



Practice of Epidemiology

How Accurate Is a Single Cutpoint to Identify High Blood Pressure in Adolescents?

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In 2007 the International Diabetes Federation (IDF) proposed single blood pressure (BP) cutpoints (systolic: ≥ 130 mm Hg and diastolic: ≥ 85 mm Hg) for the diagnosis of high blood pressure (HBP) in adolescents. Before this proposal, HBP had been defined as BP at or above the 95th percentile for age, sex, and height percentile (reference standard). In this study, we evaluated the risk for misclassification when using the IDF single-cutpoints criteria. We first applied the IDF criteria to a reconstructed population with the same age, sex, and height distribution as the population used to develop the reference standard. The proposed single cutpoints corresponded to percentiles from the 81.6th to 99.9th for systolic BP and from the 92.9th to 98.9th for diastolic BP in the reconstructed population. Using IDF criteria, there were high false-negative fractions for both systolic and diastolic BP (from 54% to 93%) in 10- to 12-year-olds and a false-positive fraction up to 35% in older subjects. We then applied the IDF criteria to 1,162 overweight/obese adolescents recruited during 1998–2000 from pediatric clinical centers in Milano, Varese, and Modena in Italy and in Zaragoza, Spain. Overall false-negative and false-positive fractions were 22% and 2%, respectively; negative predictive values were especially low for 10- to 12-year-old subjects. The use of IDF's single cutpoints carries a high risk of misclassification, mostly due to false negatives in younger subjects. The effort to simplify diagnosis could be overcome by the risk of undiagnosed HBP.

adolescence; hypertension; metabolic syndrome; obesity; overweight

Abbreviations: CDC, Centers for Disease Control and Prevention; DBP, diastolic blood pressure; FNF, false-negative fraction; FPF, false-positive fraction; HBP, high blood pressure; IDF, International Diabetes Federation; MS, metabolic syndrome; NHBPEP, National High Blood Pressure Education Program; NPV, negative predictive value; PPV, positive predictive value; SBP, systolic blood pressure.

Metabolic syndrome (MS) is a condition whose existence and definition in adults, in whom it was first characterized, are undergoing a heated debate (1–4). In children and adolescents there is no consensus on how MS should be diagnosed (5). Controversies are related mainly to 2 diverging approaches: one adapting the definition of MS from adults (6–8) and the other based on a distributional approach, which is typical in populations in which individuals are still growing (9, 10).

In 2007, the International Diabetes Federation (IDF) proposed a set of age-related criteria for the diagnosis of MS in the pediatric population (11, 12). For adolescents (i.e., 10-

to 16-year-olds), MS can be diagnosed by a finding of abdominal obesity and the presence of at least 2 of the following conditions: high blood pressure (HBP), hypertriglyceridemia, hyperglycemia, or reduced high-density lipoprotein cholesterolemia. According to the IDF criteria, the diagnosis of HBP is based on 2 single cutpoints: ≥ 130 mm Hg for systolic blood pressure (SBP) and ≥ 85 mm Hg for diastolic blood pressure (DBP), thus using the existing criteria for MS diagnosis in adults. The use of these single cutpoints is recommended regardless of other characteristics, such as age, sex, or height (12). These criteria were used in subsequent literature (13, 14).

Before the IDF proposal, the established criteria used to diagnose HBP in the pediatric population were developed by the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Children and Adolescents. These criteria were defined using the distribution, in a large US population, of blood pressure values calculated specifically for a child's sex, age, and height percentile, to account for the dependence of BP on body size (15). The condition of systolic HBP is defined by SBP at or above the 95th percentile of the reference distribution for the sex, age, and height percentile of the patient. Diastolic HBP is defined correspondingly. HBP is defined as elevated measurements of systolic and/or diastolic blood pressure. The 95th percentiles of SBP and DBP will be referred to as sex-age-height cutpoints hereafter.

The rationale for a classification accounting for age, sex, and height is that these factors influence SBP and DBP in adolescents (16), and the use of 95th percentiles enables practitioners to identify a fixed 5% fraction of subjects with systolic HBP. The same is true for diastolic HBP.

The aim of the present study was to evaluate the possibility of classification errors from using the simplified single-cutpoints IDF criteria in the diagnosis of HBP in adolescents, comparing IDF criteria with the NHBPEP sex-age-height criteria that are considered to be the reference standard for the definition of HBP. Although the NHBPEP criteria cannot be considered the reference standard to predict organ damage in adults—there are no follow-up studies linking those conditions—NHBPEP-defined hypertension has been related to early organ damage in several studies (17–20).

We evaluated classification errors made when using the single-cutpoint IDF criteria in the diagnosis of HBP in 2 different settings. First, we considered a reconstructed population of adolescents aged 10–16 years with SBP and DBP distributions that mimicked the population in which the NHBPEP criteria were derived (15). Second, we considered a large sample of white children followed in pediatric clinics and at increased risk of MS due to overweight or obesity conditions.

METHODS

IDF and NHBPEP criteria

The contrast for SBP and DBP between the IDF's simplified single-cutpoint criteria and the sex-age-height NHBPEP criteria for the diagnosis of HBP is shown in Figure 1, separately for boys and girls. The piecewise linear curves represent the NHBPEP cutpoints for specific age classes for the range of height percentiles. These cutpoints were obtained from the NHBPEP Working Group on High Blood Pressure in Children and Adolescents (15), defining the criteria from the original population as the 95th percentile in the BP distribution according to sex, age, and height percentile. In each panel, a dashed horizontal line was added to represent the IDF single cutpoints, which were defined regardless of sex, age, and height percentile. The IDF proposed cutpoint of 130 mm Hg corresponds to percentiles of the NHBPEP SBP distributions ranging from a minimum of 81.6th (for male 16-year-olds at the 95th percentile for height) to a maximum

of 99.9th (for male 10-year-olds at the 5th percentile for height). The proposed cutpoint of 85 mm Hg corresponds to percentiles of the NHBPEP DBP distributions ranging from a minimum of 92.9th (for male 16-year-olds at the 95th percentile for height) to a maximum of 98.9th (for male or female 10-year-olds at the 5th percentile for height).

Reconstructed general population

The distribution of SBP and DBP in the general population of adolescents in which the NHBPEP criteria were developed, was reconstructed, restricting ages to 10–16 years, as follows: The mean values of SBP and DBP were obtained using the parameters of the nonlinear regression models (based on sex, age, and height) published in 2004 by the NHBPEP Working Group on High Blood Pressure in Children and Adolescents (15). The standard deviation was then derived from the published table of percentiles, assuming Gaussian distribution of SBP and DBP (15). The distributions of SBP and DBP for each sex, age class, and height percentile were then derived by incorporating the obtained means and standard deviations into the corresponding parameters of the Gaussian distribution. Overall, for each type of blood pressure, 84 distributions were reconstructed (6 age classes and 7 height percentiles for each sex).

In Web Figure 1A (available at <http://aje.oxfordjournals.org/>), the distribution of SBP is represented for girls with heights at the 10th (continuous line) and 90th (dashed line) percentiles. Increasing height percentile shifts the SBP distribution to the right. This justifies the increasing values of the NHBPEP sex-age-height cutpoints with increasing height percentile within each age class (Figure 1). This graph also illustrates that, using the NHBPEP criteria, the proportion of adolescents considered to have HBP is constant regardless of height percentile (the filled and line-shaded areas are both equal to 5%), and the same is true for sex and age. In contrast, using a single IDF cutpoint, the proportion of adolescents diagnosed with HBP falls with decreasing height percentiles—that is, the solid filled area to the right of the gray line is smaller (1.5%) than the corresponding line-shaded area (4.2%). Web Figure 1B illustrates that the IDF cutpoint can also be lower than the NHBPEP cutpoint when the distribution has a higher mean, as it does among 15-year-old boys.

Overweight/obese adolescent sample

A group of white, overweight/obese subjects, aged 10–16 years, was also considered. This sample will be referred to hereafter as the clinical sample. The 1,162 children (551 (47.4%) girls) were recruited at 4 pediatric clinical centers for the care of childhood obesity: 627 subjects from Varese (Italy), 244 from Modena (Italy), 177 from Milano (Italy), and 114 from Zaragoza (Spain). Exclusion criteria were endocrine obesity, genetic syndromes, psychiatric disorders, and the presence of any other chronic disease or drug treatment. The local ethical committee approved data collection at each participating center.

Measurements of weight, height, and blood pressure were taken according to the *Anthropometric Standardization Reference Manual* (21). Body mass index was calculated as weight

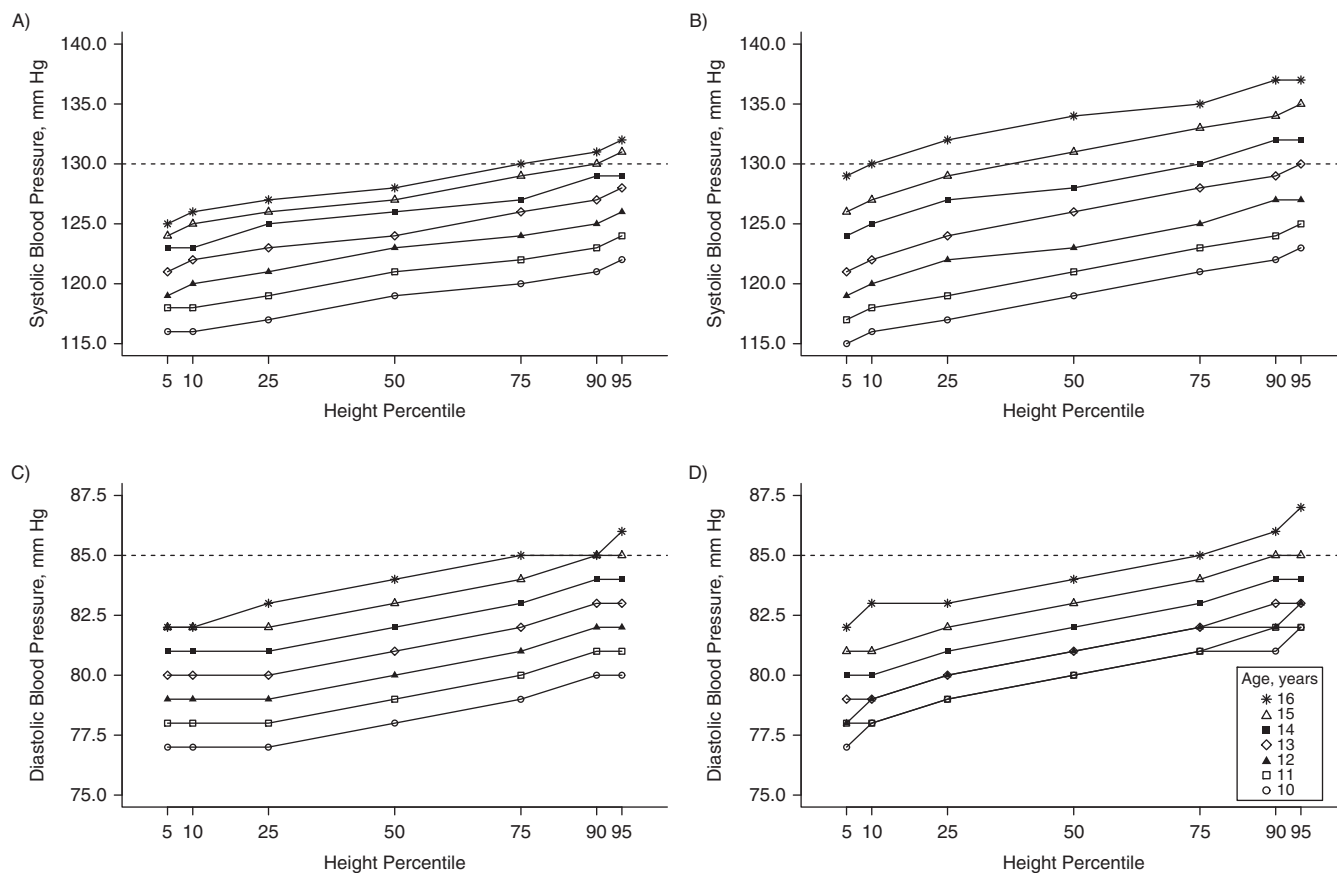


Figure 1. Cutoff values for diagnosis of high systolic and diastolic blood pressure (BP). A) Systolic BP in girls; B) systolic BP in boys; C) diastolic BP in girls; and D) diastolic BP in boys. The curves represent the standards according to the criteria of the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Children and Adolescents (95th percentile of the distribution for sex, age, and height percentile); each line represents a different age in years (10–16), and the labels on the x-axis show the height percentiles for which the cutoffs were tabulated by the NHBPEP (15). The dashed horizontal lines represent the International Diabetes Federation cutpoints for systolic BP (130 mm Hg) and diastolic BP (85 mm Hg) (11).

(kg)/height (m)². We used US Centers for Disease Control and Prevention (CDC) reference data and the LMS (lambda-mu-sigma) method to calculate *z* scores for weight, height, and body mass index (22). CDC growth charts were used because the NHBPEP reference values for SBP and DBP are based on CDC height values. Children were defined as overweight if their body mass index was ≥ 85 th and < 95 th percentile for age and sex and as obese if their body mass index was ≥ 95 th percentile for age and sex. Pubertal status was defined by a physician according to Tanner and Whitehouse (23), and the subjects were classified in stages from 1 to 5.

Blood pressure was measured using a mercury sphygmomanometer, with the appropriate cuff for the upper-arm size (15). SBP was defined by the onset of the first Korotkoff sound, and DBP was indicated by the fifth Korotkoff sound. Blood pressure measurements were performed while children were sitting with the cubital fossa supported at heart level, after at least 5 minutes of rest. We considered 3 measurements per subject, collected on different days.

Children were classified for both systolic and diastolic HBP using the reference-standard NHBPEP criteria if the

means of 3 measurements were ≥ 95 th percentile for age, sex, and height percentile (15); age and height were approximated to the nearest value. Subjects were also classified according to the simplified IDF criteria for systolic and diastolic HBP if the means of 3 measurements were ≥ 130 mm Hg for SBP or ≥ 85 mm Hg for DBP (11).

STATISTICAL METHODS

The classification errors, when using the simplified single-cutpoint IDF criteria instead of the reference standard NHBPEP criteria, were first analyzed in terms of the false-positive fraction (FPF) and the false-negative fraction (FNF) of the identification of both systolic and diastolic HBP.

FPF was the probability of classifying a participant as having HBP according to the IDF criteria when that participant did not have HBP according to the NHBPEP definition. FNF was the probability of classifying a participant as not having HBP according to the IDF criteria when that participant did have HBP according to the NHBPEP definition.

To assess the relevance of the classification errors in a clinical setting, we also assessed the positive predictive value (PPV) and the negative predictive value (NPV) of the IDF criteria. PPV was the probability of having HBP by the reference-standard NHBPEP definition when the subject was also classified as having HBP by the IDF criteria. Similarly, NPV was the probability of not having HBP according to the reference-standard NHBPEP definition when the subject was also classified as not having HBP by the IDF criteria.

Reconstructed general population

FPFs were calculated on the distributions for SBP and DBP in each sex, age class, and height percentile as the ratio between the white area between the two cutoffs (false positives) and the white area to the left of the NHBPEP cutoff, as shown for a 14-year-old boy at the 90th percentile for height in Web Figure 2A. Analogously, as shown for a 10-year-old girl at the 50th percentile for height (Web Figure 2B), the FNF was calculated directly on the distribution of the BP of interest as the ratio between the white area between the two cutoffs (false negatives) and the white area to the right of the NHBPEP cutoff (24). The same procedures were performed for SBP and DBP.

The PPV and NPV were calculated from the FPF and FNF values for each sex, age class, and percentile of height, assuming a prevalence of HBP ranging from 2% to 30% and using Bayes' theorem (24).

Overweight/obese adolescent sample

FNFs were calculated as number of false negatives (i.e., number of adolescents incorrectly classified as negative by IDF criteria) divided by the number of adolescents classified as having HBP according to the NHBPEP criteria. FPFs were calculated as the number of false positives (i.e., number of adolescents incorrectly classified as positive by IDF criteria) divided by the number of adolescents classified as not having HBP according to the NHBPEP criteria.

The NPV was calculated as the number of adolescents classified as not having HBP according to NHBPEP criteria divided by the number of adolescents classified as not having HBP according to IDF criteria, while the PPV was calculated as the number of children with HBP according to NHBPEP divided by the number of adolescents classified as having HBP according to IDF criteria. We also constructed receiver operating characteristic curves to evaluate the use of different fixed BP cutpoints, using NHBPEP as the reference standard. The receiver operating characteristic curves were obtained by plotting the true positive fraction against the FPF, varying the cutoff of choice. For DBP we let the cutoff vary from 45 mm Hg to 100 mm Hg and for SBP we let it vary from 70 mm Hg to 150 mm Hg, with 1-unit increases.

RESULTS

Reconstructed general population

FNFs for SBP and DBP in boys and girls at different ages and height percentiles are shown in Figure 2). As an example, looking at the line for SBP in male 10-year-olds (in Figure 2A), the percentage of boys who have HBP according to NHBPEP definition and are incorrectly classified as not having HBP by IDF criteria is 91%. All FNFs progressively decreased with increasing age and height percentile (Figure 2A). FNFs were higher among girls than among boys, especially for SBP with increasing age and at early ages for DBP. FNFs were also higher in subjects with a lower height percentile (see Figure 2B). The FPFs (patients classified as not having HBP by NHBPEP and incorrectly classified as hypertensive by IDF criteria) were very low. In fact, FPFs were greater than 0 only for SBP in male 15- to 16-years-olds. FPFs were present only for subjects at the highest height percentile.

Figure 3 shows NPVs according to age and sex, obtained assuming different prevalences (from 2% to 30%) of HBP in the population and averaging height across percentiles. Let us consider first a population with an HBP prevalence

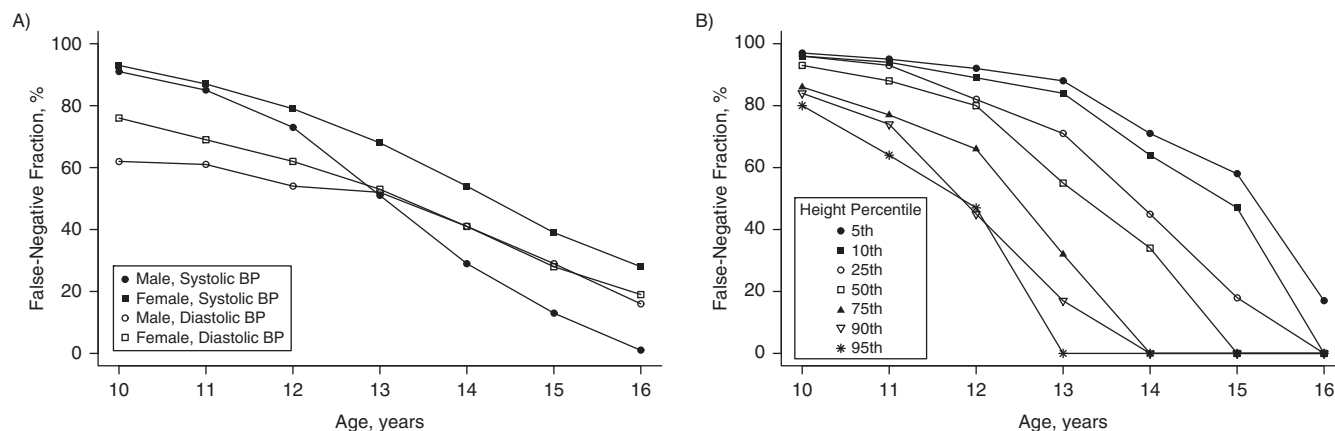


Figure 2. False negative fraction (FNF) in a reconstructed general population. A) systolic and diastolic blood pressure according to age and sex (averaged across height percentiles); B) FNF for systolic blood pressure in boys according to age and height percentile.

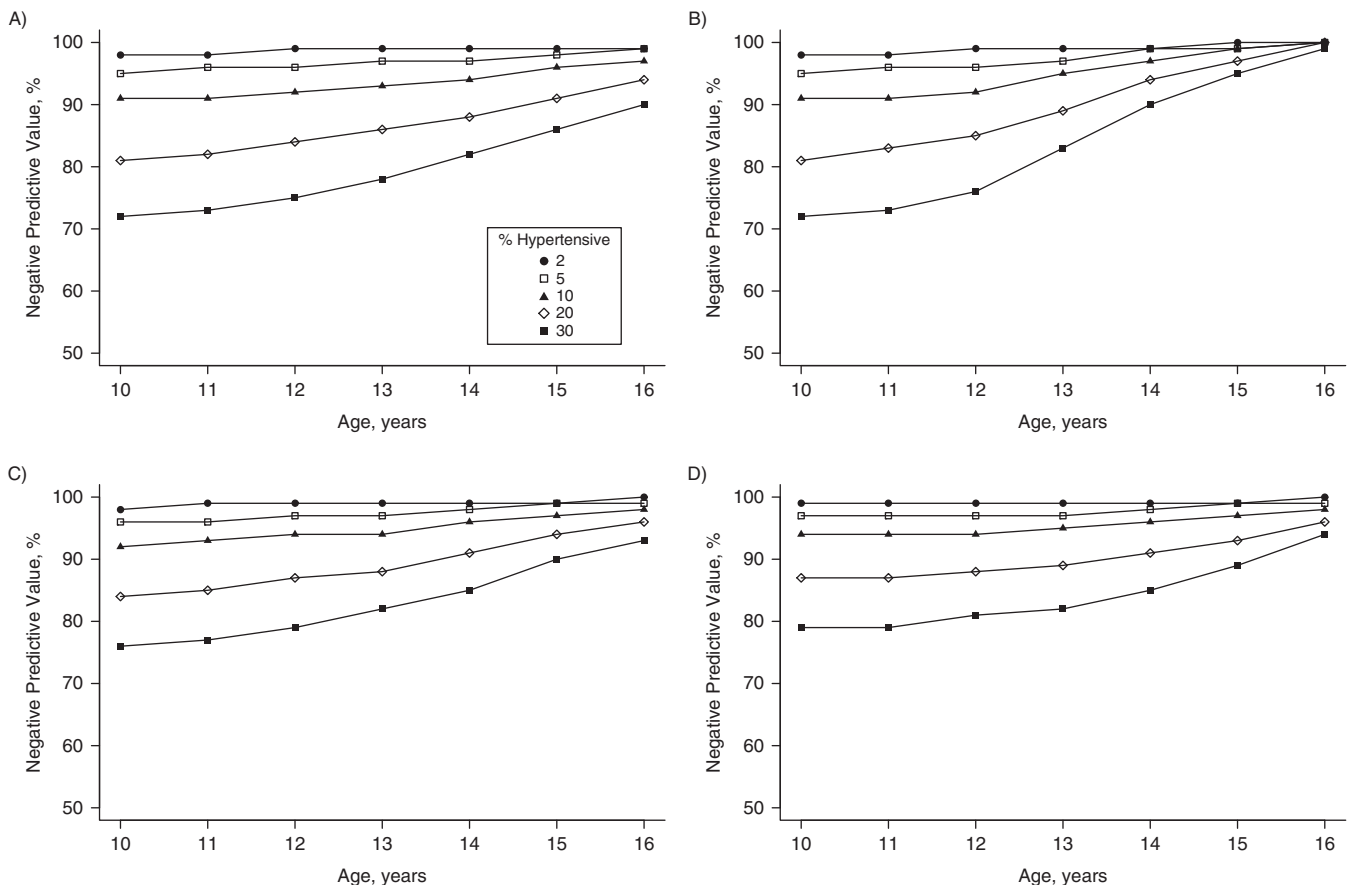


Figure 3. Negative predictive values (NPVs) as a percentage for International Diabetes Federation criteria for systolic and diastolic blood pressure (BP) in a reconstructed general population, according to age and selected prevalences of high BP (from 2% to 30%). A) Systolic BP in girls; B) systolic BP in boys; C) diastolic BP in girls; D) diastolic BP in boys.

of 2% (filled circle) and a normotension prevalence of 98%. We can see that the fraction of 10-year-old boys with normal systolic BP (according to NHBPEP criteria) in the total number of subjects classified as normotensive according to IDF criteria is 98% (Figure 3B). Thus, 2% ($100\% - 98\%$) of subjects classified as normotensive by IDF actually have HBP. Let us observe, however, that 98% is also the overall fraction of normotensive individuals in such a population, and thus 98% is the NPV that we would obtain if classifying all subjects as normotensive without measuring the BP. Therefore, in this case the IDF criteria were not useful as a means to exclude HBP.

Let us consider now a population with an HBP prevalence of 30% (filled square). We can see that the fraction of 14-year-old boys classified as normotensive by the IDF criteria among those with normal systolic BP under the NHBPEP definition is 90% (Figure 3B). In this case, the fraction of normotensive individuals is 70%, which is the NPV we would obtain if classifying all subjects as normotensive without measuring the BP. Thus, in this case there is some utility in excluding HBP. However, 10% of individuals still have HBP according to the NHBPEP definition and yet are incorrectly classified as normotensive by IDF criteria.

Overall, for both SBP and DBP, NPVs are low for younger patients and decrease with increasing prevalence of HBP, regardless of sex.

Web Table 1 shows the NPVs for prevalence of HBP by percentile of height in male 10-year-olds (SBP). The parameters are the same those for Figure 3. The lowest NPVs were associated with the lowest height percentiles. PPVs were obtained for different prevalences of hypertension, similarly to NPVs. PPVs are not listed because they were in most cases equal to 100%.

Overweight/obese adolescent sample

The characteristics of the 1,162 participants in the clinical sample are shown in Table 1. Age distribution of participants was as follows: 274 subjects aged 10 years, 267 aged 11 years, 245 aged 12 years, 177 aged 13 years, 117 aged 14 years, and 82 aged 15 years. All pubertal stages were represented: Tanner stage 1 ($n = 311$); stage 2 ($n = 293$); stage 3 ($n = 219$); stage 4 ($n = 136$); and stage 5 ($n = 203$). A total of 895 children were classified as obese and 267 as overweight. The z scores for anthropometric

Table 1. Characteristics of Obese/Overweight Adolescents Recruited From Pediatric Centers ($n = 1,162$), Italy and Spain, 1998–2000

| Variable | Median (IQR) | Minimum | Maximum |
|-----------------------|--------------|---------|---------|
| Age, years | 12 (2) | 10 | 16 |
| Weight, kg | 63.6 (18.7) | 32.5 | 122.6 |
| Weight, z score | 1.97 (0.77) | -0.70 | 3.74 |
| Height, m | 1.54 (0.14) | 1.24 | 1.86 |
| Height, z score | 0.70 (1.40) | -3.28 | 4.34 |
| BMI ^a | 26.7 (4.6) | 16.9 | 44.9 |
| BMI, z score | 1.93 (0.52) | 0.01 | 2.84 |
| Systolic BP, mm Hg | 120 (15) | 77 | 145 |
| Systolic BP, z score | 1.03 (1.38) | -3.17 | 3.49 |
| Diastolic BP, mm Hg | 70 (15) | 45 | 100 |
| Diastolic BP, z score | 0.71 (1.15) | -1.63 | 3.17 |

Abbreviations: BMI, body mass index; BP, blood pressure; IQR, interquartile range.

^a BMI was calculated as weight (kg)/height (m)².

variables and blood pressure were similar in each age class (data not shown).

The overall prevalence of HBP as defined by NHBPEP was 32%, and it was slightly higher in girls (34%) than in boys (30%). Systolic HBP was more frequent than diastolic HBP (26% vs. 14%). Considering only obese patients ($n = 895$), the fraction of those who had HBP dropped from 35% using the NHBPEP criteria to 17% using the IDF cutpoints.

Concerning the comparison between the NHBPEP definition and the IDF proposal, the observed overall FNF was 22% and the FPF was 2%. FNFs in the study sample were lower than expected based on analysis of the reconstructed general population in both sexes for both SBP and DBP: The highest values were observed in the 10–12 years age classes (from 16% to 41% for SBP and from 12% to 60% for DBP). This was to some extent expected given the high prevalence of excess weight in the study population (25–27).

FNF tended to decrease with increasing age. FPFs were detectable only in subjects aged 13 years or older and mostly for systolic BP in boys (from 4% to 35%). NPVs observed in the clinical study, for age and sex, are shown in Table 2. NPVs were higher than expected from the analysis of the reconstructed NHBPEP population, for both SBP and DBP in both boys and girls.

The receiver operating characteristic curves (Figure 4) showed that the IDF single cutpoints were not optimal for the girls in our overweight/obese population (Figure 4A). Particularly when using a cutpoint of 80 mm Hg for DBP, the FPF was still less than 1%, but sensitivity rose to 70%, which is remarkably greater than the 43% at the 85 mm Hg cutpoint. The same was true for SBP, where a cutpoint of 125 mm Hg increased the sensitivity from 45% (at the 130 mm Hg cutpoint) to 82% while increasing the FPF only from 0% to 4%. For boys (Figure 4B), the systolic IDF cutpoint performed better, while for DBP a cutpoint of 80 mm Hg increased the sensitivity from 53% to 94% with the FPF still lower than 1%.

Table 2. Negative Predictive Values and Percentage of Hypertensive Subjects, for Systolic and Diastolic Blood Pressure According to Gender and Age, Among a Clinical Sample of Overweight/Obese Adolescents Recruited From Pediatric Centers ($n = 1,162$), Italy and Spain, 1998–2000

| Sex and Age, years | NPV, % | Theoretical NPV ^a , % | % Hypertensive | % Normotensive |
|---------------------------------|--------|----------------------------------|----------------|----------------|
| <i>Systolic Blood Pressure</i> | | | | |
| Male | | | | |
| 10 | 91 | 81 | 20 | 80 |
| 11 | 92 | 73 | 27 | 73 |
| 12 | 95 | 85 | 24 | 76 |
| 13 | 100 | 89 | 20 | 80 |
| 14 | 97 | 90 | 31 | 69 |
| 15 | 100 | 95 | 29 | 71 |
| Female | | | | |
| 10 | 90 | 81 | 25 | 75 |
| 11 | 88 | 73 | 27 | 73 |
| 12 | 89 | 75 | 27 | 73 |
| 13 | 98 | 78 | 30 | 70 |
| 14 | 95 | 82 | 35 | 65 |
| 15 | 100 | 86 | 26 | 74 |
| <i>Diastolic Blood Pressure</i> | | | | |
| Male | | | | |
| 10 | 98 | 94 | 12 | 88 |
| 11 | 98 | 94 | 10 | 90 |
| 12 | 98 | 94 | 13 | 87 |
| 13 | 99 | 95 | 9 | 91 |
| 14 | 100 | 91 | 18 | 82 |
| 15 | 100 | 97 | 11 | 89 |
| Female | | | | |
| 10 | 88 | 84 | 20 | 80 |
| 11 | 89 | 85 | 18 | 82 |
| 12 | 93 | 87 | 23 | 77 |
| 13 | 100 | 94 | 12 | 88 |
| 14 | 100 | 96 | 8 | 92 |
| 15 | 100 | 99 | 6 | 94 |

Abbreviation: NPV, negative predictive value.

^a Values from the analysis of a reconstructed general population, based on the distributions tabulated by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, are reported for comparison (15).

DISCUSSION

Our work highlights the potential pitfalls of adopting a single BP cutpoint for the whole age range of 10–16 years. Until recently, elevated blood pressure in children has been defined worldwide defined according to the 95th percentile for age, sex, and height percentile (15). At the present time, there are no outcome data from long-term longitudinal surveys that

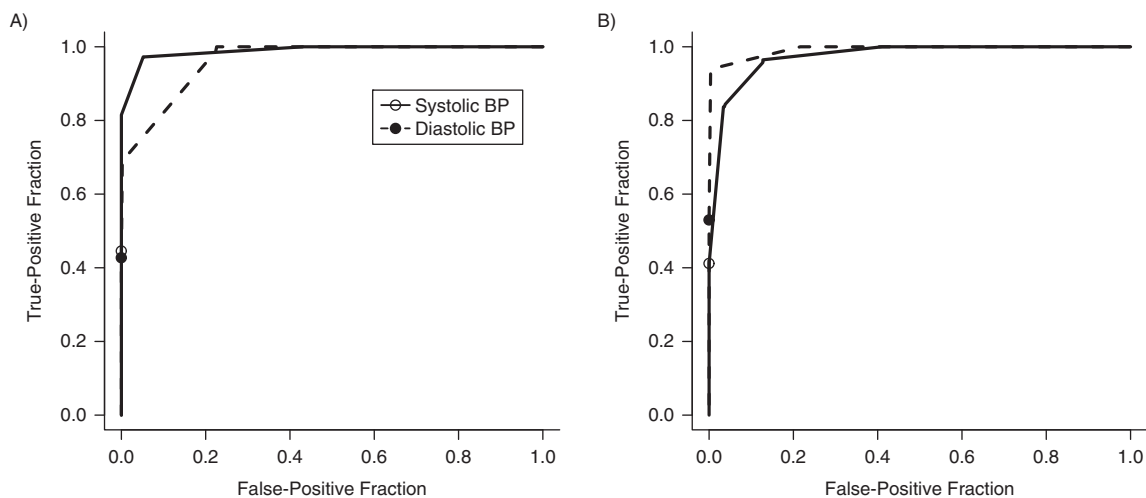


Figure 4. Receiver operating characteristic curves for a comparison of high blood pressure (BP) criteria among 1,162 overweight/obese adolescent boys and girls, Italy and Spain, 1998–2000. The criteria of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents were the reference standard (15). For diastolic BP (dashed line), we let the cutoff vary from 45 mm Hg (upper right) to 100 mm Hg (lower left), and for systolic BP (solid line) from 70 (upper right) to 150 (lower left). The empty and solid circles represent the International Diabetes Federation cutoffs for systolic (≥ 130 mm Hg) and diastolic (≥ 85 mm Hg) BP.

enable us to identify which BP values at pediatric ages are associated with health consequences later in life. However, NHBPEP-defined hypertension has been associated with early organ damage in several studies (17, 18). In addition, the existence of tracking from elevated blood pressure in childhood to hypertension later in life (28, 29), together with the well-known impact of hypertension on the risk of cardiovascular events in adults, suggests the presence of a relationship between elevated blood pressure in childhood and cardiovascular risk in adulthood. Pediatric researchers have derived age- and sex-specific cutpoints for other MS risk factors (i.e., body mass index and lipid parameters) from adult thresholds, using LMS growth-curve regression methods (30, 31), but this approach has not yet been reported for BP (32). The IDF consensus group (12) adopted the same cutpoints used for the adult MS definition (33) without taking age-related fluctuations into account. This definition has been used in recent literature (13). By contrast, the established NHBPEP criteria are based on values ≥ 95 th percentile by age, sex, and height percentile. This is a typical complexity encountered in growing populations, in which developmental changes modify blood pressure level. However, it must be pointed out that pediatricians are very familiar with the concept of percentiles—for example, for the assessment of anthropometric measurements, using growth charts. Consequently, we think that simplified single-cutpoint criteria, even if easier to use, should be recommended only after a careful evaluation of the potential classification errors.

This distributional approach has the advantage of giving a definition of pre-HBP, as a value of SBP or DBP at or above the 90th percentile but lower than the 95th percentile (26, 34). Even weaker conditions, such as transient hypertension/prehypertension in children, have received attention in the literature of late (26), and recent data have shown a

relationship between hypertension staging and the risk of left ventricular hypertrophy in adolescents (17, 18).

With an innovative approach, we showed that using the proposed IDF cutpoints can lead to an elevated percentage of false negatives, especially in younger subjects; however, a minimal degree of false positives in older subjects also has to be taken into account. This is probably due to the overt conservative quality of the IDF's proposed strategy, which does not differ by age. FNFs were higher for SBP than for DBP and for girls compared with boys. Both FNFs and FPFs were also affected by the subject's height, with increased false negatives in shorter subjects and false positives in taller ones. In general, NPVs seemed relatively high only for populations with low HBP prevalence but reduced in those with increased hypertension prevalence. However, this could delay the diagnosis of being at risk of MS as well as the subsequent adoption of preventive non-pharmacological strategies.

Among the clinical sample, 32% of overweight/obese subjects had HBP according to NHBPEP definition—a percentage similar to previously published data in overweight/obese adolescents (19, 35, 36). When the IDF criteria were used, we found a false-negative rate of 22% and a false-positive rate of 2%. In particular, the proposed single cutpoints of ≥ 130 mm Hg for SBP and ≥ 85 mm Hg for DBP underestimate HBP in children up to 13 years of age and overestimate HBP in a small proportion of older subjects, suggesting that the IDF criteria can be used, at most, to rule in elevated blood pressure. NPVs were higher among the clinical sample than expected, based on the analysis of the reconstructed general population, for SBP and DBP in both sexes. This finding was due to the shift of the BP distributions toward the higher values found in obese or overweight children, as compared with normal-weight children,

independently from the diagnosis of HBP (25). However, even if they were higher than expected, NPVs were far from what is needed from an optimal diagnostic tool: Optimal NPVs ($\geq 95\%$) were reached only in the 13–15 years age classes.

A limitation of this study is that the clinical sample is relatively small. The decision to use the reconstructed general population was motivated mainly to support, from a theoretical point of view, the results of the analysis of the clinical population. However, generalizability to populations with different ethnic and height distributions cannot be presumed. We chose an overweight/obese population because the IDF definition of MS requires abdominal obesity as a mandatory criterion.

We think that an ideal diagnostic tool for HBP should have a minimal rate of false negatives in order to identify and treat all subjects at risk, because even mild BP elevation has been shown to be associated with health consequences in adolescents (37–40). Moreover, there are recent suggestions that using simplified dichotomized cutoffs for other criteria used for MS diagnosis actually does miss a relevant proportion of adolescents with MS (40, 41). We acknowledge that the percentile method is very cumbersome to use. However, we feel that the desirable effort to simplify hypertension diagnosis, as in the spirit of the IDF proposal, seems to be undermined by the high clinical cost of undiagnosed HBP in adolescents and the subsequent lack of adequate management of affected patients.

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REFERENCES

1. Kahn R. Metabolic syndrome: is it a syndrome? Does it matter? *Circulation*. 2007;115(13):1806–1810.
2. Beaser RS, Levy P. Metabolic syndrome: a work in progress, but a useful construct. *Circulation*. 2007;115(13):1812–1818.
3. Goodman E, Daniels SR, Meigs JB, et al. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation*. 2007;115(17):2316–2322.
4. Golley RK, Magarey AM, Steinbeck KS, et al. Comparison of metabolic syndrome prevalence using six different definitions in overweight pre-pubertal children enrolled in a weight management study. *Int J Obes (Lond)*. 2006;30(5):853–860.
5. Steinberger J, Daniels SR, Eckel RH, et al. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2009;119(4):628–647.
6. Balkau B, Charles MA, Drivsholm T, et al. Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab*. 2002;28(5):364–376.
7. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539–553.
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497.
9. Brambilla P, Lissau I, Flodmark CE, et al. Metabolic risk-factor clustering estimation in children: to draw a line across pediatric metabolic syndrome. *Int J Obes (Lond)*. 2007;31(4):591–600.
10. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. *Cardiovasc Diabetol*. 2008;7:17.
11. Zimmet P, Alberti G, Kaufman F, et al. The metabolic syndrome in children and adolescents. *Lancet*. 2007;369(9579):2059–2061.
12. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents—an IDF consensus report. *Pediatr Diabetes*. 2007;8(5):299–306.
13. Elizondo-Montemayor L, Serrano-González M, Ugalde-Casas PA, et al. Metabolic syndrome risk factors among a sample of overweight and obese Mexican children. *J Clin Hypertens (Greenwich)*. 2010;12(5):380–387.
14. Tavares Giannini D, Caetano Kuschnir C, Szklo M. Metabolic syndrome in overweight and obese adolescents: a comparison of two different diagnostic criteria. *Ann Nutr Metab*. 2014;64(1):71–79.
15. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(suppl 2):555–576.
16. Leccia G, Marotta T, Masella MR, et al. Sex-related influence of body size and sexual maturation on blood pressure in adolescents. *Eur J Clin Nutr*. 1999;53(4):333–337.

17. Pieruzzi F, Antolini L, Salerno FR, et al. The role of blood pressure, body weight and fat distribution on left ventricular mass, diastolic function and cardiac geometry in children. *J Hypertens*. 2015;33(6):1182–1192.
18. McNiece KL, Gupta-Malhotra M, Samuels J, et al. Left ventricular hypertrophy in hypertensive adolescents: analysis of risk by 2004 National High Blood Pressure Education Program Working Group staging criteria. *Hypertension*. 2007;50(2):392–395.
19. Sorof JM, Lai D, Turner J, et al. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics*. 2004;113(3):475–482.
20. Lande MB, Pearson TA, Vermilion RP, et al. Elevated blood pressure, race/ethnicity, and C-reactive protein levels in children and adolescents. *Pediatrics*. 2008;122(6):1252–1257.
21. Lohman TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Books; 1988.
22. Kuczumski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data*. 2000;314:1–27.
23. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child*. 1976;51(3):170–179.
24. Pepe MS. *The Statistical Evaluation of Medical Tests for Classification and Prediction*. 1st ed. Oxford, UK: Oxford University Press; 2004.
25. Genovesi S, Giussani M, Pieruzzi F, et al. Results of blood pressure screening in a population of school-aged children in the province of Milan: role of overweight. *J Hypertens*. 2005;23(3):493–497.
26. Genovesi S, Antolini L, Giussani M, et al. Hypertension, prehypertension, and transient elevated blood pressure in children: association with weight excess and waist circumference. *Am J Hypertens*. 2010;23(7):756–761.
27. Genovesi S, Antolini L, Giussani M, et al. Usefulness of waist circumference for the identification of childhood hypertension. *J Hypertens*. 2008;26(8):1563–1570.
28. Oikonen M, Nuotio J, Magnussen CG, et al. Repeated blood pressure measurements in childhood in prediction of hypertension in adulthood. *Hypertension*. 2016;67(1):41–47.
29. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. 2008;117(25):3171–3180.
30. Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240–1243.
31. Jolliffe CJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. *Circulation*. 2006;114(10):1056–1062.
32. Rosner B, Cook N, Portman R, et al. Determination of blood pressure percentiles in normal-weight children: some methodological issues. *Am J Epidemiol*. 2008;167(6):653–666.
33. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006;23(5):469–480.
34. Genovesi S, Brambilla P, Giussani M, et al. Insulin resistance, prehypertension, hypertension and blood pressure values in paediatric age. *J Hypertens*. 2012;30(2):327–335.
35. Lurbe E, Alvarez V, Liao Y, et al. The impact of obesity and body fat distribution on ambulatory blood pressure in children and adolescents. *Am J Hypertens*. 1998;11(4):418–424.
36. Reich A, Müller G, Gelbrich G, et al. Obesity and blood pressure—results from the examination of 2365 schoolchildren in Germany. *Int J Obes Relat Metab Disord*. 2003;27(12):1459–1464.
37. Hanevold C, Waller J, Daniels S, et al. The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. *Pediatrics*. 2004;113(2):328–333.
38. Daniels SR, Loggie JM, Khoury P, et al. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. *Circulation*. 1998;97(19):1907–1911.
39. Sun SS, Grave GD, Siervogel RM, et al. Systolic blood pressure in childhood predicts hypertension and metabolic syndrome later in life. *Pediatrics*. 2007;119(2):237–246.
40. Kelly AS, Steinberger J, Jacobs DR, et al. Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. *Int J Pediatr Obes*. 2011;6(2–2):e283–e289.
41. Andersen LB, Lauersen JB, Brønd JC, et al. A new approach to define and diagnose cardiometabolic disorder in children. *J Diabetes Res*. 2015;2015:539835.