A Non-invasive Model for Detection of Undiagnosed Metabolic Syndrome in School Children and Adolescents

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Abstract

Background: We aimed to develop a non-invasive model to detect the metabolic syndrome (MetS) in school children and adolescents.

Methods: Participants were 7,330 children and adolescents aged 10–18 years, attending schools in eight Chinese localities. Participants had anthropometry measured and underwent fasting blood tests. MetS was defined as central obesity and a combination of abnormal glycaemia, hypertension, and/or dyslipidaemia. A prediction model for MetS was developed using non-invasive anthropometric and clinical parameters.

Results: The prediction model had acceptable discrimination accuracy (AUROC 0.75) and 65.7% sensitivity. While its PPV was 36.5%, 72.2% of false-positives had one other metabolic abnormality beyond central adiposity. An alternative mixed process was developed: first, all children with central adiposity and hypertension were considered as cases; secondly, a prediction model was developed on remaining normotensive children with central adiposity, yielding possibly-helpful discrimination (AUROC 0.67). This combined approach yielded higher sensitivity (75.4%) but lower PPV (30.7%) with more false-positives, of whom 57.0% had one other metabolic abnormality beyond central adiposity.

Conclusions: Most undiagnosed MetS cases could be detected in school children and adolescents with non-invasive methods. Importantly, most false-positive cases had metabolic abnormalities, so that the vast majority of cases identified by the models warranted medical follow-up.

Introduction

Obesity has emerged as one of the most serious public health concerns among children, adolescents and adults in the 21st century. The worldwide prevalence of childhood obesity has increased strikingly over the past 3 decades, increased from 0.7% in 1975 to 5.6% in 2016 in girls, and from 0.9% in 1975 to 7.8% in 2016 in boys[1, 2]. East Asia, the Middle East and north Africa, south Asia were those regions with the largest absolute increase in the number of children and adolescents with obesity[2]. In some of the largest cities in China, the prevalence of obesity among children aged 7–18 years in 2000 ranged from 9.9–11.3% in boys and 5.9–8.2% in girls[3]. By 2013, the prevalence of childhood obesity in China showed a marked increase, with 23.0% of boys and 14.0% of girls aged 2–19 years reported as overweight and/or obese[4]. The progression to obesity appears to be occurring rapidly, and Cai et al. reported that 2.8% of normal-weight children had developed obesity at follow-up 9 months later[5].

Obesity in childhood and adolescence tends to persist into adulthood[6, 7]. Importantly, obesity in childhood and adolescence is associated with a number of adverse physical and psychological outcomes, not only in the short-term but also in the long-term, including increased risk of morbidity and premature mortality[8–10]. Obesity is a pro-inflammatory state that adversely affects nearly every organ system and often has serious consequences, including hypertension, dyslipidemia, insulin resistance, and type 2 diabetes mellitus[11]. Obesity is associated with insulin resistance[12], which is the common

underlying factor leading to many of the metabolic and cardiovascular complications of obesity, being also the key factor for the group of metabolic disturbances collectively referred to the metabolic syndrome (MetS)[11]. Together, obesity and the MetS are associated with markedly increased risk of cardiometabolic diseases, several forms of cancer[13, 14], as well as a number of adverse psychosocial outcomes including depression, anxiety, and eating disorder[8, 15].

Children with obesity are at a much greater risk of developing MetS. The worldwide MetS prevalence in children and adolescents varies according to the adopted definition, but estimates based on the International Diabetes Federation (IDF) definition vary widely from 0.9–11.4% [16–18]. A recent review reported that the prevalence of MetS in the general population was 3.3%, but 11.9% in overweight children and 29.2% in those with obesity[19, 20]. Notably, the prevalence of MetS in children and adolescents is greater in boys than in girls (5.1% vs 3.0%, respectively)[21]. In China, a 2015 meta-analysis estimated the prevalence of MetS (as per IDF) at 2.9% in boys and 1.8% in girls, but 0.2% in children with normal weight, 4.7% in those with overweight, and 17.3% in youth with obesity[22]. However, the exact prevalence seems to vary depending on the adopted definition, ranging from 3.3–5.4% among children aged ≥ 10 years [18, 23, 24].

The definition of MetS may vary to some extent, but all include a measure of central adiposity in addition to the following key characteristics: hyperinsulinemia or insulin resistance, dyslipidemia, hypertension, and diabetes or pre-diabetes. Thus, to diagnose MetS it is necessary to draw fasting blood samples to measure fasting glucose and lipid profile. As a result, it is not possible to diagnose MetS by non-invasive means, which makes it difficult to identify children and adolescents with this condition in non-clinical community settings. Thus, we aimed to develop a prediction model for the MetS without the use of invasive methods (i.e. blood samples) for children and adolescents. It is important to detect the MetS in youth as early as possible, so that clinical intervention can halt its progress to more serious metabolic dysfunctions, in particular type 2 diabetes mellitus and cardiovascular disease.

Methods

Ethics approval

The original study was approved by the Medical Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine, which was the lead centre (#2009013). Written informed consent from parents (or guardians) and children (where appropriate) were obtained, but this study involved solely the use of anonymized data. This study was conducted according to the guidelines of the Declaration of Helsinki

Study population

Participants were children and adolescents aged ≥10 but <18 years of age attending schools in 2009–2010 in eight cities across China, namely Beijing, Chongqing, Hangzhou, Lanxi, Nanning, Shanghai,

Tianjin, and Xiaoshan. Exclusion criteria for this study was any pre-diagnosed chronic heart, lung, kidney, endocrine, or metabolic disease.

Participants underwent clinical assessments at their school performed by research nurses, while wearing examination gowns. Standing height was measured to the nearest mm using a stadiometer, while bare feet. Weight was measured with electronic scales to the nearest 0.1 kg, and body mass index (BMI) calculated as per standard formula. The hip circumference was measured around the fullest part of the hips with the participant standing straight with their feet together. Waist circumference was measured to the nearest mm with a tape measure around the participant's body in the horizontal plane, at the level of the midpoint between the lowest rib and the iliac crest, on bare skin when in a state of expiration. Waist-to-hip and waist-to-height ratios were subsequently calculated.

Systolic (SBP) and diastolic (DBP) blood pressures were measured using a sphygmomanometer on the right upper arm while seated, and after a 5-minute rest. Blood pressure was measured twice, and the average of the two measurements recorded. The presence of acanthosis nigricans was diagnosed by the research nurses, as it is recognized as an important risk factor for the diagnosis of MetS[25].

All participants underwent blood tests on the morning of the assessment after an overnight fast, when venous blood samples were drawn. Fasting glucose and lipid profile were assessed, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol. In addition, all participants underwent a simplified oral glucose tolerance test after receiving an oral glucose solution (3.75 g/kg), with blood samples drawn at 0 and 120 minutes.

Definition of metabolic syndrome

The International Diabetes Federation (IDF) criteria for the MetS must include central obesity, which is usually defined as waist circumference ≥90th percentile for age and sex[18]. In China, apart from the IDF criteria, MetS is also defined based on waist-to-height ratio as it is easier to adopt in routine clinical practice without the need to refer to standardized charts[26]. According to the 2012 guideline[24] from the Chinese Medical Association, the MetS can be diagnosed in children and adolescents aged 10 to 18 years of age as:

1) Central obesity: waist circumference ≥90th percentile for age and sex, which is equivalent to a waist-to-height ratio ≥0.48 for boys and ≥0.46 for girls in China[27].

AND

2) Any two of the following:

a) Fasting triglycerides ≥1.47 mmol/L;

b) Fasting HDL <1.03 mmol/L OR non-HDL-C ≥76 mmol/L;

c) Hypertension defined as SBP ≥130 mmHg OR DBP ≥85 mmHg;

d) Impaired fasting glucose (≥6 mmol/L) OR impaired glucose tolerance (2-hour blood glucose ≥7.8 and <11.1mmol/L) OR type 2 diabetes.

Prediction model

We used a combination of screening tools based on readily obtained clinical characteristics and a prediction model to identify youth with MetS using non-invasive methods. In addition, it should be noted that international guidelines discourage the diagnosis of the MetS in children younger than 10 years of age. Thus, our study population included only participants aged ≥10 years. As a result, a total of 7,330 children and adolescents with complete anthropometric and clinical data were included (Supplementary Figure S1).

A number of anthropometric, demographic, and clinical parameters were evaluated for inclusion in a prediction model, namely BMI, waist-to-hip ratio, waist-to-height ratio, age, sex, SBP, DBP, and the presence of acanthosis nigricans. Pairwise associations between continuous variables were examined to identify cases of high collinearity based on Pearson's correlation coefficients. In the event of high collinearity (|r| ≥0.5), one parameter was eliminated according to its practicality in routine practice.

The model's discrimination was estimated using the area under the receiver operating characteristic curve (AUROC), as follows: poor (<0.60), possibly helpful (≥0.60 and <0.70), acceptable (≥0.70 and <0.80), excellent (≥0.80 and <0.90), and outstanding (≥0.90)[28, 29]. Model calibration (i.e. the extent to which it correctly estimates risk[28]) was assessed as per Hosmer-Lemeshow test[29], with satisfactory calibration identified as p>0.05.

Selected parameters were included as predictors in a logistic regression model, where the outcome was MetS. Multiple iterations of the model were developed, with model discrimination and calibration assessed, until the most parsimonious model with the best discrimination was reached. Once the final model was developed, its accuracy and predictive capacity were assessed using the following parameters:

$$Sensitivity = \frac{\text{n true positives}}{(\text{n true positives} + \text{n false negatives})}$$

$$Specificity = \frac{\text{n true negatives}}{(\text{n true negatives} + \text{n false positives})}$$

$$Positive\ predictive\ value\ (PPV) = \frac{\text{n true positives}}{(\text{n true positives} + \text{n false positives})}$$

$$Negative\ predictive\ value\ (NPV) = \frac{\text{n true negatives}}{(\text{n true negatives} + \text{n false negatives})}$$

We have defined the threshold for MetS diagnosis at or above the 67th percentile of the probability distribution (i.e. the top tertile). Statistical analyses were performed in SPSS v25 (IBM Corp, Armonk, NY, USA) and SAS v9.4. There was no imputation of missing data.

Results

There were 289 MetS cases in our study population, so that the overall prevalence was 3.9% (Table 1). A total of 1,561 individuals (21.3%) had central obesity (Table 1), i.e. the mandatory requirement to meet the Chinese criteria for MetS, and these participants were considered for the prediction model development (Supplementary Table S1).

Table 1
Demographic and clinical data on the study population.

n		**7,330**
Age (years)		12.8 [11.4, 13.9]
Sex ratio (males)		4,093 (55.8%)
Child BMI status [1]	**Underweight/normal weight**	5,285 (72.1%)
	Overweight	775 (10.6%)
	Obesity	1,270 (17.3%)
Hypertension		605 (8.3%)
Acanthosis nigricans		320 (4.4%)
Abnormal glycaemia		676 (9.2%)
Abnormal triglycerides		968 (13.2%)
Dyslipidaemia		1,062 (14.5%)
Metabolic syndrome		289 (3.9%)
Central obesity [2]		1,561 (21.3%)
Age data are median [quartile 1, quartile 3]; all other data are n (%).		
BMI, body mass index.		
[1] Underweight/normal weight was defined as BMI < 1.036 standard deviation scores (SDS), overweight ≥ 1.036 SDS and < 1.645 SDS, and obesity ≥ 1.645 SDS, according to WHO standards.		
[2] Defined as a waist-to-height ratio ≥ 0.48 for boys and ≥ 0.46 for girls.		

Prediction model

The final prediction model for MetS included as predictors age, waist-to-height ratio, hypertension (yes vs no), acanthosis nigricans (yes vs no), and sex (Supplementary Table S2). The model's discrimination was acceptable (AUROC 0.75; 95% CI 0.72, 0.79) and was satisfactory calibrated (Hosmer-Lemeshow test p = 0.76); its detailed performance is outlined in Fig. 1. The model's sensitivity was 65.7%, detecting 190 of the 289 MetS cases in the population, so that the PPV was 36.5% (Table 2). Of the 320 false-positive cases, 231 (72.2%) had one other MetS parameter beyond central adiposity (Table 2). Notably, the cases identified by the model as likely to have MetS included all individuals who were hypertensive.

Table 2
Performance of the two models developed for the prediction of metabolic syndrome (MetS) in children and adolescents in China.

	Prediction model	Hypertension + Prediction model
MetS cases in population (n)	289	289
Total with central adiposity (n)	1,561	1,561
Total number predicted to have MetS [n (%)]	520 (33.3%)	711 (45.5%)
Real cases of MetS detected (n)	190	218
Sensitivity (%)	65.7%	75.4%
Specificity (%)	74.1%	61.2%
Positive predictive value (%)	36.5%	30.7%
Negative predictive value (%)	90.5%	91.8%
Wrong predictions with 1 MetS component [n (%)]	231 (44.4%)	281 (39.5%)
Wrong predictions otherwise healthy [n (%)]	99 (19.0%)	212 (29.8%)

Mixed approach

As hypertension in children and adolescents is a condition that warrants clinical intervention, we also developed a mixed approach based on the presence or absence of hypertension followed by the implementation of a prediction model. The detailed performance of this mixed approach is described in Fig. 2. Overall, 287 children and adolescents had hypertension (18.4%), of whom 48.4% had MetS (Fig. 2).

The associated prediction model was developed on the normotensive population (n = 1,274; Supplementary Table S3), and the final predictors included were age, waist-to-hip ratio, BMI, acanthosis nigricans, and sex (Supplementary Table S4). Its discrimination was worse than the overall model, deemed as possibly helpful (AUROC 0.66; 95% CI 0.61, 0.71), although it was satisfactorily calibrated (Hosmer-Lemeshow test p = 0.41).

The mixed approached detected three-quarters (n = 218) of all MetS cases in the population (sensitivity 75.4%), with a PPV of 30.7% (Table 2). It detected a greater number of false-positive cases (n = 493), of whom 57.0% (n = 281) had one other MetS parameter beyond central adiposity, with the remaining 212 cases being otherwise healthy (Table 2).

Discussion

We observed that 3.9% of our population of school children and adolescents had undiagnosed MetS (298 cases). Obesity and MetS are strong risk factors for increased morbidity and mortality in both short- and long-terms[11, 30]. In particular, the presence of the MetS per se in childhood is predictive of cardiovascular and metabolic disease in adulthood many years later[30, 31]. Thus, early diagnosis of MetS is important, so that early intervention can halt its progression to type 2 diabetes and other severe cardiometabolic complications.

We showed that it is possible to detected most cases of undiagnosed MetS in children and adolescents using non-invasive school-based assessments. While the two methods described detected a number of false-positive cases, the vast majority of these had central adiposity as well as another MetS component, so that referral for medical follow-up would be warranted.

However, the proper diagnosis of MetS requires examinations that are invasive and costly. Thus, they are not appropriate or viable to be applied at a population level, particularly for children and adolescents. While several studies have previously developed risk scores for the prediction of the MetS in children and adolescents, the vast majority of these relied on parameters derived from invasive methods (i.e. blood samples)[32–38]. A limited number of studies have relied on non-invasive methods for the prediction of MetS in youth[39, 40]. Ramírez-Vélez et al.'s proposed the use of the triponderal index for MetS diagnosis amongst youth in Colombia[39]. In Brazil, Oliveira & Guedes also proposed the use of single indicators for MetS diagnosis in children and adolescents[40], specifically waist circumference, BMI, and/or waist-to-height ratio. However, the suggested cut-offs in those studies are likely to be population-specific, as they have very poor accuracy in our cohort, with the Colombian model classifying over half of our cohort as having MetS, while the Brazilian model would classify as such 20 to 29% of our participants depending on the parameter used (c.f. our actual MetS prevalence of 3.9%). Thus, it is likely that the use of a single parameter is unlikely to be applicable across different populations and ethnic groups. It would therefore be of interest, to have our proposed model validated in other ethnicities.

According to the National Health and Nutrition Examination Survey from 2011 to 2014, 29% of adults have hypertension, with non-Hispanic blacks having the highest prevalence of 41.2%[41]. Current epidemiological data suggest that the prevalence of pediatric hypertension is 0.04%, while at least 1 in 10 children is prehypertensive[42]. Among the obese children, the prevalence of hypertension is about 11% in USA and Asia[43, 44]. These studies also showed that increased prevalence of pediatric hypertension is associated with the obesity epidemic.

As hypertension is an important component of the metabolic syndrome and a modifiable risk factor for cardiovascular disease, our mixed approached was developed on the assumption that children and adolescents with both central obesity and hypertension should be referred for medical follow-up, irrespective of the presence of additional metabolic abnormalities. As a result, we propose a decision-making process that could be adopted in schools that would likely identify most youth with MetS, as well as large number of children and adolescents with other cardiometabolic abnormalities (Fig. 3). We

believe that it would be possible to apply this proposed system in schools, which would rely on school nurses and doctors, but would require a relatively limited amount of resources.

Our study has several limitations. First, while our model was developed from a large population sample, we were not able to validate our findings in other cohorts. This was especially a result of missing data on key parameters for a large proportion of the overall cohort. In addition, our model was developed for a rather homogeneous population composed in its vast majority by Han Chinese, so that our findings cannot be directly extrapolated to other populations without adequate validation. Nonetheless, key strengths of our study include a large data set collected on children across 8 different Chinese cities by trained research nurses, so that none of our anthropometric or clinic data relied on self report.

Conclusions

Using a large cohort of children and adolescents in China, we developed relatively simple models for detection of metabolic syndrome based on non-invasive parameters that are readily obtained in schools and other community settings. Early detection of MetS and other cardiometabolic abnormalities in children and adolescents is important to halt its progression to type 2 diabetes and other more severe conditions. Our proposed decision-making model has the potential to be widely implemented in schools and other community settings. Thus, it would be important to validate it in other cohorts to ascertain its accuracy.

Declarations

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Author contributions: JFF were responsible for funding acquisition; HL, JFF, and JGBD conceived and designed the study; JFF, LL, CG, FL, GL, FX, SC, GD, KH, CW, and XC had oversight over data collection; YH, JY, HL, and JGBD and were responsible for data curation, translation, checking, and cleaning; JGBD was responsible for data analysis; HL and JGBD wrote the manuscript with critical input from all other authors; All authors have approved the submission of the final version of this manuscript.

Conflicts of interest: This was an investigator-initiated study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript. The authors have no financial or non-financial conflicts of interest to disclose that may be relevant to this study.

Data availability statement: The study data cannot be made available in a public repository due to the strict conditions of the ethics approval. However, the anonymised data on which this manuscript was based could be made available to other investigators upon bona fide request, and following all the necessary approvals (including ethics) of the detailed study proposal and statistical analyses plan. Any queries should be directed to Prof JunFen Fu (fjf68@qq.com).

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Figures

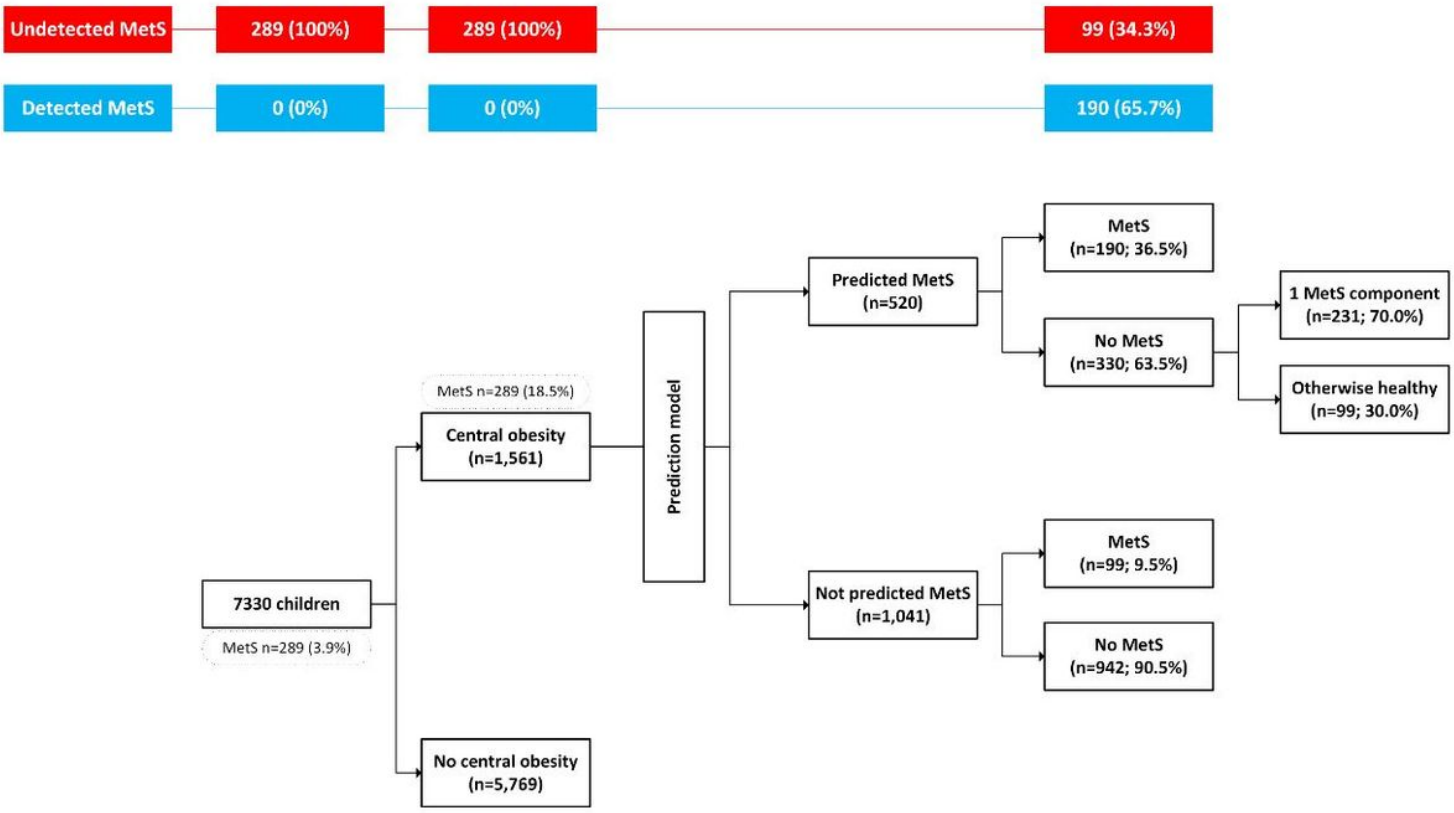

Figure 1

Detailed performance of a prediction model for the detection of the metabolic syndrome (MetS) among children and adolescents in China.

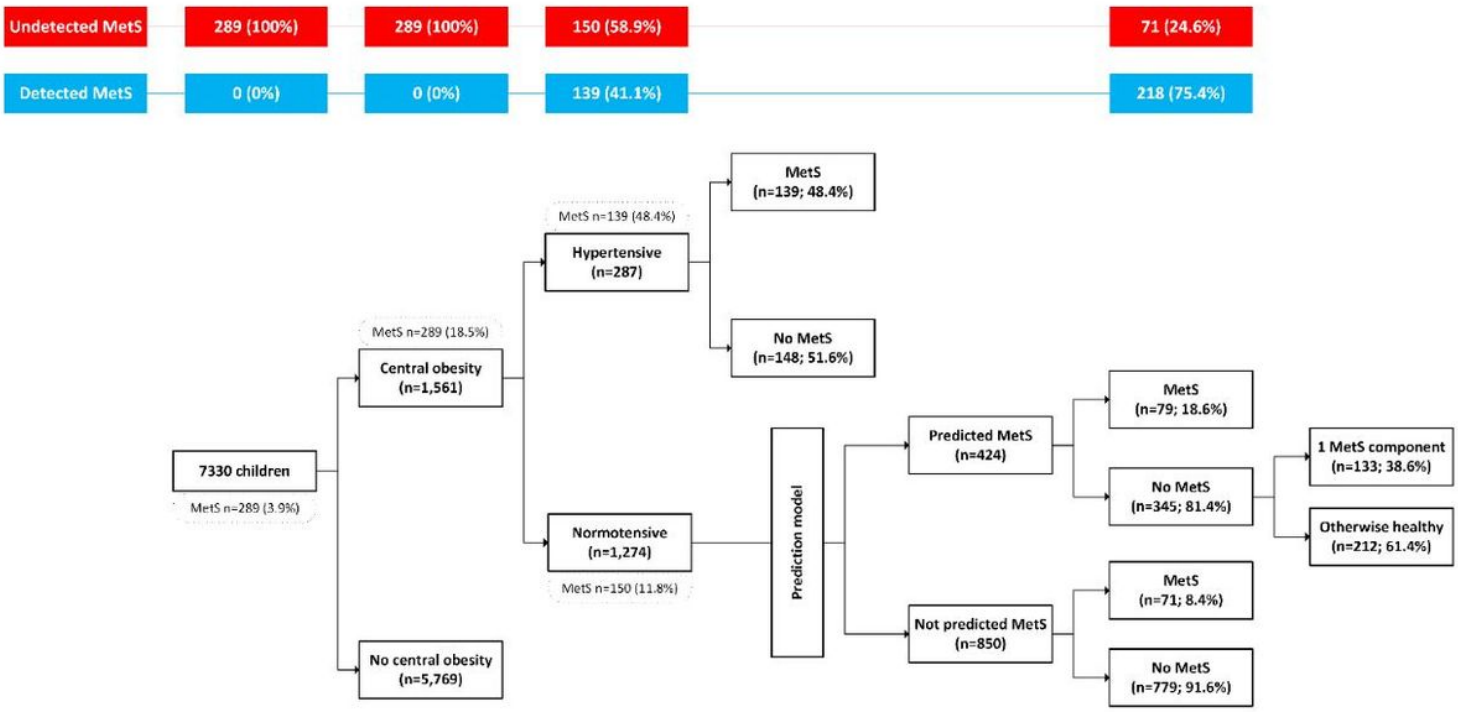

Figure 2

Detailed performance of a mixed approach incorporating hypertension and a prediction model for the detection of the metabolic syndrome (MetS) among children and adolescents in China.

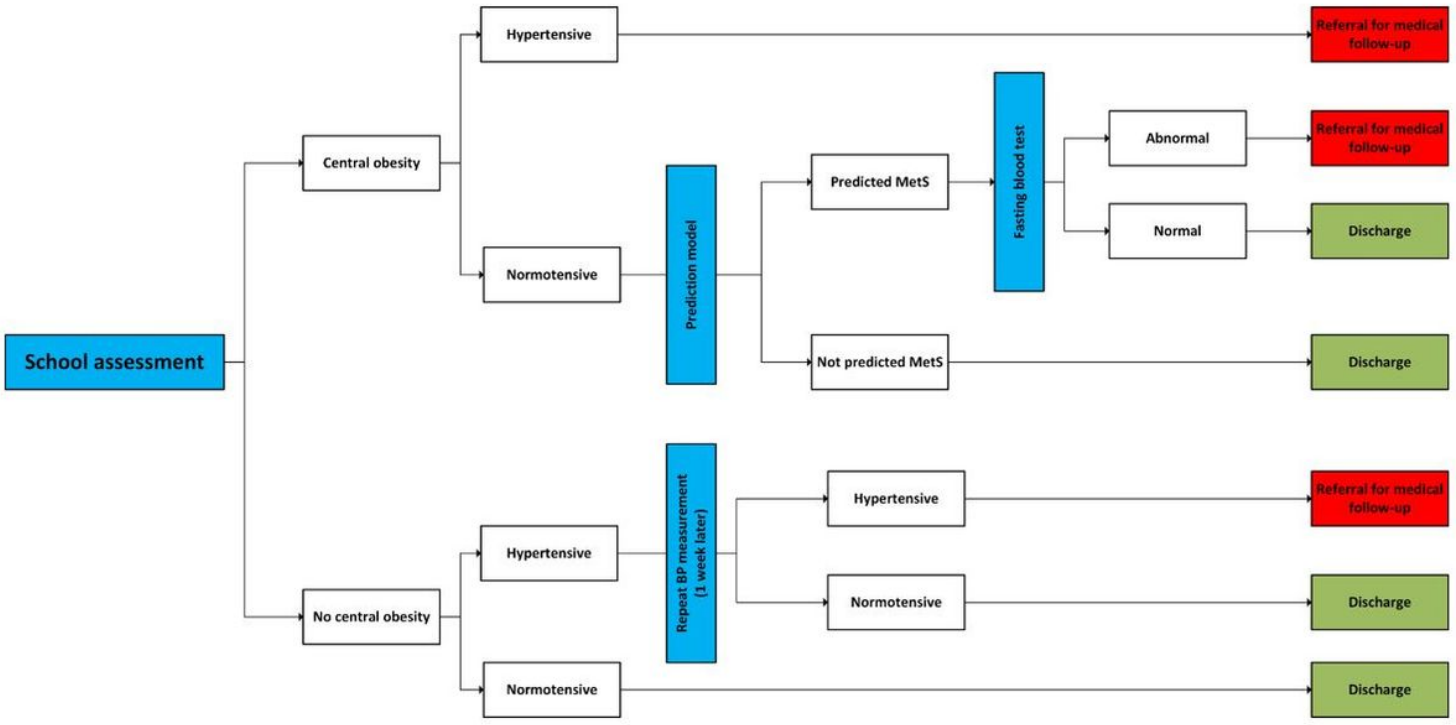

Figure 3

Proposed decision-making model for for the detection of the metabolic syndrome (MetS) and associated cardiometabolic abnormalities among children and adolescents in China.

Supplementary Files

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- SupplementaryMaterial.pdf