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The American Academy of Pediatrics hypertension guidelines identify obese youth at high cardiovascular risk among individuals non-hypertensive by the European Society of Hypertension guidelines

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Abstract

Background: Two different systems for the screening and diagnosis of hypertension (HTN) in children currently coexist, namely, the guidelines of the 2017 American Academy of Pediatrics (AAP) and the 2016 European Society for Hypertension (ESH). The two systems differ in the lowered cut-offs proposed by the AAP versus ESH.
Objectives: We evaluated whether the reclassification of hypertension by the AAP guidelines in young people who were defined non-hypertensive by the ESH criteria would classify differently overweight/obese youth in relation to their cardiovascular risk profile.
Methods: A sample of 2929 overweight/obese young people (6–16 years) defined non-hypertensive by ESH (ESH^{-}) was analysed. Echocardiographic data were available in 438 youth.
Results: Using the AAP criteria, 327/2929 (11%) young people were categorized as hypertensive (ESH^{-}/AAP^{+}). These youth were older, exhibited higher body mass index, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), triglycerides, total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) ratio, blood pressure, left ventricular mass index and lower HDL-C ($p<0.025$–0.0001) compared with ESH^{-}/AAP^{-}. The ESH^{-}/AAP^{+} group showed a higher proportion of insulin resistance (i.e. HOMA-IR $\geq$3.9 in boys and 4.2 in girls) 35% *vs.* 25% ($p<0.0001$), high TC/HDL-C ratio ($\geq$3.8 mg/dl) 35% *vs.* 26% ($p=0.001$) and left ventricular hypertrophy (left ventricular mass index $\geq 45\,g/h^{2.16}$) 67% *vs.* 45% ($p=0.008$) as compared with ESH^{-}/AAP^{-}.

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Conclusions: The reclassification of hypertension by the AAP guidelines in young people overweight/obese defined non-hypertensive by the ESH criteria identified a significant number of individuals with high blood pressure and abnormal cardiovascular risk. Our data support the need of a revision of the ESH criteria.

Keywords
Cardiometabolic risk factors, hypertension, left ventricular hypertrophy, paediatric obesity

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Introduction

For more than one decade the tables for screening and diagnosis of hypertension (HTN) in childhood, proposed by the Fourth Report, represented the major reference system for HTN in the world.[1] Not later than 2016, the European Society for Hypertension (ESH) introduced a fixed cut-off of 140/90 mmHg in adolescents aged ≥16 years, while maintaining unchanged the Fourth Report criteria in young people <16 years of age.[2] Recently the American Academy of Pediatrics (AAP) has proposed new cut-offs for the screening and diagnosis of HTN, which differ from both the Fourth Report and the ESH.[3] The cut-offs of systolic (SBP) and diastolic blood pressure (DBP) have been lowered, while a single cut-off of 130/80 mmHg was recommended in adolescents aged 13 years or more, as established in adults.[4]

This decision has opened a large debate not only on the adults' criteria, since the ESH decided to maintain the cut-off of 140/90 mmHg, but also on the paediatric criteria, since the European guidelines have not been revised yet. These contrasting positions on the definitions of HTN in children may create confusion and contrasting results, with evident effects in both clinical practice and epidemiological studies.

Recent studies demonstrated that the AAP criteria identified a higher proportion of hypertensive young people with abnormal cardiometabolic risk[5] or target organ damage,[6] as compared with the Fourth Report criteria. On the contrary, a recent Italian study did not support the advantage of using the AAP guidelines versus the Fourth Report/ESH guidelines.[7]

Since children and adolescents with obesity represent the largest category at risk of HTN, evaluating which guidelines (AAP or ESH) have the highest sensitivity in detecting cardiovascular risk (CVR) is crucial.

Therefore, our study aimed to investigate whether the reclassification of HTN by the AAP guidelines in young people who were defined non-hypertensive by the ESH criteria would identify overweight/obese (OW/OB) young people at higher CVR.

Methods

Study population

The study sample was part of the CARITALY Study's population. This is a cross sectional study undertaken by the Childhood Obesity Study Group of the Italian Society of Paediatric Endocrinology and Diabetology to analyse the cardiometabolic risk factors in Italian OW/OB children and adolescents referred to secondary or tertiary centres for the diagnosis and care of obesity.[8] All children aged 6–16 years observed in the period 2003–2016 who were defined non-hypertensive according to the ESH criteria (ESH^{-}), in whom complete anthropometric and biochemical data were available, were included into the study ($N = 2929$). Exclusion criteria were: genetic or endocrine obesity, pharmacological treatment, diabetes, previously diagnosed HTN. The study was conducted in accordance with the 1975 Declaration of Helsinki, revised in 1983, and informed consent was obtained from the parents or tutors of all participants.

Anthropometric and biochemical variables

All anthropometric variables, such as height, weight and waist circumference were measured in each centre by a single trained operator as elsewhere described.[8] Body mass index (BMI) was calculated by the following formula: weight/height^2 (kg/m^2) and transformed into standard deviation score (SDS), based upon the Italian BMI normative curves as elsewhere described.[9] Biochemical data relative to cardiometabolic risk profile, that is, plasma glucose and insulin, total cholesterol (TC), triglycerides and high-density lipoprotein cholesterol (HDL-C) were measured in all participants in the fasting state and analysed in the centralized laboratory of each centre. All centres belong to the Italian National Health System and are certified according to International Standards ISO 9000 (www.iso9000.it/), undergoing semi-annual quality controls and inter-lab comparisons. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated using a standard formula: [fasting plasma glucose (mg/dl) × fasting plasma insulin (μU/ml)/405].

The TC to HDL-C (TC/HDL-C) ratio was also calculated as index of atherogenic dyslipidaemia.[10–12]

Blood pressure measurement

SBP and DBP were measured by standard procedures as recommended by the ESH.[2] Briefly, after 5 min of resting in a quiet room, BP was measured by using an appropriate sized arm cuff on the right arm and an aneroid sphygmomanometer. Three measurements were obtained every 2 min and the mean of the last two values was used in the analyses. K1 was used for SBP and K5 for DBP, as elsewhere described.[13]

Echocardiographic evaluation

Echocardiographic measurements were available in 438 young people observed in the Pozzuoli and Rome centres, as elsewhere described.[14,15] The echocardiographic evaluation was performed in each centre using a commercial instrument by a single expert operator. Left ventricular mass, expressed in grams (g), was calculated with standard procedures[16] and normalized according to the method of Chinali et al.,[17] that is, g/h$^{2.16}$ (left ventricular mass index (LVMi)). Relative wall thickness adjusted for age (RWT$_a$) was calculated from posterior wall thickness (PWT), interventricular septum thickness (IVST) and left ventricular diastolic diameter (LVDD) using the formula (PWT+IVST)/LVDD. It was normalized for age using the formula RWT – 0.05 $\times$ age (years) – 10, as suggested by de Simone et al.[18]

Definitions

Non-hypertensive status was defined according to the ESH reference values[2] (ESH–): SBP and/or DBP <95th percentile for gender, age and height for young people <16 years or a single cut-off <140/90 mmHg for young people aged $\geq$16 years. The AAP reference values were used to reclassify HTN (ESH$^-$/AAP$^+$): SBP and/or DBP $\geq$95th percentile for age, gender and height in children <13 years or a single cut-off $\geq$130/80 mmHg for adolescents $\geq$13 years.[3] Overweight and obesity were defined on the basis of individual BMIs for age and gender that intercept the cut-off of $\geq$25 and $\geq$30 kg/m^2 at 18 years as recommended by the World Obesity Federation.[19] Insulin resistance was defined by the 75th percentile of HOMA-IR in our population by gender, that is, HOMA-IR $\geq$3.9 in boys and $\geq$4.2 in girls. The 75th percentile of the TC/HDL-C ratio, that is, >3.8 mg/dl in both sexes, was considered as an index of high TC/HDL-C ratio. Left ventricular hypertrophy (LVH) was defined by a value of LVMi $\geq$45 g/h$^{2.16}$ as recommended by the ESH.[2,17]

Statistical analysis

Data were expressed as mean $\pm$ standard deviation. The variables with skewed distribution were log-transformed for the statistical analyses and back-transformed for presentation in the tables.

Comparisons between ESH categories were performed using Student's *t* test. Chi-square or Fisher's exact test, as appropriate, were used to compare proportions. To evaluate the association (odds ratio (OR), 95% confidence interval (CI)) of the CVR factors between individuals categorized as non-hypertensive by both the ESH and AAP guidelines (ESH$^-$/AAP$^-$) and those who were reclassified as hypertensive by the AAP guidelines (ESH$^-$/AAP$^+$), we performed a logistic regression analysis adjusted for centres, age and BMI. The statistical analysis was performed using the IBM SPSS Statistics, version 20.0. A p value <0.05 was considered statistically significant.

Results

The overall sample was divided into two groups: the first included 2602 (89%) young subjects who were categorized as non-hypertensive by both the ESH and AAP guidelines (ESH$^-$/AAP$^-$), the second included 327 (11%) who were reclassified as hypertensive by the AAP guidelines only (ESH$^-$/AAP$^+$) (Table 1, left panel). The reclassified group with HTN according to AAP guidelines only (ESH$^-$/AAP$^+$) was older and showed higher levels of BMI, BMI-SDS, HOMA-IR, triglycerides, TC/HDL-C ratio, SBP and DBP, and lower HDL-C.

The characteristics of the subsample with echocardiographic examination are shown in Table 1 (right panel). Compared with the overall sample, children who underwent echocardiography did not differ in age (respectively 10.4 $\pm$ 2.7 *vs.* 10.6 $\pm$ 2.4 years, $p = 109$) and gender distribution (respectively 53% males *vs.* 52%, $p = 0.643$), while the percentage of ESH$^-$/AAP$^+$ individuals was slightly lower (9% *vs.* 11%). Youth classified as ESH$^-$/AAP$^+$ showed higher values of LVMi as compared with young people ESH$^-$/AAP$^-$ ($p = 0.016$).

CVR factors

To confirm the strength of the association between CVR and HTN, we compared the proportion of insulin resistance or high TC/HDL-C ratio in ESH$^-$/AAP$^+$ and ESH$^-$/AAP$^-$ groups. As shown in Figure 1, the proportion (95% CI) of young people with insulin resistance or high TC/HDL-C ratio in the overall sample was significantly higher in the reclassified group compared with the ESH$^-$/AAP$^-$ group. Similarly, in the

Table 1. Comparison between young people categorized as non-hypertensive by both the ESH and the AAP guidelines (ESH⁻/AAP⁻) and those who were reclassified as hypertensive by the AAP guidelines (ESH⁻/AAP⁺) in the overall sample and in the subsample with echocardiographic examination.

	Overall sample			Sub-sample with echocardiographic examination		
	ESH^-/AAP^-	ESH^-/AAP^+	*p* value	ESH^-/AAP^-	ESH^-/AAP^+	*p* value
Subjects, *n* (%)	2602 (89)	327 (11)		399 (91)	39 (9)	
Age	10.6 ± 2.4	11.1 ± 2.5	<0.0001	10.3 ± 2.5	11.5 ± 2.7	0.003
Male gender, *n* (%)	1329 (501	181 (55)	0.145	206 (52)	25 (64)	0.136
BMI, kg/m^2	27.9 ± 4.4	29.5 ± 5.0	<0.0001	25.8 ± 5.1	27.8 ± 4.1	0.018
BMI-SDS	2.0 ± 0.5	2.2 ± 0.6	<0.0001	1.8 ± 0.4	2.0 ± 0.5	0.020
WhtR	0.61 ± 0.07	0.63 ± 0.06	0.002	0.58 ± 0.09	0.61 ± 0.05	0.092
FPG, mg/dl	85.5 ± 8.3	85.4 ± 8.1	0.967	84.1 ± 7.5	84.2 ± 6.6	0.920
HOMA-IR	3.3 ± 2.8	3.7 ± 2.3	0.001	2.7 ± 1.9	3.7 ± 2.3	0.001
Total cholesterol, mg/dl	157.9 ± 29.9	159.7 ± 32.1	0.302	161.9 ± 30.5	154.5 ± 40.0	0.165
HDL-C, mg/dl	49.7 ± 12.2	48.1 ± 11.8	0.029	51.6 ± 11.7	44.9 ± 12.2	0.001
Triglycerides, mg/dl	89.2 ± 45.6	95.9 ± 50.3	0.031	83.1 ± 42.7	93.2 ± 47.8	0.137
LDL-C, mg/dl	90.4 ± 27.0	92.4 ± 28.0	0.197	93.7 ± 27.0	91.0 ± 32.9	0.563
TC/HDL-C ratio	3.3 ± 0.9	3.5 ± 1.0	0.005	3.3 ± 0.9	3.6 ± 1.2	0.021
Systolic BP, mmHg	104.9 ± 10.6	118.2 ± 6.9	<0.0001	104.4 ± 8.8	119.0 ± 6.4	<0.0001
Diastolic BP, mmHg	62.2 ± 7.4	72.6 ± 8.6	<0.0001	61.7 ± 7.0	71.2 ± 9.0	<0.0001
LVMi, g/h$^{2.16}$	–	–	–	44.9 ± 14.5	50.7 ± 13.5	0.018
RWTa	–	–	–	0.354 ± 0.06	0.359 ± 0.06	0.556

Values are presented as mean ± SD or *n* (%).
ESH: European Society for Hypertension; AAP: American Academy of Pediatrics; BMI: body mass index; SDS: standard deviation score; WhtR: waist to height ratio; FPG: fasting plasma glucose; HOMAR-IR: Homeostatic Model Assessment of Insulin Resistance; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC/HDL-C ratio: total cholesterol to high-density lipoprotein cholesterol ratio; BP: blood pressure; LVMi: left ventricular mass index; RWTa: relative wall thickness adjusted for age

subsample with echocardiographic examination the proportion of LVH was higher in the ESH^-/AAP^+ group than in the ESH^-/AAP^- group.

In the overall group the ORs (95% CIs) for insulin-resistance or high TC/HDL-C ratio (adjusted for centres, age and BMI) were respectively 1.33 (1.03–1.72, $p = 0.029$) and 1.36 (1.06–1.75, $p = 0.014$) in the ESH^-/AAP^+ compared with ESH^-/AAP^- (Table 2, left panel). In particular, the ORs for insulin resistance or high TC/HDL-C ratio were higher in the subsample with echocardiographic examination compared with the overall sample (Table 2, right panel). Furthermore, the OR for LVH was 2.32 (1.15–4.67, $p = 0.019$) in ESH^-/AAP^+ compared with the ESH^-/AAP^- group.

Discussion

This study demonstrates that, in a very large sample of Caucasian OW/OB young people categorized as non-hypertensive by the ESH, around 11% were reclassified as hypertensive according to the AAP guidelines ($ESH^-/AAP+$). These subjects showed higher BP levels and an abnormal CVR profile, defined by insulin resistance, high TC/HDL-C ratio and LVH.

In recent years, the publication of the AAP guidelines has generated a heated debate on which are the most appropriate criteria for the screening and diagnosis of HTN in children and adolescents.[20,21] As a result of the lowered blood pressure (BP) cut-offs, the new guidelines are undoubtedly expected to increase the number of young people at risk of HTN as compared with the criteria of the Fourth Report[5–7] or the ESH.[13] However, on the basis of the results provided by the present study, the use of the AAP reference values allows the identification of young people with a greater burden of CVR who would have been missed using the ESH criteria.

Indeed, our data clearly demonstrate that the individuals reclassified as hypertensive by the AAP guidelines[3] showed a 30% higher probability of having insulin resistance and atherogenic dyslipidaemia than those who were confirmed as non-hypertensive by the same guidelines. With regard to insulin resistance, our results are in agreement with Maffeis et al., who reported that this condition was a strong risk factor

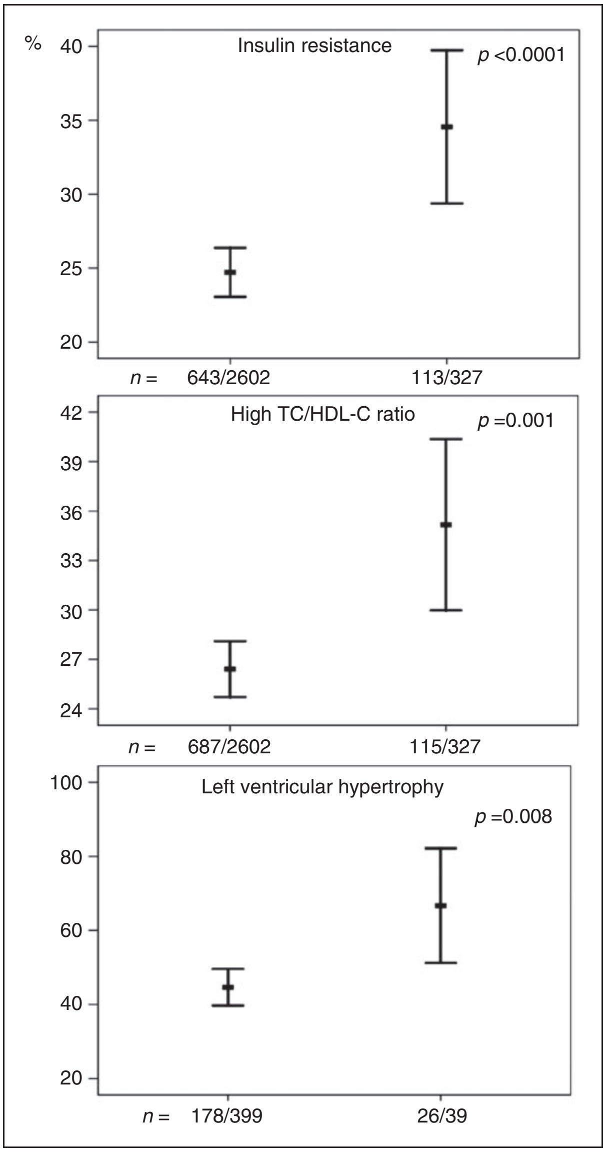

Figure 1. Proportions (95% confidence interval) of young people with insulin resistance, high total cholesterol to HDL-cholesterol (TC/HDL-C) ratio and left ventricular hypertrophy in the group categorized as non-hypertensive by both the European Society for Hypertension (ESH) and the American Academy of Pediatrics (AAP) guidelines (ESH^{-}/AAP^{-}) (left error bar) and the group reclassified as hypertensive by the AAP guidelines (ESH^{-}/AAP^{+}) (right error bar).

for high BP in a large sample of obese children.[22] Certainly, there is a strict link between hyperinsulinaemia, a consequence of insulin resistance, and sympathetic nervous system activation.[23]

Concerning the association between CVR factors and the different classification systems of HTN, Sharma et al. demonstrated for the first time in a multi-ethnic population that young individuals reclassified as hypertensive by AAP were more likely to be overweight or obese, with higher lipid levels compared with individuals defined as hypertensive by the Fourth Report 2004.[5] In line with these findings, we found that young individuals with OW/OB reclassified as hypertensive by the AAP criteria showed higher levels of TC/HDL-C ratio, which is considered a marker of atherogenic dyslipidaemia[10–12] and a strong independent predictor of cardiovascular events in adults.[24] Noteworthy, this abnormal cardiovascular profile was independent of BMI.

LVH associated with HTN

Extending previous findings by Sharma et al. on lipids,[5] our study demonstrates that individuals reclassified as hypertensive by the AAP criteria have also higher odds of LVH than those classified as non-hypertensive by both ESH and AAP.

With regard to the strength of association of LVH with HTN classified according to the AAP or the Fourth Report, Khoury et al. demonstrated that in 96 obese adolescents categorized as hypertensive (most of them were also affected by diabetes) the proportion of LVH was 31% using the AAP classification system compared with 21% using the Fourth Report system, with a 48% increase,[6] confirming the higher sensitivity of the AAP guidelines. In contrast, Antolini et al., in a sample of 951 Italians encompassing 222 normal weight and 729 OW/OB individuals, observed that in hypertensive individuals with LVH 46% were identified by the Fourth Report/ESH while the value was 53% with AAP criteria with a smaller increase of 15%.[7] These contrasting data may depend on the characteristics of the population studied and on the cut-offs applied for the identification of LVH.

CVR associated with AAP criteria

In the present study we adopted a different approach to evaluate the differences between AAP and ESH criteria. We compared cardiometabolic features in a very large sample of OW/OB young individuals, comparing subjects who were categorized as non-hypertensive by both the ESH and AAP guidelines (ESH^{-}/AAP^{-}) with those who were reclassified as hypertensive by the AAP guidelines (ESH^{-}/AAP^{+}), and we demonstrated that the AAP criteria identified a subgroup of individuals with a worse CVR profile.

The association between obesity, abnormal cardiometabolic risk factors, HTN and LVH represents a threatening cluster in children and adolescents, approximating what ensues in adults.[25] In particular the presence of LVH is a strong risk factor for cardiovascular events, such as cardiac failure or cardiovascular disease.[26] The combination of these conditions should not be overlooked in children and adolescents with

Table 2. Probability (odds ratio (95% confidence interval)) of insulin resistance, high TC/HDL-cholesterol ratio, and left ventricular hypertrophy in young people reclassified as hypertensive by the AAP guidelines (ESH⁻/AAP⁺) compared with young people categorized as non-hypertensive by both the ESH and the AAP guidelines (ESH⁻/AAP⁻) in the overall sample and sub-sample with echocardiographic examination.

	Overall sample			Sub-sample with echocardiographic examination		
	ESH^-/AAP^-	ESH^-/AAP^+	*p* value[a]	ESH^-/AAP^-	ESH^-/AAP^+	*p* value[a]
Subjects, *n* (%)	2602 (89)	327 (11)		399 (81)	39 (9)	
Insulin resistance	1.00	1.33 (1.03–1.72)	0.029	1.00	2.32 (1.12–4.82)	0.023
High TC/HDL-C ratio	1.00	1.36 (1.06–1.75)	0.014	1.00	2.12 (1.05–4.25)	0.036
Left ventricular hypertrophy	–	–		1.00	2.32 (1.15–4.67)	0.019

[a]*p* value adjusted for centres, age and body mass index.
ESH: European Society for Hypertension; AAP: American Academy of Pediatrics; TC/HDL-C ratio: total cholesterol to high-density lipoprotein cholesterol ratio

obesity, since an intensive treatment aimed at reducing BP can decrease the degree of LVH and consequently their cardiovascular risk.[27]

As far as we know, there are no longitudinal studies that assessed the relationship between HTN classified according to the new paediatric criteria in children and adolescents, and cardiovascular events in adult age. Interestingly, our results may be supported by a recent multiethnic longitudinal study (The Cardia Study) performed in very young adults (age range 18–30 years). This study showed an increased risk of cardiovascular events in individuals categorized as high normal BP or hypertensive on the basis of the new criteria as compared with normotensive individuals.[28]

The strength of our study is based on the comprehensive analysis of both biochemical and echocardiographic CVR profile associated with HTN in a vary large population of obese. Furthermore, the greatest risk for both CVR factors and LVH observed using the AAP versus ESH criteria was independent of BMI. This study presents also some limitations, such as the cross-sectional design and the lack of normal-weight individuals; moreover, it would have been more valuable to have a multiethnic sample of youth.[29,30] However, young people with OW/OB represent the largest category of subjects at risk of HTN. Therefore the decision concerning the method for the diagnosis of HTN is critical in this category, both from a clinical point of view and in terms of CVR prevention. We measured BP in one visit, and we are aware that the diagnosis of HTN requires at least two controls on different occasions, but all previous epidemiological studies addressing this topic were based on the measurement obtained on one single occasion.[1–3,5,7,13] Lastly, risk of bias concerning the subgroup with echocardiograms was limited. Echocardiograms were performed only in Rome and Pozzuoli Hospitals and all children who were scheduled for a medical exam underwent echocardiogram. Accordingly, selection bias could not occur due to personalized indications.

To the best of our knowledge, this is the first study to demonstrate in a very large sample of Italian youth with OW/OB that the revised AAP criteria are more effective in identifying children at high CVR than the ESH criteria, which substantially overlap with the cut-offs proposed by the 2004 Fourth Report, with the exception of the cut-offs for adolescents aged $\geq$16 years. Because designing outcome studies is unpractical in this age range, we may take advantage of prevalence of LVH in our sub-analysis group with echocardiograms, under the assumption that LVH is a surrogate (intermediate) end-point for cardiovascular morbidity and mortality.[31] Thus, based on prevalence of LVH, use of more strict criteria may suggest a better approach to reduce long-term outcome.

In conclusion, the use of AAP 2017 criteria may allow an earlier identification and management of high-risk obese youth in order to prevent the progression of cardiovascular damage. Therefore, our study supports the need for a revision of the ESH criteria for the screening and diagnosis of HTN in children with OW/OB.

Author contribution

PDB conceived and designed the study, and performed the statistical analyses. PDB, MGB, GdS and GV contributed to the analysis and interpretation of the data. PDB and GV drafted the manuscript. MRL, MGB, CM, AM, MM, EMdG, ADS, GC, NM, LG, CC, LP were responsible for the acquisition of patients and data. PDB and GV agree to be accountable for all aspects of work ensuring integrity and accuracy. All authors critically read and revised the manuscript and approved the final version.

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Declaration of conflicting interests

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