24 cm, Adult 24–32 cm, Large adult 32–40 cm	Neonate #1 #5, Infant, Child, Small adult, Adult, Large adult	Nippon Colin (Komaki, Japan) and Colin Medical Instruments (San Antonio, TX)
Fukuda Denshi DS-7000/NIBP-701 (Fukuda Denshi Co., Tokyo, Japan) (29)	119/42.2 ± 21.0 years	33/119 (15 pediatric (3–12), 18 neonate/infant (< 3))	ANSI/AAMI, BHS	Pass, pass-grade A	Intraarterial-neonates and infants, auscultatory-children and adults	na	na	Infant cuff, Child cuff, Large/Regular/ Small Adult cuff	Fukuda Denshi
Microlife WatchBP Office (Microlife AG, Widnau, Switzerland) (30)	88/3–70 years	37/88 (3–12 years)	ANSI/AAMI/ ISO	Pass	Auscultatory mercury sphygmomanometer (Baumanometer; WA Baum Co., Inc., New York, New York, USA)	K5	Small 14–22 cm, Medium 22–32 cm, Large 32–42 cm	Medium 22–32 cm, Large 32–42 cm	Microlife, Widnau Switzerland, University of Athens Special Account for Research Grants
Midmark IQvitals Zone (Midmark Corporation, USA) (31)	85/3–77 years	35/85 (7–17 years)	ANSI/AAMI/ ISO	Pass	Manual auscultation	K5	na	Child, Small adult, Adult, Adult long, Large adult, Large adult long, Thigh	Midmark Corporation
Nihon Kohden PVM-2701/Impluse-1 (32)	110/na	41/110 (<12 years)	ANSI/AAMI/ ISO	Pass	Auscultatory mercury sphygmomanometer	K4	na	Infants 8–13 cm, Children: Small 12–18 cm Standard 15–23 cm, Adults: Standard 21–30 cm Large 23–36 cm, Thigh 33–45 cm	University of Tennessee Clinical Research Center and the Tennessee Clinical Trials Network, Nihon Kohden
Omron HBP-1300 (Omron Healthcare Co., Kyoto, Japan) (33)	85/4–72 years	35/85 (<12 years)	ANSI/AAMI/ ISO	Pass	Auscultatory mercury sphygmomanometer	K4	SS 12–18 cm, S 17–22 cm, M 22–32 cm, L 32–42 cm, XL 42–50 cm	SS 12–18 cm, S 17–22 cm, M 22–32 cm, L 32–42 cm, XL 42–50 cm,	Guangzhou Boji Medical Biotechnological Co. Ltd.

(Continued)

TABLE 3 (Continued)

Device (References)	No. of patients/ age range	No. of pediatric patients/ age range	Validation protocol	Result	Test device	DBP definition (K4 or K5)	Cuff sizes used	Device commercially available cuff sizes	Funding
Successful validation including only children									
Omron HBP-1320 (Omron Healthcare Co., Kyoto, Japan) (34)	88/4–70 years	38/88 (4–12 years)	ANSI/AAMI/ ISO	pass, pass	Auscultatory mercury sphygmomanometer	K5	SS 12 to 18 cm, S 17 to 22 cm, M 22 to 32 cm, L 32 to 42 cm, XL 42 to 50 cm	SS 12–18 cm, S 17–22 cm, M 22–32 cm, L 32–42 cm, XL 42–50 cm	nr
Omron M3500 (Omron Healthcare Co., Kyoto, Japan) (35)	135./≥3 years	35/135 (3–12 years)	ANSI/AAMI/ ISO	Pass	auscultatory mercury sphygmomanometer	K4 and K5	Super small: 12–18 cm, Small: 17–22 cm, Standard: 22–32 cm, Large: 32–42 cm, Xlarge: > 42 cm	*Standard* IEC adult cuff or GS cuff M *Optional* IEC adult oversized cuff IEC children cuff (9 cm, 7 cm), Adult cuff (S, M, L, XL), GS cuff (SS, S, L, XL)	OMRON (Japan)
Welch Allyn Pro BP 2000 (Welch Allyn, Skaneateles Falls, New York, USA) (36)	88/ ≥3 years	35/88 (3–12 years)	ANSI/AAMI/ ISO	Pass	Auscultatory mercury sphygmomanometer	K4	Child 15–21 cm, Small adult 20–26 cm, Adult 25–34 cm, Adult long 32–43 cm, Adult large long 32–43 cm, Thigh 40–55 cm	Child 15–21 cm, Small adult 20–26 cm, Adult 25–34 cm, Adult long 32–43 cm, Adult large long 32–43 cm, Thigh 40–55 cm	Welch Allyn
Welch Allyn ProBP 3400 (Welch-Allyn Medical Products, New York, USA) (37)	111, ≥3 years	14/111 (3–12 years)	ANSI/AAMI, BHS	Pass, pass-grade A	Auscultatory mercury sphygmomanometer	K5	na	Small child (12 cm) to thigh (55 cm)	nr
Welch Allyn SureBP, StepBP (Welch-Allyn Medical Products, New York, USA) (38)	102/ ≥3 years	15/102 (3–12 years)	ANSI/AAMI, BHS	Pass, grade A	Auscultatory mercury sphygmomanometer	K5	na	Extra small 15–24 cm, Standard wide 22–42 cm, Extra large 40–54 cm	nr
Welch-Allyn Spot Vital Signs (Welch-Allyn Medical Products, New York, USA) (39)	5–77 years, 47 ± 16	na, >5 years	ANSI/AAMI	Pass	Auscultatory mercury sphygmomanometer (Tycos brand sphygmomanometer; Tycos, Inc., Arden, North Carolina, USA)	K5	na	Neonate: #1: 3.3–5.6 cm #2: 4.2–7.1 cm #3: 5.4–9.1 cm #4: 6.9–11.7 cm #5: 8.9–15 cm, Infant 9.8–13.3 cm, Small child 12.4–16.8 cm, Child 15.8–21.3 cm, Small adult 20–27 cm, Adult 25.3–34.4 cm, Large adult 32.1–43.4 cm, Thigh 40.7–55 cm	Welch Allyn, Inc.
YuWell YE900 (Jiangsu Yuyue Medical Equipment and Supply, China) (26)	85/3–12 years	35/85 (4–11 years)	AAMI/ESH/ ISO	Pass	Auscultatory mercury sphygmomanometer (YuYue, Jiangsu Province, China)	K5	18–22 cm (small), 22–32 cm (medium), and 32–42 cm (large)	na	YuYue Medical Equipment & Supply Co., Ltd.

DBP, diastolic blood pressure; na, not available; nr, not reported.

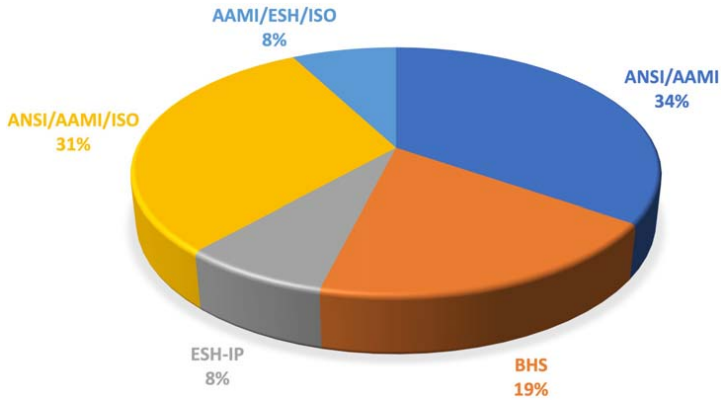

FIGURE 1
Validation protocols used in studies assessing accuracy of BP measuring devices in children and adolescents.

successful validation of devices usually reported as pass or fail in review articles (9). The same criteria apply for pediatric studies although no studies have been performed to evaluate the suitability of these criteria in pediatric patients. However, only criterion 1 is necessary to be reported in the case of 35 subject studies. Of note, in case of a validation study including children in a general population study, both criteria should be reported separately for the pediatric subgroup.

The example of validated office blood pressure devices in children and adolescents

A systematic search using Medline from inception to May 30, 2022, was performed to identify studies validating the accuracy of office BP monitors in the pediatric population alone or as a subgroup of the study population. We used the following search terms: (Office) AND (Blood Pressure) AND (Validation) AND (Monitor) OR (Device) AND (Children) OR (Adolescents). A hand-searching was also conducted for eligible studies. The reference list of each article included was checked for extra bibliography. Duplicates were removed. We included studies in the English language only. Two independent reviewers (KE and CS) screened titles and abstracts independently, and full texts were investigated for eligible studies. Differences between the two reviewers regarding study eligibility were resolved by a third reviewer (SS). Finally, study and population characteristics were extracted from each included study.

The search resulted in 21 studies with successful validation in children and adolescents (**Supplementary Figure 1**) (21–39). Validated devices for office BP measurement, children and adolescents using different available validation protocols are presented in **Table 3**. The accuracy of BP measuring devices was assessed using the ANSI/AAMI and the AMSI/AAMI/ISO protocol in almost 80% of the validation studies in children and adolescents (**Figure 1**). About half of the studies were performed before 2010. Few office BP devices were validated based on two different protocols, both the ANSI/AAMI and the BHS protocols (n = 4) (21, 29, 37, 38) or the BHS and the ESH-IP (n = 2) (23, 24, 39). In all studies, devices passed the validation criteria by both protocols for systolic and diastolic BP with the exception of the Dinamap Procare-200 device that failed for the diastolic BP with ESH protocol criteria (24). One device that has been assessed by two studies was evaluated as passed in one of them but failed in the other one (23, 39). In one study, 3 devices were evaluated simultaneously (23).

Only 6 out of 7 studies that included exclusively pediatric population fulfilled the pass criteria. Three used the ESH-IP protocol (23, 24), which is not designed for children, two the BHS protocol, and three the ANSI/AAMI/ISO protocol. Among studies that used the ANSI/AAMI/ISO protocol, two had an inadequate sample size, leaving only 1 study that used the ANSI/AAMI/ISO protocol to provide the best available validation evidence for office BP devices in children (25).

The test device used in almost all studies was a mercury sphygmomanometer measuring BP by the auscultatory method. Intra-arterial measurement as a test method was used in 2 studies (22, 29), one of them including only neonates and infants (29). Most studies included two trained observers for the BP measurements as recommended and most of them were health professionals.

Seven out of twenty-one validating studies did not meet the criteria for the age range required based on the selected protocols. None of the studies reported the required age distribution in the population. Only five studies met both the sample age and sample size required for a validation study. Although the available protocols do not specify the required ratio of female–male participants for children's studies, most of the studies that defined their population, recruited the same percentage of patients of each sex.

Among studies that used the AAMI protocol the one that included 85 children reported both validation criteria 1 and 2. Also in studies including both the general population and children both validation criteria 1 and 2 were used. In the studies including 35 children with an existent validation study for adults, only criterion 1 was used. Funding by the industry was reported in eight studies (25, 28–33, 35, 36).

Pitfalls during validation procedure

Several validation studies in children or including children in the general population lack adequate reporting of validation data according to validation recommendations or not fulfill all requirements (**Table 3**). Common pitfalls include:

Sample size

The requirements for sample size were satisfied in 12 out of 21 studies. For example, the validation study by Alpert et al., using the ANSI/AAMI/ISO protocol included only children, but the sample size was less than the required sample size of at least 85 subjects (36). The same number of subjects was included by Mattu et al. (21) in a validation study for a BP measuring device intended for use in children but considered adequate as there was already an existent validation study for the general population (21).

Cuff size

In about half of the studies, no data were reported regarding the cuffs used for the validation procedure. Moreover, in several cases, information about commercially available cuffs for the validated device was not reported in manufacturer's sites. Manufacturers may provide only one adult cuffs with the device and pediatric cuff sizes are usually sold separately as extra accessories. In the validation studies that included both children and adults, 6 out of 13 studies used for the validation procedure the cuffs provided by the manufacturer along with the device (**Table 3**). Cuff sizes used during the validation with the description of cuffs' length and width were usually reported, but only 4 of them reported the number of subjects tested for different cuff sizes. In the validation studies that included only children, 2 out of 6 studies used the same size cuffs as provided for the validation, and only 3 out of 6 studies reported the number of subjects tested for each cuff size. Details on the selection of cuff size, midarm circumference of the population and/or midarm circumference by cuff size used were scarcely reported.

Definition of diastolic blood pressure

Most of the included studies used K5 for the definition of diastolic BP, as it is suggested by BHS and AAMI protocols. Some studies didn't report by which Korotkoff sound (K4 or K5) was diastolic BP defined. K4 was reported in four studies while one study reported both K4 and K5 for all participants (35). Five studies used ANSI/AAMI/ISO protocol but reported K5 (25, 26, 30, 31, 33).

Validation criteria

Validation criterion 1 was used in all studies. Results for children were reported together with those of older participants (adults) in the case of studies in the general population, and only one study (1 out of 13) reported data on criterion 1 separately for children (28).

Conclusion

The level of evidence-based upon pediatrics studies for the established validation criteria in children and adolescents needs to be assessed to evaluate the suitability of these criteria in children and adolescents. When evidence does not exist then extrapolation of data from adult studies is usually applied, but limitations of such strategy need to be acknowledged and gaps of evidence would serve as motivation for designing the new research activities. This is the case for BP measuring devices validation studies in children and adolescents. In addition, most validation studies analyzed children's data along with adult ones posing significant uncertainty on the accuracy of the BP measuring validated devices in the pediatric population. Given that automated oscillometric BP devices become extensively popular in routine clinical practice for the diagnosis of high BP in childhood the need of validation protocols addressing the needs and special characteristics of children and adolescents is emerging to ensure accurate evaluation of BP levels in childhood.

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Author contributions

SS an EL: conceptualization. SS, AC, KE, CS, CA, PP, JC, and GH: writing—original draft preparation. SS and AC: writing—review and editing. All authors have read and agreed to the current version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1001878/full#supplementary-material

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Determining the prevalence of childhood hypertension and its concomitant metabolic abnormalities using data mining methods in the Northeastern region of Hungary

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Objective: Identifying hypertension in children and providing treatment for it have a marked impact on the patients' long-term cardiovascular outcomes. The global prevalence of childhood hypertension is increasing, yet its investigation has been rather sporadic in Eastern Europe. Therefore, our goal was to determine the prevalence of childhood hypertension and its concomitant metabolic abnormalities using data mining methods.

Methods: We evaluated data from 3 to 18-year-old children who visited the University of Debrecen Clinical Center's hospital throughout a 15-year study period (n = 92,198; boys/girls: 48/52%).

Results: We identified a total of 3,687 children with hypertension (2,107 boys and 1,580 girls), with a 4% calculated prevalence of hypertension in the whole study population and a higher prevalence in boys (4.7%) as compared to girls (3.2%). Among boys we found an increasing prevalence in consecutive age groups in the study population, but among girls the highest prevalences are identified in the 12-15-year age group. Markedly higher BMI values were found in hypertensive children as compared to non-hypertensives in all

age groups. Moreover, significantly higher total cholesterol (4.27 ± 0.95 vs. 4.17 ± 0.88 mmol/L), LDL-C (2.62 ± 0.79 vs. 2.44 ± 0.74 mmol/L) and triglyceride (1.2 (0.85-1.69) vs. 0.94 (0.7-1.33) mmol/L), and lower HDL-C (1.2 ± 0.3 vs. 1.42 ± 0.39 mmol/L) levels were found in hypertensive children. Furthermore, significantly higher serum uric acid levels were found in children with hypertension (299.2 ± 86.1 vs. 259.9 ± 73.3 μmol/L), while glucose levels did not differ significantly.

Conclusion: Our data suggest that the calculated prevalence of childhood hypertension in our region is comparable to data from other European countries and is associated with early metabolic disturbances. Data mining is an effective method for identifying childhood hypertension and its metabolic consequences.

KEYWORDS

adolescents, blood pressure, children, data mining, hypertension, metabolic parameters, obesity, prevalence

1. Introduction

Childhood hypertension presents a considerable public health challenge worldwide, as it is a potent risk factor for adult hypertension with predictive values varying between 19 and 65% (1). Indeed, it is thought that the origin of the onset of hypertension in adults stems from childhood (tracking phenomenon) (2). The number of children diagnosed with hypertension has significantly grown in the past few decades. The rise in numbers is associated mainly with the obesity epidemic and in part with high salt intake, which may not be related to the economic status of a given country (3). Hypertension is common in adolescents undergoing puberty and in children who are overweight or obese. Some further factors increase the risk of primary hypertension, such as low birth weight, male sex, a sedentary lifestyle, a family history of hypertension and African-American ethnicity (4). According to recent data, primary hypertension is now the leading form of hypertension in childhood, especially in adolescents (5). Adolescents usually have primary hypertension, making up 85 to 95% of cases. Childhood hypertension, particularly in preadolescents, can be secondary to an underlying disorder. The parenchymal disease of the kidneys is the most common secondary cause of hypertension in early childhood. Endocrine diseases contribute to elevated blood pressure. Pheochromocytoma, hyperthyroidism, hyperaldosteronism and the impact of pharmaceuticals (e.g., oral contraceptives, sympathomimetics and some dietary supplements) can be cited as well (6).

The universal screening of hypertension in childhood needs to be improved, as its low prevalence leads to the misdiagnosis of childhood hypertension (7). Furthermore, identifying arterial hypertension is challenging in children and adolescents since standards and definitions are complex during body growth. Therefore, designing cardiovascular outcome studies becomes a challenge, too.

Due to the different positions of current guidelines, the global definition of hypertension in children and adolescents is precarious. Therefore, evaluating the prevalence of hypertension in this age group is complicated on a global scale (8). In Europe, the Scientific Council and the Working Group on Hypertension in Children and Adolescents of the European Society of Hypertension (ESH) updated its 2009 guidelines in 2016 (9).

A former cross-sectional, population-based study conducted in a Hungarian city (Debrecen, population 230,000) found that more than two decades ago the prevalence of hypertension was 2.53% in adolescents (15-18 years of age) (10). Other studies show that the most probable prevalence of childhood and adolescent hypertension is estimated to be 3.5% (11, 12). A recently published random-effects meta-analysis of 47 articles estimates the pooled prevalence of childhood hypertension to be 4.00% (95% CI, 3.29-4.78%) (13). Screening for childhood hypertension in Eastern Europe is relatively poor despite the fact that the findings of a large number of studies are available. We aim to identify childhood hypertension in our region by evaluating a period of 15 years using data mining methods to analyze a rather large population. Although this method is not widely used in epidemic studies, it is an excellent way to define prevalence in large patient cohorts. To date, this is the first paper providing data on childhood hypertension in Europe to embrace the benefits of data mining methods. A large pediatric patient population is selected to calculate the estimated prevalence of

hypertension and some significant concomitant diseases and metabolic parameters.

2. Patients and methods

2.1. Screening patients for hypertension

As we have delineated previously in other studies of ours (14–16), various methods of data mining used on mass hospital data are ideal for screening for medical diagnoses in cases of hypertension and other conditions. The clinical diagnosis of hypertension was based on the competence of our highly educated pediatricians. Most of them were specialists in endocrinology and nephrology at our University Center. They precisely followed the available international guidelines. According to the current recommendations, they define hypertension by three consecutive elevated blood pressure readings - the measured values compared to age-specific reference values. Our specialists used devices validated for clinical accuracy. The diagnosis of hypertension was based on textual history data (phrases hypertension and its synonyms) and diagnosis codes for hypertension (International Statistical Classification of Diseases and Related Health Problems 9th and 10th Revision, WHO) recorded in the source data.

Via the University of Debrecen Clinical Center we have gained access to anonymous medical records compiled in the Northeastern region of Hungary for the purpose of software development. The source data included the totality of medical records from the clinical centre from a period of 1 January 2007 to 31 December 2021. Our team and our cooperating partner, Black Horse Group Ltd., launched a data mining project wherein we were permitted to make use of their medical system framework entitled "AescuLab"[1]. Data extracted from the clinical records underwent a multistep procedure of anonymization for purposes of protecting patients' private particulars, while the tables of specific case and patient data were detached from real persons. We made use of open-source tools such as https://numpy.org/; http://pandas.pydata.org/ well as certain scripts and solutions developed on our own for cleaning data and completing missing or corrupt sections of data, compiling a totalized and integrated data source from isolated data with laboratory cases, anamneses, national diagnosis codes as well as statistical data on the patients. Our serializing and buffering methods ensured that the data as processed to ward off problems that might be taken for granted in the case of such an enormous data source. As a pre-processing step, textual information was processed through parsing and stemming[2], bag-of-words (BOW) modeling. We ranked phrases by the "Term Frequency/Inverse Document Frequency" (TF-IDF) method (17) and carried out word2vec (W2V) modeling in Keras[3] in order to spot key role phrases (18). When creating BOW models, documents are outlined as histograms of reoccurring terms/words but the models do not take into account any sequential structure, resulting in the representation being vigorous and invariant where documents would consist of deviating elements of sequences. Further, using W2V models ensures that terms and phrases are described as elements in a vector space defined by a neural network, a straightforward language model using contextual terms to identify sequential elements utilizing the structure of the sequence. These two models are equally efficient in determining the significance of words/expressions by ranking them on the basis of their IDF score (17) or perplexity (18). In addition, we compiled a term list using professional vocabularies and utilized string-matching algorithms to exert control over misspellings and to recover the corrupted terminology from fragmented data.

Some of the data that we extracted and processed contains normal anamneses which have not yet undergone any processing and thus necessitate the use of pre-processing methods such as text extraction and content identification focusing on regular terminology. The resulting data yields a finite set full of phrases with the number of occurrences per document recorded, with another value added where previous medical checkups were conducted. Initially our term list ran several million items, but using the aforementioned methods yielded a much more accessible list of 250,000 phrases. Linking cases, patient records and diagnoses helped to display the patients' medical histories as temporal sequences of events closely linked to the patients, which format facilitated the pinpointing of patients with hypertension.

The work complies with the guidelines of the Declaration of Helsinki. The protocol was approved by local and regional ethical committees.

2.2. Determining cardiovascular risk factors amongst laboratory settings

As the data sets compiled were based in various different data structures, the initial step was to establish joint representation to facilitate statistical analysis. This type of structure is necessary to ensure the detection of specific 'attributes'. For instance, high blood pressure might crop up in the text-based data in the guise of various different words, as a parameter or derivative of real measurements. Different data extraction tools were developed and applied to the source data. Another challenge we faced was data cleansing, as we had

1 www.aesculab.net

2 http://hunspell.github.io/

3 https://keras.io/

to complete missing or corrupt fragments of data, where each type of corrupted data had to be treated in a different manner. For instance, the deployment of gap-stopping binary variables with mean values is a method that is ambiguous and thus it had to be eschewed, so all such individual cases were interpreted as normal phrases. In the light of the sheer magnitude of data, further serializing and streaming techniques were developed to optimize the final query engine, which is able to manage partial data and might identify attributes utilizing deduction. These included parsing, stemming, the filtering of stop-words and building dictionaries from unigrams and bigrams after the phrases/words were cleaned manually. Utilizing the TF-IDF (term frequency-inverse document frequency) and word embeddings techniques we found data with phrases and Word embeddings in Hungarian were trained on traditional corpora, which necessitated compiling our language model using the available text as data. We established a Gated Recurrent Unit model (19), a recurrent neural network where cleaned unigrams and bigrams were compiled as dictionaries. Our output data structure appeared thus: an 'attribute' was linked to a patient upon the existence of one of certain specific events. A regular expression was identified or had a high probability where on the basis of the language model it was a phrase or emerged as data from laboratory measurements.

2.3. Laboratory analysis

We measured routine laboratory parameters, including glucose, urea, creatine and uric acid from fresh sera using a Cobas c501 analyzer (manufactured by Roche Ltd., Mannheim, Germany) in the Laboratory Medicine Unit, Clinical Centre, University of Debrecen. The measurement of total cholesterol levels is performed through enzymatic and colorimetric tests (cholesterol oxidase-p-aminophenazone—GPOD-PAP; Modular P-800 analyzer; Roche/Hitachi). The measurement of HDL cholesterol and LDL cholesterol levels was carried out using a homogenous enzymatic and colorimetric assay (Roche HDL-C as well as third generation for HDL cholesterol and Roche LDL-C plus second generation for LDL cholesterol). We performed tests according to the recommendations of the manufacturer.

2.4. Statistical analysis

Recorded anonymous patient data from the University of Debrecen Clinical Center's clinical IT system was used. We gained access to the data source in HL7 format, partially cleaned and pre-processed by the university's partner company, Aesculab Medical Solutions, Black Horse Group Ltd., who cleaned the data to be used for their data mining and machine learning objectives. Leveraging the database at the outset ensured the avoidance of system errors which might have resulted from the manner in which the original clinical data was recorded, spanning 15 years (from 2007 to 2021), containing the entirety of the clinical centre's patient record database with all the textual, diagnostic and laboratory particulars. We extracted the data through queries from the PostgreSQL 13.x database, which yielded enormous text files, which were then used as a kickoff for subsequent statistical analysis. The population involved in the study included the number of patients treated at the University of Debrecen throughout this period, totaling 92,198 persons, whose data were derived from all departments and all inpatient and outpatient information sources available from the above specified time period.

Statistical analysis was carried out through the deployment of Python-supported data mining packages. Data cleaning and processing were performed by utilizing Python 3.8, IPython 7.29, Cython 0.29, Pandas 0.23 and Numpy 1.22 under Conda 4.10 environment with Dask. Machine learning applied to refine data selection and perform deep textual analysis leveraged SciKit-Learn 1.0 and Pytorch 1.09. Unpaired t-tests conducted for statistical significance analysis maintained a significance level of 95%. We created statistical figures with the MatPlotLib 3.5 software package.

3. Results

Based upon the data source containing laboratory cases, textual history data, diagnosis codes and patient statistic data, we evaluated each child from ages 3 to 18 years that visited the University of Debrecen Clinical Center's hospital during the 15-year study period (total number of 3 to 18-year-old children n = 92,198; boys/girls: 44,380/49,084; 48/52%). We identified a total of 3,687 children with hypertension (2,107 boys and 1,580 girls), which means that the calculated prevalence of hypertension in the whole study population is 4%, a higher prevalence in boys (4.7%) as compared to girls (3.2%). We divided the study population into five age groups (3-6 years; 6-9 years, 9-12 years, 12-15 years and 15-18 years). The 3-6 year-old age group was defined as the period above the age of 3 years and below the age of 6 years. We found an increasing prevalence in the consecutive age groups in the whole study population (1.54; 2.64; 4.0; 5.49 and 5.56%, respectively), and in the boys (1.66; 2.6; 4.57; 6.48 and 8.22%), while in girls the highest prevalence was identified in the 12-15-year-old age group (1.39; 2.69; 3.4; 4.6 and 3.8% was found, respectively) (**Figure 1**).

We found a strong linear correlation between age and the number of children diagnosed with hypertension in the whole study population (R2 = 0.93), in boys (R2 = 0.91) and

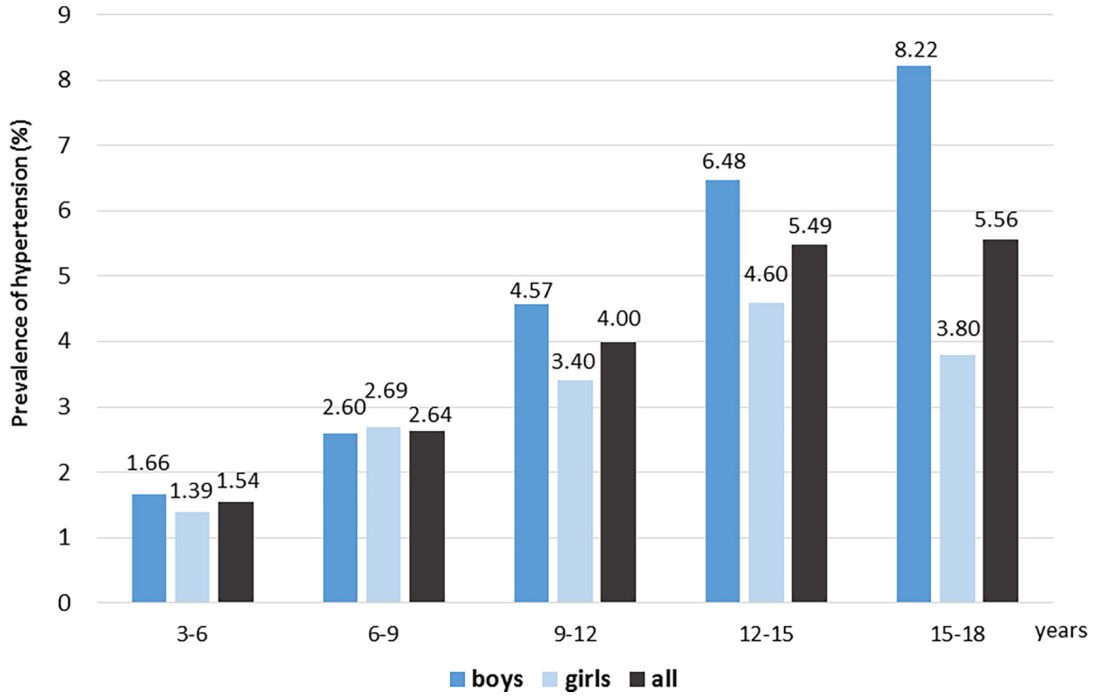

FIGURE 1
Prevalence of hypertension in different age and gender groups.

in girls (R2 = 0.93). Likewise, an exponential correlation was detected between the cumulative number of children in various age groups diagnosed with hypertension in the whole study population (R2 = 0.97), in boys (R2 = 0.98) and girls (R2 = 0.96) (**Figure 2**).

We also evaluated the prevalence of the most significant concomitant diseases. We found a markedly and significantly higher prevalence of obesity (49.7 vs. 6.16%), diabetes mellitus (7.17 vs. 1.27%), renal diseases (2.81 vs. 0.51%) and thyroid diseases (8.74 vs. 6.22%) in hypertensive children as compared to normotensives. Obesity was the most prevalent concomitant disease in all patient groups, with the highest prevalence documented in the 6-9-year-old and the 9-12–year-old age groups (65%). Moreover, we found higher BMI values in hypertensive children as compared to the normotensive group in all studied patient groups (25.6; 26.7; 28.1 and 29.7 vs. 20.1; 21.4; 22.6 and 24.6 kg/m^2 in the 6-9–year-old, 9-12–year-old, 12-15–year-old and 15-18–year-old groups, respectively) (**Figure 3**).

Table 1 lists the laboratory parameters. We found significantly higher total cholesterol (4.27 ± 0.95 vs. 4.17 ± 0.88 mmol/L), LDL-C (2.62 ± 0.79 vs. 2.44 ± 0.74 mmol/L) and triglyceride (1.2(0.85-1.69) vs. 0.94(0.7-1.33) mmol/L), and lower HDL-C (1.2 ± 0.3 vs. 1.42 ± 0.39 mmol/L) levels in children with hypertension compared to the normotensive children in the whole study population (**Figure 4**) and in all age groups (**Table 1**). Except for the first age group, total cholesterol level was higher in hypertensive children compared to the normotensive group. Furthermore, significantly higher serum uric acid levels were found in children with hypertension (299.2 ± 86.1 vs. 259.9 ± 73.3 μmol/L). There were no reportable differences in glucose, urea and creatine levels between the hypertensive and normotensive groups throughout the various age groups.

The prevalence of several secondary causes resulting in hypertension such as hyperthyroidism, hyperaldosteronism, Cushing syndrome, phaeochromocytoma, hyperparathyroidism and chronic renal disease was a shade higher in the most hypertensive age groups, but because of the scarcity of cases, we could not perform statistical analysis. Indeed, the documentation of rare causes of secondary hypertension appears to be insufficient and inaccurate.

4. Discussion

Data mining techniques gained ground in clinical diagnostics, and we can use them for several purposes, including research in the biomedical and healthcare fields (20). Since data on childhood hypertension in the Eastern European regions are scarce, and we have successfully used data mining methods for screening some rare hereditary dyslipidemias previously (14, 16), we aimed to investigate a 15-year period and a large pediatric patient population to calculate the estimated

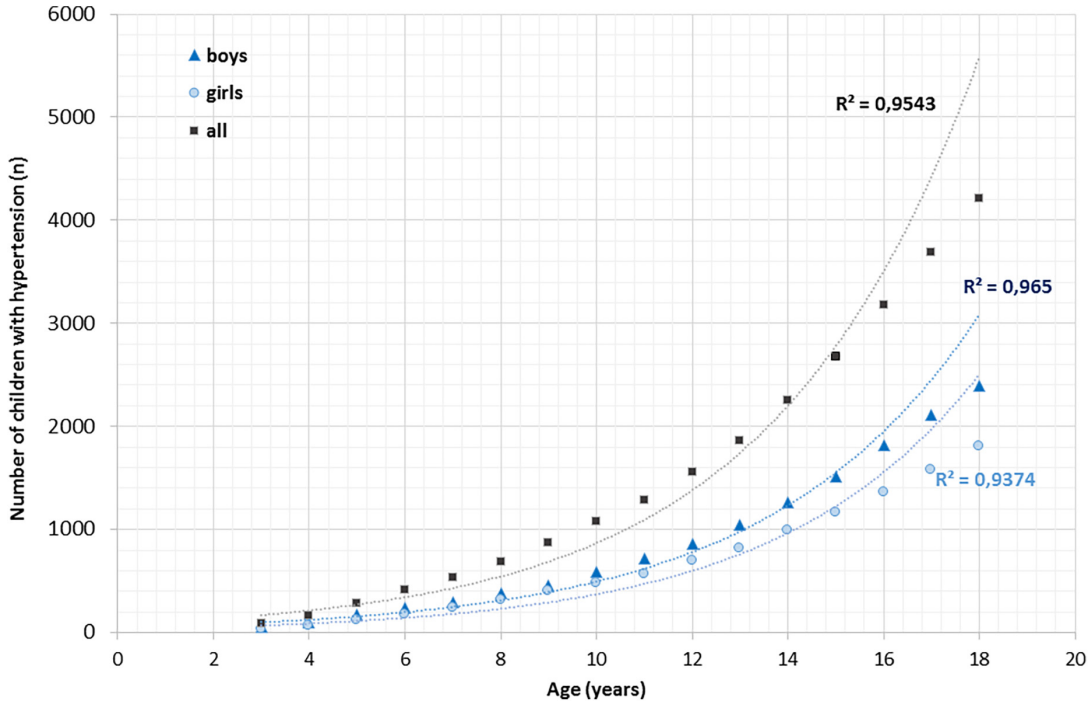

FIGURE 2
Exponential correlation between age and cumulative number of children with hypertension.

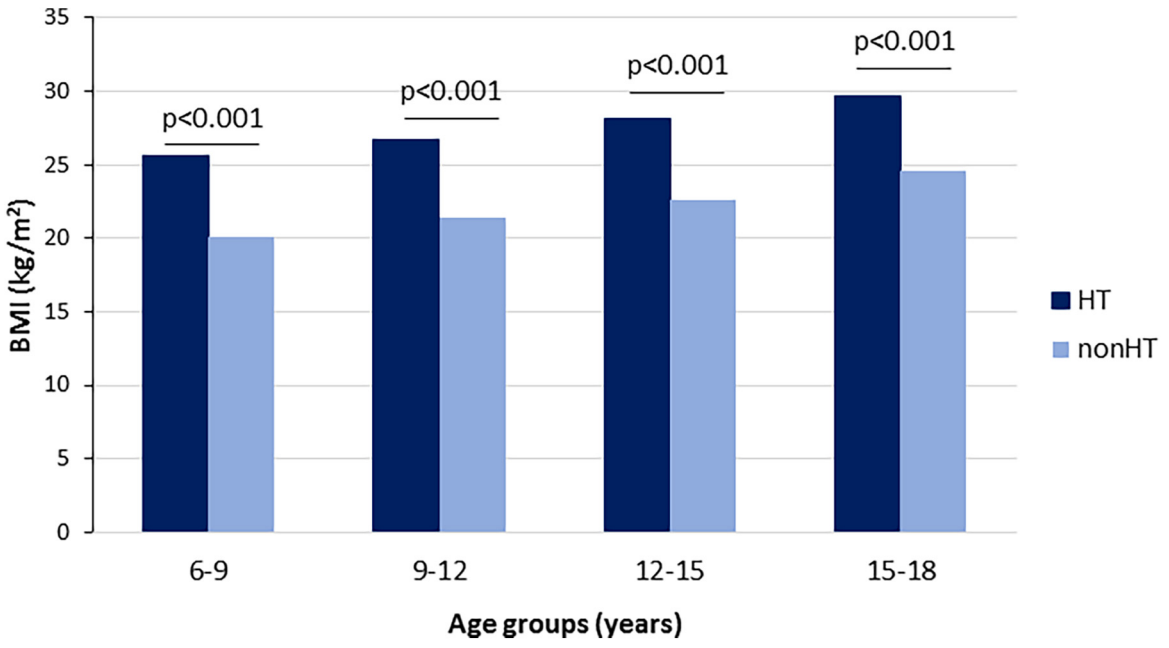

FIGURE 3
Average body mass index (BMI) values in children with and without hypertension in different age groups.

prevalence of childhood hypertension and its concomitant diseases using data mining methods. Our data suggest that the calculated prevalence of childhood hypertension in Hungary, at least in our region, is 4%. It is comparable to the data of other European countries and is in line with the result of a recent meta-analysis (13). In agreement with the literature data, the

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TABLE 1 Laboratory parameters of the study population.

	3-6 ys		6-9 ys		9-12 ys		12-15 ys		15-18 ys	
	HT	Non-HT	HT	Non-HT	HT	Non-HT	HT	Non-HT	HT	Non_HT
N	195 (68.7%)	14756 (80.5%)	300 (74.3%)	12699 (85.9%)	409 (68.9%)	11747 (82.4%)	704 (72.6%)	13346 (79.9%)	978 (68.3%)	18856 (77.5%)
Glucose (mmol/L)	**4.74 ± 0.81**	**5.02 ± 1.72**	5.05 ± 3.4	5.05 ± 1.44	**4.90 ± 1.17**	**5.13 ± 1.7**	5.07 ± 1.52	5.16 ± 1.43	5.09 ± 1.2	5.06 ± 1.19
TC (mmol/L)	**4.08 ± 1.05**	**4.14 ± 0.99**	**4.25 ± 0.90**	**4.12 ± 0.82**	**4.31 ± 0.94**	**4.14 ± 0.82**	**4.23 ± 0.93**	**4.12 ± 0.81**	**4.30 ± 0.97**	**4.24 ± 0.92**
LDL-C (mmol/L)	**2.52 ± 0.77**	**2.50 ± 0.88**	**2.60 ± 0.74**	**2.44 ± 0.74**	**2.68 ± 0.79**	**2.43 ± 0.71**	**2.58 ± 0.79**	**2.39 ± 0.65**	**2.64 ± 0.82**	**2.46 ± 0.76**
HDL-C (mmol/l)	**1.2 ± 0.31**	**1.38 ± 0.36**	**1.21 ± 0.32**	**1.39 ± 0.39**	**1.18 - ± 0.28**	**1.39 ± 0.37**	**1.19 ± 0.3**	**1.42 ± 0.38**	**1.22 ± 0.31**	**1.46 ± 0.41**
TG (mmol/L)	**1.2 (0.78-1.56)**	**1.0 (0.7-1.4)**	**1.14 (0.83-1.7)**	**0.93 (0.69-1.3)**	**1.3 (0.9-1.76)**	**0.98 (0.7-1.41)**	**1.19 (0.85-1.6)**	**0.94 (0.7-1.3)**	**1.13 (0.85-1.64)**	**0.9 (0.68-1.3)**
Uric acid (μ mol/L)	**241 ± 67.4**	**228 ± 59.8**	**259 ± 73.1**	**247 ± 66.9**	**283 ± 82.3**	**262 ± 72.6**	**309 ± 90.3**	**275 ± 73.4**	**316 ± 82.4**	**273 ± 76.7**
Urea (mmol/L)	4.1 (3.5-5.0)	4.03 (3.4-4.7)	4.13 (3.5-4.9)	4.05 (3.5-4.8)	4.2 (3.5-4.8)	4.1 (3.5-4.8)	4.18 (3.6-4.9)	4 (3.4-4.7)	4.2 (3.6-5.0)	4.0 (3.3-4.8)
Creatine (μ mol/L)	31.5 (26.2-38)	32 (27-40)	39 (33-46.3)	43 (35-53)	46 (39-55.5)	50 (42-61.5)	57 (47.1-66.4)	56 (49-66)	63 (54-74)	62 (53-72)

Values are presented as mean ± standard deviation or median (lower quartile - upper quartile). Number of patients (*n*) indicates the number of cases with available laboratory data (percent compared to the complete study group).
Significant differences ($p < 0.05$) between the study groups are marked with bold letters. HDL-C, high-density lipoprotein-cholesterol; HT, hypertensive; LDL-c, low-density lipoprotein cholesterol; non-HT, non-hypertensive; TC, total cholesterol; TG, triglyceride.

prevalence of hypertension increases with age from 1.54% up to 5.56%, showing gender differences and a markedly higher ratio of hypertension in boys. In adolescent boys (from 15 to 18 years), the prevalence of hypertension was more than twice the average (8.22%), highlighting the importance of screening in this subpopulation.

As far as hypertension etiology is concerned, the traditional separation is primary and secondary classification. Primary hypertension in children is mainly hereditary. The inheritance pattern is multifactorial and modified by environmental factors and diet, such as highly processed food and sodium intake (21). Although we could not extract data on these parameters, a recent study reported that sodium intake exceeds while potassium does not reach dietary recommendations in Hungary (22). A multicenter paper proved that almost half of the daily energy intake of children from eight European countries including Hungary came from ultra-processed foods (23). A significant connection between obesity and hypertension is well-documented among children. Our data also highlight the importance of obesity in this patient population: we found significantly higher BMI values and markedly higher obesity prevalence in hypertensive children. As in adults, obesity due to poor diet and inactivity is the most important predisposing factor for metabolic abnormalities in childhood, including dyslipidemia, hyperinsulinemia and hyperuricemia (24). Insulin resistance and hyperinsulinemia might contribute to enhanced renal sodium reabsorption or increased sympathetic nervous system activity (25). We found that the prevalence of diabetes was significantly higher among children with hypertension in all age groups. The impact of diet components on gene expression or fructose intake on uric acid levels also contributes to harmful metabolic changes (26). Although we have no data on diet components and fructose intake of the study population, serum uric acid levels were significantly higher in the hypertensive groups compared to the normotensive children. A former study found a positive association between uric acid and blood pressure, insulin and triglycerides in overweight and obese youths (27). We also found significantly higher serum triglyceride levels in all hypertensive age groups accompanied by lower HDL-C and higher LDL-C levels, indicating the complex disturbance of lipid metabolism. While dyslipidemia is common in adulthood, especially in overweight and obese population, its early appearance associated with childhood hypertension is astonishing and alarming, highlighting the importance of immediate laboratory screening at the moment of recognition. Although the pharmacological management of childhood dyslipidemia should be reserved for special situations, lifestyle intervention can be indicated at any age.

In secondary hypertension, there is an identifiable cause in the background. Secondary hypertension is relatively common in infants and young children (28). The causes of hypertension vary with age. Renal artery thrombosis or stenosis, congenital

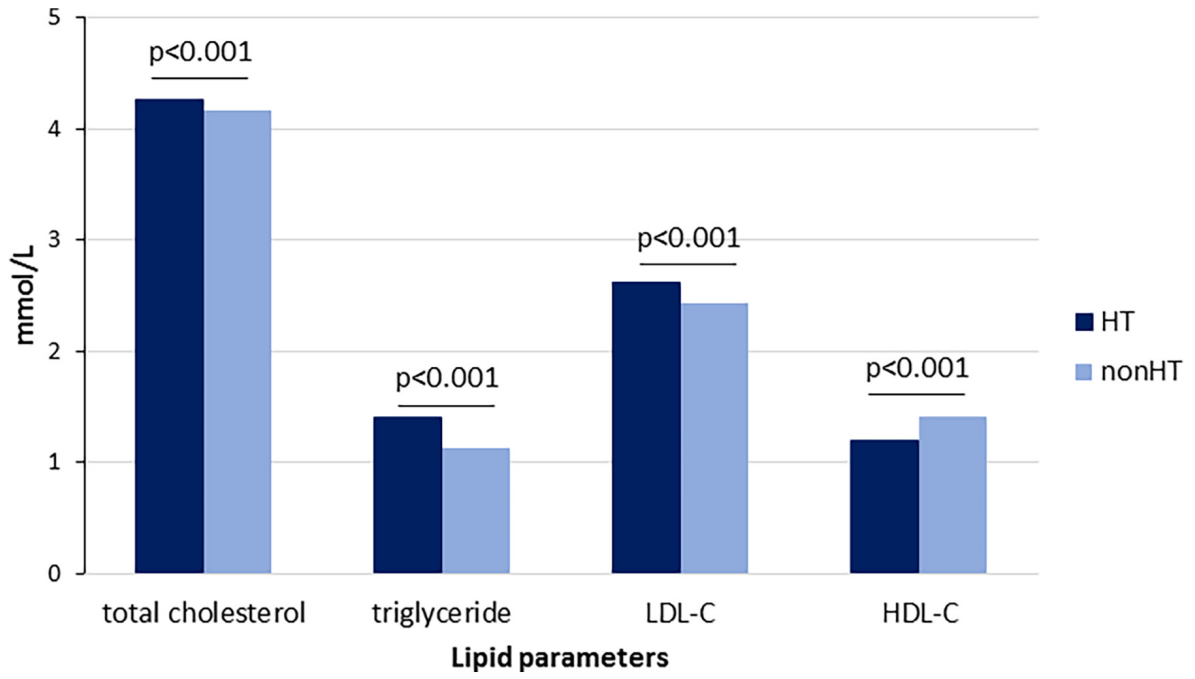

FIGURE 4
Serum lipid parameters in children with and without hypertension in the whole patient population.

renal malformations, coarctation of the aorta or various endocrinological disorders can be the underlying cause of hypertension, although renal abnormality is the leading problem (21). Our data also demonstrated a higher prevalence of renal diseases in hypertensive children. Although we could not identify children with renal artery occlusion/stenosis or aortic coarctation, we found that the prevalence of several endocrine disorders was significantly higher in the hypertensive groups indicating their possible pathogenic role in hypertension. In adolescent females taking oral contraceptives is associated with hypertension. Unfortunately, data on the medication of adolescents enrolled in the study is not accessible.

Our study is not without some limitations. Hospitalgoers, both children and adults, represent a population that differs from the average population. Therefore, our calculations might overestimate the prevalence of hypertension, for example, the frequency of some secondary forms. The University of Debrecen Clinical Center is a regional centre for pediatric endocrinology and nephrology care that provides specialized, multidisciplinary care to children and adolescents with endocrine and renal disorders. We studied a relatively large cohort of children, which may not directly represent the total pediatric population in our region but may provide data. Unfortunately, we were unable to assess data on family history, diet and lifestyle habits. Additionally, a larger population is needed to define the contribution of secondary causes leading to childhood hypertension since their recording in medical documentation is precarious and inaccurate. Furthermore, we also collected data on patients' antihypertensive medication. However, we could find only a few children treated with antihypertensive agents. In general, pediatricians administered beta-blockers and ACE-inhibitors in severe cases but primarily suggested lifestyle modification to the patients and their parents. We could not provide statistical data due to the low number of cases. Still, we believe that our data mining method verified their impact on the diagnostic process of childhood hypertension.

The rising prevalence of pediatric hypertension carries problematic global health dimensions. Childhood hypertension is no longer a condition characterized by elevated blood pressure values but rather a chronic disease associated with metabolic complications at presentation. Therefore, timely screening and interventions for these early metabolic complications are essential to prevent morbidity and mortality in the future. Hence, there is a pressing need for comprehensive pan-European action to increase knowledge on the prevention, diagnosis and treatment of high blood pressure in children and adolescents. To provide answers to questions and challenges, a multidisciplinary network was established recently, maintained and funded by the European Cooperation in Science and Technology (COST) Association, which will promote coordinated and collaborative activities on personalized preventive measures for children and adolescents across Europe (29). Till then, national datasets may contribute to our knowledge of the prevalence and characteristics of childhood hypertension.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author Contributions

DP and MH: the study design. ÁN, BD, and ZK: development of methodology. ÁN, BD, and BN: collection of data. DP, MH, ÁD, ÁN, and LM: analysis and/or interpretation of data. DP, BK, and MH: writing (not revising) all or sections of the manuscript. TS: manuscript review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Waist-to-height-ratio is associated with sustained hypertension in children and adolescents with high office blood pressure

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Background: Waist-to-height-ratio (WHtR) has been proposed as another indicator for cardiometabolic risk factors including hypertension. Normally, hypertension can be diagnosed in the office setting by detecting high blood pressure for three occasions. However, patients with high office blood pressure may not exhibit high blood pressure outside the office. Ambulatory blood pressure monitoring (ABPM) is a procedure to measure blood pressure over 24-h. Sustained hypertension is characterized as hypertension detected by both office measurement and ABPM. This study aimed to evaluate the performance of WHtR in the diagnosis of sustained hypertension in patients with high office blood pressure.

Materials and methods: Demographic data, height, body weight, body mass index (BMI), and waist circumference were retrospectively reviewed in children and adolescents who underwent ABPM due to persistently high office blood pressure. Patients were separated into two groups: a sustained hypertension group and a normal ABPM group. BMI was adjusted to z-score using the WHO Anthroplus software. WHtR was calculated by the formula: waist circumference (cm)/height (m). The performances of different parameters were analyzed using the receiver operating characteristic (ROC) curve and multivariate logistic regression.

Results: Sixty patients (63% male) with a mean age of 12.9 ± 3.7 years had persistently high office blood pressure. Twenty-nine (48.3%) had high ambulatory blood pressure parameters so-called "sustained hypertension." The sustained hypertension group had a higher mean BMI z-score (2.32 vs. 1.31, $p = 0.01$) and a higher mean WHtR (57.7 vs. 49.2 cm/m, $p < 0.001$) than those of the normal ABPM group. For the diagnosis of sustained hypertension, the ROC analysis revealed that WHtR had a greater area under the ROC curve (AUC) than that of BMI z-score (0.772 vs. 0.723). WHtR remained associated with sustained hypertension (OR 1.2, 95% CI 1.022–1.408, $p = 0.026$) after adjusting for age, gender, and BMI z-score.

Conclusions: Apart from being a more user-friendly metric, WHtR tended to outperform BMI z-score in predicting sustained hypertension in children and adolescents with persistently high office blood pressure.

KEYWORDS

waist-to-height-ratio, body mass index, ambulatory blood pressure monitoring, sustained hypertension, children, adolescents

1. Introduction

The increased prevalence of hypertension in children and adolescents has become a major public health issue (1, 2). Several studies have found that high blood pressure in childhood increased the likelihood of adult hypertension, which is a major contributor to cardiovascular disease later in life (3, 4). A report from the Thai National Health Examination Survey (5) showed that 9.4% of adolescents aged 10–19 years had high blood pressure and this prevalence was higher than those of the recent national surveys from South Korea and Canada (6, 7). Obesity was found to be an important determinant to high blood pressure seen in Thai school-aged children. It was revealed that obesity was significantly associated with high blood pressure and it increased the risk of pre-hypertension and hypertension by 9 and 10.6-fold, respectively (8, 9).

Systematic reviews showed an association between hypertension and body mass index (BMI) together with various measures of abdominal adiposity and the hypertension rates increased in a graded manner as adiposity increased (10–14). Generally, adiposity indicator such as BMI is correlated with hypertension (15–18). Meanwhile, abdominal obesity has also been recognized as a risk factor for hypertension in children and adolescents by using different measuring methods and various indices such as waist circumference (WC) and waist-to-height-ratio (WHtR) (18–24). WHtR can be calculated by dividing WC by height to represent an individual's size. WHtR varies only slightly across age and gender, therefore it does not need to be expressed as a z-score as does BMI (25). Some studies in children even suggested that WHtR was more strongly linked to high blood pressure than was BMI (26–28), while the others indicated that WHtR had a weaker relation to blood pressure compared to that of BMI (29, 30). As a result, the performances of these parameters for predicting hypertension in children and adolescents remain unclear.

Normally, hypertension in children and adolescents can be diagnosed in the office setting by detecting blood pressure greater than the 95th percentile for gender, age, and height for three occasions. However, some children and adolescents may have high blood pressure in the office but do not show high blood pressure outside the office. In 2017, the American Academy of Pediatrics clinical practice guidelines recommended that ambulatory blood pressure monitoring (ABPM) be used to confirm hypertension in children and adolescents who have persistently high office blood pressure for three occasions (3). ABPM is a procedure in which blood pressure is measured every 20–30 min over 24-h using a portable device. Those with high blood pressure for both office measurement and ABPM are called having "sustained hypertension." Previous studies on the relationship between BMI, WHtR, and the diagnosis of hypertension in children and adolescents typically defined hypertension mainly by using office blood pressure measurement with only a few studies employing ABPM in children and adolescents with obesity (31–33). The present study aimed to evaluate the performances of BMI z-score and WHtR in the diagnosis of sustained hypertension detected by ABPM in children and adolescents with high office blood pressure.

2. Materials and methods

2.1. Participating patients

Patients aged ≥6 years referred to the pediatric hypertension clinic at Ramathibodi Hospital Mahidol University due to high office blood pressure on three occasions and subsequently underwent 24-h ABPM were enrolled in the present study. Exclusion criteria included patients who did not have sufficient ABPM data, were previously diagnosed with hypertension, and had any underlying diseases or received any medications that may affect blood pressure.

2.2. Anthropometric data

Demographic data, height, body weight, BMI, and waist circumference were collected. Waist circumference was measured while standing straight using a measurement tape with a precision of 1 mm. The tape was placed at the midline between the bottom of the lowest rib and the iliac crest. WHtR was calculated by the following formula: waist circumference (cm)/height (m) and BMI was adjusted to z-score for age and gender using the World Health Organization (WHO) Anthroplus software (34). Obesity was defined as a BMI z-score > 2.

2.3. Blood pressure measurement

Office blood pressure was measured with an oscillometric device two times in the right arm while seated, using standard blood pressure measurement practice and appropriate cuff size. An average of the two blood pressure values was considered to be a blood pressure value for each occasion. High office blood pressure is defined as a systolic blood pressure (SBP) or a diastolic blood pressure (DBP) ≥95th percentile for gender, age, and height in children aged < 13 years; or ≥ 130/80 mmHg in children aged ≥ 13 years for three occasions according to the current pediatric guidelines (3). For office blood pressure, mean blood pressure was an average of the blood pressure values from three occasions while maximum blood pressure was the highest blood pressure value among three occasions.

ABPM was performed using a TM-2430 (A&D, Japan) device, which has been validated for use in pediatric patients (35). An appropriate cuff for each patient was applied on the non-dominant arm by the trained healthcare provider. The device was set to record blood pressure every 20 min during awake and every 30 min during sleep for a period of 24-h. Patients were instructed to continue their normal daily activities, avoid strenuous activities, and record their activities including the actual sleep and awake periods. In each patient, ABPM data were considered sufficient if there were ≥40 valid blood pressure readings for the entire 24-h period. Hypertension by ABPM is defined as a mean SBP or a mean DBP ≥ 95th percentile for gender and height, and SBP or DBP load ≥25% for either awake or asleep or both periods while prehypertension is defined as a mean SBP or a mean DBP < 95th percentile for gender and height, but SBP or DBP load ≥25% for either awake or asleep or both periods according to the guidelines by the American Heart Association (36). Based on the results of ABPM, patients were separated into two groups: a sustained hypertension group and a normal ABPM group. The normal ABPM group included patients with prehypertension and white coat hypertension.

To compare blood pressure parameters between patients of different ages, genders, and heights, blood pressure parameters were converted to blood pressure indices with the following formula: blood pressure value/cut-off value for high blood pressure for each patient.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS® Software, Version 26. The distribution of each parameter was tested with the Kolmogorov-Smirnov test. Descriptive data were presented as number (percentage), mean ± standard deviation (SD), or median (interquartile range, IQR) as appropriate. Demographic data were compared between the sustained hypertension group and the normal ABPM group. For comparative analysis, the chi-square test or Fisher's exact test was used for categorical data; and the Student *t*-test or Mann–Whitney *U*-test was used for continuous data, as appropriate. The receiver operating characteristic (ROC) curve was used to analyze the performances of the BMI z-score and WHtR for the diagnosis of sustained hypertension. Univariate logistic regression analysis was used to test the parameters associated with sustained hypertension. The parameters that were significantly associated with sustained hypertension from the univariate analysis, were further added to the multivariate logistic regression model. A $p \leq 0.05$ was defined as statistical significance.

3. Results

3.1. Patient characteristics

A total of 72 patients with persistently high office blood pressure were enrolled in the present study. Twelve patients with congenital anomalies of the kidney and urinary tract, attention deficit hyperactivity disorder, systemic lupus erythematosus, vesicoureteral reflux, obstructive sleep apnea, and coarctation of aorta were excluded as their underlying diseases or medication uses might affect blood pressure. Among sixty patients (38 males) with a mean age of 12.9 years, 29 patients (48.3%) had sustained hypertension. The demographic and clinical data between the two groups are shown in Table 1. A higher mean BMI z-score (2.32 ± 1.51 vs. 1.31 ± 1.49, $p = 0.01$) and a more proportion of obesity [20 (69%) vs 10 (32%), $p = 0.04$] were detected in the sustained hypertension group compared with the normal ABPM group. The sustained hypertension group also had a substantially higher mean waist circumference (86.7 ± 17.8 vs. 77.7 ± 16.7, $p = 0.048$) and a higher mean WHtR (57.7 ± 8.5 vs. 49.2 ± 9.2, $p < 0.001$) than those of the normal ABPM group.

3.2. ABPM parameters and phenotypes

The ABPM parameters between the sustained hypertension and normal ABPM groups are shown in Table 2 and the ABPM phenotypes between the obesity and non-obesity groups are shown in Table 3. Of 31 patients in the normal ABPM group, 12 patients had white coat hypertension and 19 patients had prehypertension, accounting for 20 and 31.7% of all high office blood pressure patients, respectively. In the sustained hypertension group ($N = 29$), seven patients had isolated daytime hypertension, 11 patients had isolated nocturnal hypertension and the remaining 11 patients had both daytime and nocturnal hypertension, accounting for 11.7, 18.3, and 18.3% of all high office blood pressure patients, respectively.

TABLE 1 Demographic and clinical data among the study population.

Parameters	All patients ($N = 60$)	Sustained hypertension ($N = 29$)	Normal ABPM ($N = 31$)	*p*-value
Age (years)	12.9 ± 3.7	12.1 ± 3.5	13.7 ± 3.7	0.76
Male, *N* (%)	38 (63)	16 (55)	22 (71)	0.21
Body weight (kg)	62.7 ± 23.8	63.8 ± 25.4	61.7 ± 22.6	0.73
Height (m)	1.54 ± 0.20	1.50 ± 0.21	1.58 ± 1.82	0.13
BMI (kg/m^2)	25.5 ± 6.4	27.1 ± 6.3	23.9 ± 6.1	0.05
BMI z-score	1.80 ±1.57	2.32 ± 1.51	1.31 ± 1.49	0.01*
Obesity, *N* (%)	30 (50)	20 (69)	10 (32)	0.04*
Waist circumference (cm)	82 ± 17.7	86.7 ± 17.8	77.7 ± 16.7	0.048*
Waist to height ratio (cm/m)	53.3 ± 9.8	57.7 ± 8.5	49.2 ± 9.2	<0.001*
Mean office SBP index	1.02 ± 0.07	1.04 ± 0.06	1.00 ± 0.07	0.09
Mean office DBP index	1.02 ± 0.07	1.03 ± 0.66	1.01 ± 0.76	0.38
Maximum office SBP index	1.07 ± 0.08	1.08 ± 0.06	1.05 ± 0.09	0.14
Maximum office DBP index	1.08 ± 0.07	1.09 ± 0.07	1.07 ± 0.75	0.35

Data presented as mean ± standard deviation. *p ≤ 0.05.

TABLE 2 Ambulatory blood pressure parameters between the sustained hypertension and normal ABPM groups.

Parameters	All patients ($N = 60$)	Sustained hypertension ($N = 29$)	Normal ABPM ($N = 31$)	*p*-value
Daytime SBP index	0.96 ± 0.07	1 ± 0.07	0.92 ± 0.05	<0.001*
Daytime DBP index#	0.87 (0.10)	0.88 (0.10)	0.85 (0.08)	0.021*
Nighttime SBP index	0.96 ± 0.08	1.01 ± 0.07	0.91 ± 0.05	<0.001*
Nighttime DBP index#	0.91 (0.10)	0.92 (0.12)	0.89 (0.08)	0.203
24-h SBP index#	0.98 (0.09)	1.01 (0.06)	0.94 (0.07)	<0.001*
24-h DBP index#	0.89 (0.09)	0.92 (0.09)	0.86 (0.08)	0.01*

Data presented as mean ± standard deviation. #Median (IQR). *p ≤ 0.05.

TABLE 3 Ambulatory blood pressure phenotypes between the obesity and non-obesity groups.

Parameters	All patients ($N = 60$)	Obesity ($N = 30$)	Non-obesity ($N = 30$)	*p*-value
Normal ABPM group	31 (51.7)	10 (33.3)	21 (70)	
- White coat hypertension	12 (20)	3 (10)	9 (30)	0.053
- Pre-hypertension	19 (31.7)	7 (23.3)	12 (40)	0.165
Sustained hypertension group	29 (48.3)	20 (66.7)	9 (30)	
- Isolated daytime hypertension	7 (11.7)	6 (20)	1 (3.3)	0.044*
- Isolated nocturnal hypertension	11 (18.3)	7 (23.3)	4 (13.3)	0.317
- Both daytime and nocturnal hypertension	11 (18.3)	7 (23.3)	4 (13.3)	0.317

Data presented as N (% of total patients). *p ≤ 0.05.

TABLE 4 Multivariate analysis of parameters associated with sustained hypertension.

Parameters	Univariate analysis			Multivariate analysis		
	Exp (β)	95% CI	*p*-value	Exp (β)	95% CI	*p*-value
Demographic data						
Age	0.875	0.754–1.017	0.081	0.890	0.764–1.038	0.139
Gender	1.986	0.684–5.769	0.207	1.586	0.515–4.880	0.422
Anthropometric data						
BMI	1.088	0.997–1.187	0.058			
BMI z-score	1.632	1.087–2.449	0.018*	0.691	0.296–1.611	0.392
Waist circumference	1.032	0.999–1.066	0.055			
Waist to height ratio	1.123	1.044–1.209	0.002*	1.2	1.022–1.408	0.026*
Office BP indices (for each 0.1 increase)						
Mean office SBP	1.999	0.897–4.455	0.090			
Mean office DBP	1.395	0.674–2.887	0.369			
Maximum office SBP	1.703	0.842–3.444	0.138			
Maximum office DBP	1.426	0.680–2.991	0.348			

BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure. *$p \leq 0.05$.

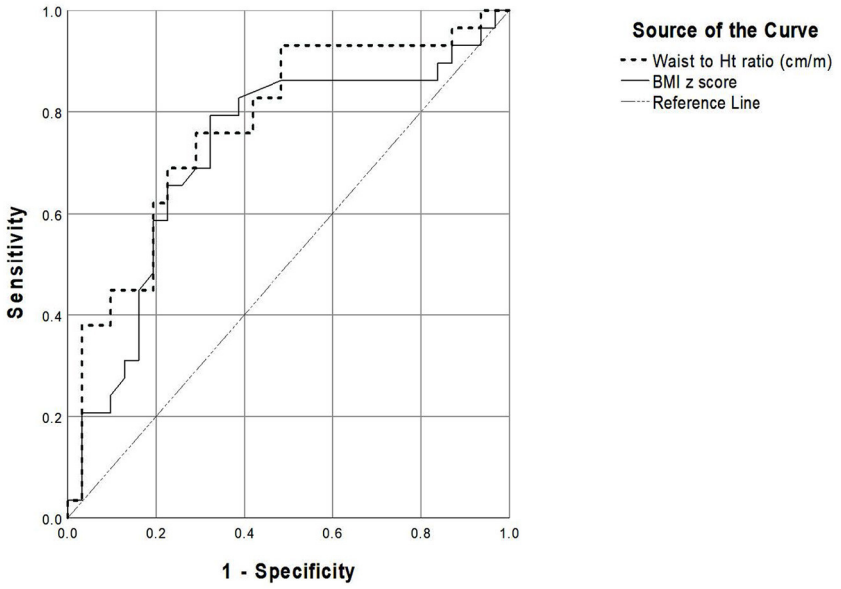

FIGURE 1
The receiver-operating characteristic curve representing performance of the parameters for detecting sustained hypertension.

3.3. Parameters associated with sustained hypertension

Univariate analysis revealed that BMI z-score and WHtR were significantly associated with sustained hypertension as shown in Table 4. In addition, having obesity was 4.7 times (95% CI 1.571–13.866, $p < 0.01$) higher risk of sustained hypertension compared with those who did not have obesity while having WHtR $\geq$ 50 cm/m was 6.7 times (95% CI 2.004–22.041, $p < 0.01$) higher risk of sustained hypertension compared with those who had a WHtR < 50 cm/m. However, multivariate analysis revealed that WHtR was the only factor associated with sustained hypertension (OR 1.2; 95% CI 1.022–1.408, $p = 0.026$).

TABLE 5 Adiposity parameters for detecting sustained hypertension.

Indicators	Cut-off	Sensitivity	Specificity	AUC	95% CI	*p*-value
BMI z-score	1.0	86.2	38.7	0.723	0.588–0.858	0.003*
	1.5	82.8	51.6			
	2.0	69	67.7			
WHtR (cm/m)	45	93.1	29	0.772	0.651–0.893	<0.001*
	50	82.8	58.1			
	55	62.1	80.6			

AUC, area under the curve; 95% CI, 95% confidence interval. *$p \leq 0.05$.

3.4. Performance of BMI z-score and WHtR

For the diagnosis of sustained hypertension, the ROC analysis revealed that WHtR had a greater area under the curve (AUC) than that of BMI z-score (0.772 vs. 0.723, respectively). WHtR ≥ 50 cm/m had a sensitivity of 82.8% and a specificity of 58.1% whereas BMI z-score > 2 had a sensitivity of 69% and a specificity of 67.7% to detect sustained hypertension (Figure 1, Table 5).

4. Discussion

Among children and adolescents suspected to have hypertension due to the detection of persistently high office blood pressure, the present study revealed that 48.3% had sustained hypertension. This was consistent with the previous studies reporting the prevalences of sustained hypertension ranging from 20 to 54% (37–39). The present study also showed that WHtR tended to outperform BMI z-score for the prediction of sustained hypertension.

The associations between ABPM parameters and obesity have been well-described. The previous studies reported that white coat hypertension was seen in 10–30% of pediatric patients with obesity (31, 40, 41). These results were consistent with the present study that white coat hypertension was seen in 10% of patients. For nocturnal hypertension, the prevalences ranged from 17 to 23% in pediatric patients with obesity (41, 42) compared to the prevalence of 46.6% in the present study. It was postulated that patients with obesity had high nighttime blood pressure than daytime blood pressure due to poor sleep quality caused by snoring, altered function of the autonomic nervous system, or an impaired ability to excrete sodium (40).

In the present study, not only BMI z-score but also was WHtR significantly higher in the sustained hypertension group than the normal ABPM group. After adjusting with age, gender, and BMI z-score, WHtR was found to be the only independent parameter associated with sustained hypertension. In addition, WHtR at the cut-off point > 0.5 showed a good sensitivity of 82.8% while BMI z-score at the cut-off point of >2 (WHO criteria for obesity) showed a sensitivity of 69% to detect sustained hypertension. Therefore, WHtR tended to be a slightly better parameter for predicting sustained hypertension than BMI z-score.

While WHtR is a parameter representing abdominal obesity, BMI is a parameter representing total body mass. As BMI cannot distinguish between fat and fat-free mass, an elevated BMI may not entirely reflect adiposity accumulation (43). On the other hand, WHtR is related to the amount of intra-abdominal visceral fat, which is more closely related to cardiovascular risk compared with total body mass represented by BMI (21, 44). For implementing across various age groups, BMI varies significantly according to child growth and pubertal development, so it must be stated as a z-score to age and gender. On the contrary, WHtR varies slightly by age and gender and does not need to be stated as a z-score because waist circumference and children's height increase continuously as they age in the same boundary value (25, 44). As a result, WHtR becomes a simpler index to calculate. Not only for sustained hypertension, WHtR also was reported to perform well to predict metabolic syndrome in a national survey of Thai adolescents (45).

Although many studies (10, 21, 26–29) had shown a strong association between WHtR and hypertension, some other studies showed that BMI z-score is slightly superior to or equal to WHtR (14, 18, 30, 46). The discordant results of those studies from the present study could be due to variation in the study designs. Those studies used different definitions of hypertension and most used one- to two-visits of office blood pressure measurements, or used persistently elevated office blood pressure. However, the present study categorized hypertension according to the results of ABPM as recommended by the current pediatric guidelines (3).

The available data regarding the performance of WHtR and the results of ABPM in children and adolescents with persistently high office blood pressure are limited. To our knowledge, this is the largest study that analyzed the performance of WHtR in predicting sustained hypertension by using ABPM. Nonetheless, the present study had some

limitations. Firstly, auscultatory blood pressure was not performed for office blood pressure measurement. The other metabolic abnormalities associated with cardiovascular risks such as dyslipidemia and insulin resistance had not been collected. Data regarding the end-organ damages such as left ventricular mass index which is well-known and associated with sustained hypertension were unavailable. Lastly, the number of patients included in the present study was small. A larger study needs to be conducted to explore the performance of WHtR in predicting the risk of sustained hypertension among children with persistently high office blood pressure.

In conclusion, sustained hypertension was detected in 48.3% of the patients with persistently high office blood pressure. Apart from being a more user-friendly metric, WHtR tended to outperform BMI z-score in predicting sustained hypertension confirmed by ABPM.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee for Human Research of Ramathibodi Hospital (MURA 2022/327). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

NN, AS, KP, WP, SC, PS, and KT designed the study. NN, AS, KP, and WP performed the study. NN, AS, and KP drafted and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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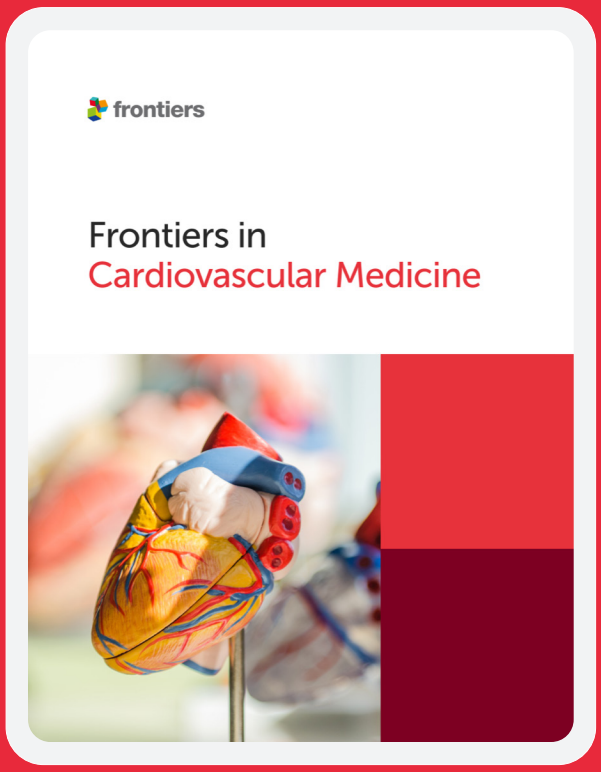

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