Establish a noninvasive model to screen metabolic dysfunction-associated steatotic liver disease in children aged 6–14 years in China and its applications in high-obesity-risk countries and regions

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Summary

Background The prevalence of metabolic-associated steatotic liver disease (MASLD) is rising precipitously among children, particularly in regions or countries burdened with high prevalence of obesity. However, identifying those at high risk remains a significant challenge, as the majority do not exhibit distinct symptoms of MASLD. There is an urgent need for a widely accepted non-invasive predictor to facilitate early disease diagnosis and management of the disease. Our study aims to 1) evaluate and compare existing predictors of MASLD, and 2) develop a practical screening strategy for children, tailored to local prevalence of obesity.

Methods We utilized a school-based cross-sectional survey in Beijing as the training dataset to establish predictive models for screening MASLD in children. An independent school-based study in Ningbo was used to validate the models. We selected the optimal non-invasive MASLD predictor by comparing logistic regression model, random forest model, decision tree model, and support vector machine model using both the Beijing and Ningbo datasets. This was followed by serial testing using the best performance index we identified and indices from previous studies. Finally, we calculated the potential MASLD screening recommendation categories and corresponding profits based on national and subnational obesity prevalence, and applied those three categories to 200 countries according to their obesity prevalence from 1990 to 2022.

Findings A total of 1018 children were included ($N_{Beijing}$ = 596, N_{Ningbo} = 422). The logistic regression model demonstrated the best performance, identifying the waist-to-height ratio (WHtR, cutoff value ≥0.48) as the optimal noninvasive index for predicting MASLD, with strong performance in both training and validation set. Additionally, the combination of WHtR and lipid accumulation product (LAP) was selected as an optimal serial test to improve the positive predictive value, with a LAP cutoff value of ≥668.22 cm × mg/dL. Based on the obesity prevalence among 30 provinces, three MASLD screening recommendations were proposed: 1) "Population-screening-recommended": For regions with an obesity prevalence ≥12.0%, where MASLD prevalence ranged from 5.0% to 21.5%; 2) "Resources-permitted": For regions with an obesity prevalence between 8.4% and 12.0%, where MASLD prevalence ranged from 2.3% to 4.4%; 3) "Population-screening-not-recommended": For regions with an obesity

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prevalence <8.4%, where MASLD prevalence is difficult to detect using our tool. Using our proposed cutoff for screening MASLD, the number of countries classified into the "Population-screening-recommended" and "Resources-permitted" categories increased from one and 11 in 1990 to 95 and 28 in 2022, respectively.

Interpretation WHtR might serve as a practical and accessible index for predicting pediatric MASLD. A WHtR value ≥0.48 could facilitate early identification and management of MASLD in areas with obesity prevalence ≥12.0%. Furthermore, combining WHtR ≥0.48 with LAP ≥668.22 cm × mg/dL is recommended for individual MASLD screening. Moreover, linking these measures with population obesity prevalence not only helps estimate MASLD prevalence but also indicates potential screening profits in regions at varying levels of obesity risk.

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Keywords: Metabolic dysfunction-associated steatotic liver disease; Pediatrics; Waist-to-height ratio; Screening recommendation categories

Research in context

Evidence before this study

With the global rise in childhood obesity, there is a corresponding rise in the prevalence of metabolic-associated steatotic liver disease (MASLD). However, there remains a scarcity of widely acceptable and validated MASLD screening tools for children, both in China and worldwide. On January 15, 2024, we conducted a comprehensive literature search across the PubMed, China National Knowledge Infrastructure, and Wanfang databases. The terms ("children" OR "students" OR "teenagers" OR "adolescents") AND ("NAFLD" OR "MAFLD" OR "MASLD") AND ("screening" OR "predictor" OR "diagnosis") AND ("noninvasive parameters") were searched, focusing on articles published in English or Chinese without date restrictions. The existing literature primarily emphasizes the development of MASLD diagnostic models using blood biomarkers and imaging indicators. There has been limited exploration into MASLD diagnostic models that integrate anthropometric indicators such as body mass index (BMI) and waist-to-height ratio (WHtR). A notable collective limitation across these studies is the absence of external validation. Furthermore, none of these studies have proposed a practical MASLD screening strategy or recommendations based on local obesity characteristics specifically for children.

Added value of this study

School-based data from two cities in China were utilized to develop and validate a noninvasive predictive model for pediatric MASLD. Ultimately, WHtR was identified as the optimal predictor, with a proposed cutoff value of 0.48. Based on the close association between pediatric MASLD and obesity observed in 160,124 Chinese children, 30 provinces were categorized into three groups: 1) "Population-screening-recommended": Provinces with a pediatric prevalence of obesity ≥12.0%; 2) "Resources-permitted": Provinces with a pediatric prevalence of obesity between 8.4% and 12.0%; and 3) "Population screening-not-recommended": Provinces with a pediatric prevalence of obesity <8.4%. These classifications were then extended to 200 countries based on their obesity prevalence from 1990 to 2022. Over the past three decades, there has been significant growth in the number of countries classified into the "Population-screening-recommended" and "Resources-permitted" categories, indicating a rising burden of pediatric MASLD.

Implications of all the available evidence

The WHtR appears to be a simple, efficient, and cost-effective noninvasive index for predicting pediatric MASLD worldwide. It is recommended that MASLD screening should be extended to children aged 6–14 years with a WHtR ≥0.48 in regions where obesity prevalence ≥12.0%. For areas where the obesity data is unavailable, screening should target children with WHtR ≥0.48 and LAP ≥668.22 cm × mg/dL. The cost-effectiveness and performance of WHtR as a screening tool should be further validated in diverse populations and ethnic groups. Nevertheless, given the escalating global challenge posed by pediatric obesity and MASLD, implementing this screening tool could significantly enhance early identification and management of pediatric MASLD. This proactive approach has the potential to alleviate the disease burden of MASLD both in childhood and later stages of life.

Introduction

Nonalcoholic fatty liver disease (NAFLD), now referred to as metabolic dysfunction-associated steatotic liver disease (MASLD),[1,2] primarily involves the accumulation of excess fat in hepatic cells and stands as a predominant cause of chronic liver disease in children.[3] Globally, MASLD affects approximately 13% of children and adolescents,[4] with about two-thirds of cases potentially persisting into adulthood without detection or intervention.[5] In Chinese pediatric populations, NAFLD prevalence ranged from 4.4% to 7.0%,[6–8] and an estimated 7.0–11.2 million children aged 6–14 years.[9] Children with MASLD are at heightened risks of developing severe liver diseases early in life, as well as hypertension, metabolic syndrome, type 2 diabetes, chronic kidney disease, cardiovascular diseases, and premature mortality. These conditions impose significant healthcare and socioeconomic burdens.[10–14]

MASLD usually presents without symptoms, making detection challenging without medical equipment assistance. While liver biopsy remains the gold standard for diagnosis, its use is limited by factors such as sampling errors, costs, and the risk of bleeding.[15] Imaging techniques such as ultrasound, magnet resonance imaging (MRI), and FibroScan® improve diagnostic accuracy but are often restricted to hospital settings and rely on specialized expertise, hindering their use in population-wide screening efforts. To address these challenges, several studies have proposed predictive models for MASLD screening based on accessible parameters such as the body mass index (BMI)-z score, aspartate-aminotransferase (AST)-to-platelet ratio index (APRI),[16] fibrosis-4 (FIB-4) index,[16,17] triglyceride-glucose (TyG) index,[18] visceral adiposity index (VAI),[19] lipid accumulation product (LAP),[20] and so on.[21] Among these, models combining TyG and BMI or waist-to-height ratio (WHtR) have shown promise in predicting MASLD.[18] However, their reliance on invasive blood draws limits their scalability as screening tools for the broader pediatric population. Additionally, many of these parameters have been derived from hospital-based populations, or single-center studies, lacking comprehensive external validation. This underscores the critical need for a validated and practical screening tool that not only facilitates early detection and management by healthcare professionals but also empowers the public to take proactive health measures.

Notably, MASLD is strongly correlated with weight status across populations. Globally, 34–52% of children with obesity are affected by MASLD,[22–24] with the prevalence reaching nearly 45% in China among these individuals.[8,25] As the cost-effectiveness of screening test with defined sensitivity and specificity hinges on the prevalence of the disease, populations at high risk of obesity stand to benefit the most from the MASLD screening efforts. Recent consensus and previous recommendations advocate for screening children who are overweight or obese (OWOB) for MASLD.[14,26] However, there is currently no national or regional recommendation for population-wide MASLD screening in areas with varying prevalence rates. In response to the research priorities outlined in the recent consensus statement by Lazarus et al., 2023,[27] which emphasizes the need for evaluating risk prediction models for fatty liver disease across diverse populations, there is a clear imperative to develop and validate screening strategies that can be tailored to specific demographic groups.

In the present study, we aimed to 1) systematically evaluate and compare existing screening predictors of MASLD in two school population datasets, one for training and the another for external validation; 2) identify the optimal predictor as the screening tool of MASLD; 3) clarify the application scope of the screening tool by using the Chinese National Survey on Students' Constitution and Health (CNSSCH), which is, so far, the largest nationally representative sample of school-age children in China; and 4) widely disseminate our screening tool and recommendations to highlight trends in the number of countries necessitating screening over a span of 32-year period across 200 countries. The availability of these datasets provides an opportunity to set the cutoff threshold for further screening. It can also improve the cost-effectiveness of health monitoring and takes shortages of health resource into account, considering the uneven regional economic development and the varying weight status in children.

Methods

Participants

Two data sets were used for model development: the Beijing data encompassed a wider age range compared to the Ningbo data. Therefore, we designated the Beijing data as our training set and the Ningbo data as our validation set. The statistical power of sample size is detailed in Appendix 4 Table S1.

Training set

The data were extracted from a school-based survey which was conducted in Changping District, Beijing, in April 2023, as previously documented.[28] A total of 1500 children from grades 1 to 4 in six primary schools and grade 7 in six secondary schools participated in the baseline survey. Of those, 596 children had complete information about abdominal ultrasonography, anthropometric measurements, and fasting blood samples, while 820 children were excluded due to the absence of abdominal ultrasonography, 83 children were excluded due to the absence of blood samples, and one student was excluded due to the absence of anthropometric measurements. No significant differences in basic characteristics were observed between the overall population of the training set and those who underwent

ultrasound measurements, or between the ultrasound subgroup and the population included in the final analysis (Appendix 4 Table S2). Written informed consent was obtained from all participants and their parents, and the study received approval from the Ethics Committee of Review Board of Peking University Health Science Center (Approval No. 00001052–22018).

Validation set

Data for external validation were obtained from children enrolled in the "Optimizing Intervention Effects in Children and Adolescents" (OptiChild study) in Ningbo City, Zhejiang Province, China (NCT05482165). This study involved 425 children at grade 3 from six primary schools in the Haishu, Yinzhou, and Zhenhai districts of Ningbo city. Those children underwent FibroScan® examinations to detect steatosis, anthropometric measurements, and fasting blood sample collection. Three children were excluded due to missing crucial laboratory tests, leaving 422 children for validation. Written informed consent was obtained from all participants and their parents, and the study received approval from the Ethics Committee of Ningbo First Hospital (Approval No. 2021-R168).

Screening population set

The data was obtained from the CNSSCH 2019, the largest nationally representative cross-sectional survey conducted between September and November 2019, encompassing school-age children aged 6–22 years in China. The CNSSCH was conducted with a multistage stratified random cluster sampling method, and the health, weight status, and well-being of the children were monitored. A detailed description of the CNSSCH has been published previously.[29,30] In total, 273,168 children completed the survey and provided anthropometric data. The principals determined the process for obtaining informed consent (i.e., written, verbal, active, or passive) for all schools, and informed consent was obtained from all participants and their parents. This survey was approved by the Ethics Committee of Review Board of Peking University Health Science Center (Approval No. 00001052-19095). To align with the age range of the children in the training set, we included 160,124 counterparts aged 6–14 years in the current study.

Measurements of hepatic steatosis

Training set

This study used ultrasound scanners (GE Vivid i, Probo Medical, USA; M9, Mindray Medical, China) for diagnosing hepatic steatosis. The children were classified into four groups (grade 0–3) based on the presence of hepatorenal echo contrast, liver parenchymal brightness, deep attenuation, and vascular blurring.[31] Grades 1–3 were classified as having steatotic liver disease (SLD), while grade 0 indicated the absence of SLD.

Validation set

This study utilized a FibroScan® Handy (Echosens, Paris, France) for diagnosing hepatic steatosis. It enables quantitative measurements of fat content, as indicated by the controlled attenuation parameter (CAP), with hepatic steatosis defining as a CAP ≥248 dB/m.[32]

Definition of pediatric MASLD

The diagnosis of MASLD was based on the diagnosis of hepatic steatosis and the presence of at least one of the following cardiometabolic risk criteria[1]: 1) BMI ≥ the 85th percentile for age/sex or waist circumference (WC) >the 95th percentile; 2) fasting plasma glucose (FPG) ≥5.6 mmol/L; 3) BP ≥ the 95th percentile[33] or ≥130/80 mmHg for children aged <13 years and ≥130/85 mmHg for children aged ≥13 years; 4) serum triglyceride (TG) concentration ≥1.15 mmol/L for children <10 years-old and ≥1.70 mmol/L for children ≥10 years-old; 5) high-density lipoprotein cholesterol (HDL-C) concentration ≤1.0 mmol/L. The exclusion criteria included factors such as excessive pure alcohol consumption (males ≥140 g/week and females ≥70 g/week) and any other combination etiology through the survey.[34] In the validation set, we conducted surveys to investigate other potential causes of liver damage, such as viral hepatitis, drug-induced fatty liver, Wilson's disease, autoimmune hepatitis, and alcohol consumption. None of the participants reported any of these conditions or excessive alcohol consumption. Given the low incidence of these confounding factors in the young school-age population,[14] we did not account for these factors in the training set.

Anthropometric measurements and clinical examination

Training set

Well-trained health professionals conducted measurements of height, weight, WC, and body fat percentage (BFP) using standardized procedures. Height was measured to the nearest 0.1 cm using a mechanical height meter, while weight, after children removed their coats and shoes, was measured to the nearest 0.1 kg using a mechanical weight scale. WC was measured (nearest to 0.1 cm) as the circumference midway between the lowest costal point and the upper edge of the iliac crest. BFP was measured to the nearest 0.1% using the body composition analyzer (Tanita BC-420, Tanita, Middlesex, United Kingdom). BMI was calculated as weight (kg) divided by the square of height (m^2), while the WHtR was calculated as waist (cm) divided by height (cm). Besides, we also calculate the BMI z-scores. Five percent of the children were randomly selected and underwent repeated examinations to ensure the accuracy of the measurements. Fasting blood samples were collected and tested using standard laboratory procedures to measure FPG, TG, and HDL-C levels.

Validation set

Trained health professionals at community healthcare centers conducted anthropometric measurements following standard protocols. Height was measured to the nearest 0.1 cm using a mechanical height meter, while weight, after children removed their coats and shoes, was measured to the nearest 0.1 kg using a body composition instrument (Inbody770, Biospace, California, USA). WC was measured (nearest to 0.1 cm) as the circumference midway between the lowest costal point and the upper edge of the iliac crest. BFP was measured to the nearest 0.1% using a body composition instrument. BMI and WHtR were calculated as mentioned above. Fasting blood samples were collected and FPG, HDL-C, and TG levels were analyzed using autoanalyzer (Beckman Coulter AU5800, Brea, USA).

Screening population set

The measurements of height, weight, and WC were the same as those used for the training set.

Definition of overweight/obese

We classified all children into non-overweight/obese (Non-OW/OB, BMI Z score ≤1), overweight (OW, 1 < BMI Z score ≤2), and obese (OB, >2 for BMI Z score) groups according to the World Health Organization (WHO) criterion.[35,36]

Statistical analyses

Characteristic of children

All continuous variables with a normal distribution were displayed as the mean ± standard deviation (SD), while variables with a non-normal distribution were displayed as the median and interquartile range (IQR). Categorical variables are described as the number and percentage. In this study, we assessed normality using the Shapiro–Wilk test with the Shapiro test function in R. If the *P*-values for both groups were greater than 0.05, we considered the data normally distributed. For data meeting normality, we used Levene's test to check for homogeneity of variance. Student's *t* test, the Kruskal–Wallis test, and the Chi-square test (all expected cell frequencies ≥5) or Fisher's exact test (any expected cell frequency <5) were applied to detect significant differences where appropriate.

Construction of the prediction model

The steps for constructing the prediction model and selecting the best-performing model and indices are as follows: 1) The logistic regression (LR) model, random forest (RF) model, decision tree (DT) model, and support vector machine (SVM) model were constructed, the area under the receiver operating characteristic curve (AUC), Youden index, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and their 95% confidence interval (CI) with bootstrap method were calculated for each model. The model with the highest AUC, the LR model, accompanied by its ability to provide a cut-off value, was selected as the best-performing model and included in the next step. 2) The best-performing model was used in the training set and we tested the linearity assumption (Appendix 4 Table S3). Various indices were selected based on previous literature and expert judgment, focusing on indicators and combinations closely associated with MASLD. These included the following indices we defined (WHtR, BFP, BMI, WHtR + BMI, WHtR + BFP, BMI + BFP, the result of collinearity test was displayed in Appendix4 Table S4), and indices from previous studies,[18–20,37] such as the VAI, LAP, TyG, TyG-BMI and TyG-WC, TyG-WHtR, were compared. Equations for these indices are detailed in Appendix 2. 3) Evaluated the performance of each index in the training set and validated in the validation set. 4) Select the best performance index. After that, we used the calibration plot to assess the reliability of the model.[38] Finally, we chose WHtR as the best performance index and further did serial tests using WHtR and indices from previous studies (VAI, LAP, TyG, TyG-BMI and TyG-WC, TyG-WHtR) to improve the PPV.

Explore the relationship between obesity prevalence and MASLD prevalence

The optimal model and index were employed to screen the entire screening population. For each province, we could calculate the screening positive rate by the following equation:

Screening positive rate = (Screening positive number)/(Total number)

where *"Screening positive number"* represented the number of children predicted with MASLD in each province with the screening model, and *"Total number"* represented the total number of children in each province.

Based on the relationship between true prevalence, specificity, sensitivity, and the result of screening, we calculate the true positive rate with the following equation (Appendix 3):

True positive rate = (1 − Specificity − Screening positive rate)/(1 − Specificity − Sensitivity)

The "*True positive rate*" represented the MASLD prevalence in each province of the screening population set, "*Specificity*" and "*Sensitivity*" were calculated from the LR model for WHtR in the training set, the *"Screening positive rate"* represented the percentage of children predicted with MASLD in each province by our prediction model, as defined before.

Based on our model and the above equation, we predicted MASLD prevalence for each province. Based

on both prevalence of obesity and predicted MASLD prevalence across provinces, we explored the recommended population screening threshold for obesity prevalence and set the 40th percentile and 80th percentile to evaluate the feasibility of the screening due to the better performance.

Explore the applicability of the proposed index

To further test the applicability of the proposed index, we explored the trends for the MASLD prevalence of 200 countries from 1990 to 2022 by using our recommended population screening threshold based on obesity prevalence. A worldwide age-sex-year-specific prevalence of obesity for each country in 1990, 2000, 2010, and 2022 was obtained from the NCD-RisC.[39,40] To calculate the prevalence of obesity for children aged 6–14 years for each country in these years, the age-year (in 1990, 2000, 2010, and 2021) specific population and sex ratio (for children aged 5–14 years in 1990, 2000, 2010, and 2021) were calculated for each country by using data from the United Nations.[9]

Sensitivity analyses

The parameter and thresholds derived in the general population were also applied to children with OWOB from both the training set and validation set based on the WHO criterion. Considering all children were from China, we additionally used the Chinese criterion[27] to define the children as obese with observed BMI ≥95th age- and gender-specific BMI percentile value for sensitivity analysis. When exploring the relationship between obesity prevalence and MASLD prevalence, we also set two tertiles as cut-off values. While fitting the predicting model, age and sex were used as predictors to predict the selection probability and inverse probability weighting was used by using the inverse of selection probability as the weight. Additionally, we adjusted for school cluster effect in our model.

All analyses and data visualization were performed with R version 4.2.1, and a two-tailed P value < 0.05 was considered to be statistically significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. HW and YS had final responsibility for the decision to submit for publication.

Results

Characteristics of the children

There were 1018 children included ($N_{Beijing}$ = 596, N_{Ningbo} = 422) in this study. The prevalence of MASLD was 4.4% (26 out of 596) in the training set and 10.4% (44 out of 422) in the validation set. In the training set, MASLD predominantly affected boys aged 6–14 years and children who were OWOB; as indicated by elevated WC, BFP, and TG (Table 1). Furthermore, compared to non-MASLD children, those with MASLD exhibited elevated values across various indices, including BMI, WHtR, LAP, VAI, TyG, TyG-BMI, TyG-WC, and TyG-WHtR, along with a diminished level of HDL-C. Consistently, in the validation set, compared to their non-MASLD counterparts, children affected by MASLD exhibited similar characteristics to those observed in the training set.

Comparison of different indices in the best-performing model

The LR model was selected as the best-performing model (Appendix 1 Figure S1). The AUC for all indices ranged from 0.604 to 0.949 in the training set and from 0.718 to 0.848 in the validation set (Fig. 1). In the training set, the WHtR [AUC = 0.949, 95% CI (0.924, 0.968)] had the highest AUC among all indices. However, the TyG-BMI performed better in the validation set [AUC = 0.848, 95% CI (0.796, 0.901)] than others, followed closely by TyG-WHtR [AUC = 0.814, 95% CI (0.746, 0.881)] and BMI [AUC = 0.813, 95% CI (0.736, 0.871)]. WHtR [AUC = 0.776, 95% CI (0.696, 0.856)] only showed significant difference with TyG-BMI and TyG-WHtR. The results of sensitivity analyses for children with OWOB under both the WHO and Chinese criteria were similar to those of the main analysis, with narrowed differences between training and validation sets (Appendix 4 Figures S2 & S3). Considering the performance and accessibility of each index, the WHtR was ultimately chosen as the best performance index and the cutoff value was ≥0.48 from the model conducted in the training set (Appendix 5 Table S6). The calibration plot was shown in Appendix 4 Figure S4. The cutoff value was also ≥0.48 in inverse probability weighting model and the inverse probability weighting model adjusted for school cluster effect (Appendix 5 Tables S7 and S8). In the serial tests, WHtR&LAP showed the second highest PPV in both the training set and validation set (Appendix 4 Figure S5), and the cutoff value of LAP was ≥668.22 cm × mg/dL (Appendix 5 Table S4).

Exploring the recommended population screening threshold for obesity prevalence with CNSSCH

Fig. 2 and Appendix 4 Table S5 show the predicted MASLD prevalence in the CNSSCH using WHtR and its relationship with the obesity prevalence (based on the WHO criterion) in each province. Considering the application and the prediction of each province, two cutoff values (40th percentile and 80th percentile) were set manually to assess the feasibility of the screening. The 40th and 80th percentiles of the prevalence of obesity based on the WHO criterion for 30 provinces were 8.4% and 12.0%, respectively. When separated

Characteristics and indices	Training set			Validation set		
	Non-MASLD (n = 570)	MASLD (n = 26)	*P*	Non-MASLD (n = 378)	MASLD (n = 44)	*P*
Age (years)	9.2 (8.2, 10.6)[a]	9.5 (8.9, 10.4)	0.308	8.5 (8.3, 8.8)	8.6 (8.3, 8.8)	0.464
Female sex, n (%)	295 (52)	4 (15)	0.001	148 (39)	16 (36)	0.845
BMI	17.5 (15.5, 20.4)	24.9 (22.5, 27.6)	<0.0001	19.4 (18.4, 20.9)	22.4 (21.1, 24.2)	<0.0001
WC	59.0 (53.2, 67.3)	82.4 (75.3, 88.1)	<0.0001	65.0 (61.0, 69.0)	73.0 (68.4, 76.3)	<0.0001
WHtR	0.42 (0.39, 0.46)	0.55 (0.52, 0.58)	<0.0001	0.48 (0.04)[b]	0.53 (0.05)	<0.0001
BFP	17.5 (12.5, 26.0)	39.9 (34.5, 45.6)	<0.0001	29.0 (5.8)	35.6 (6.3)	<0.0001
FPG	81.7 (77.8, 85.5)	82.1 (78.9, 85.9)	0.585	88.7 (84.7, 93.5)	91.5 (86.5, 96.1)	0.047
TG	59.3 (45.2, 78.8)	74.8 (60.7, 94.3)	0.004	67.3 (52.3, 87.7)	91.7 (78.6, 126.0)	<0.0001
HDL-C	64.6 (55.3, 73.8)	57.2 (48.9, 63.8)	0.003	58.2 (52.2, 65.4)	53.6 (48.6, 59.1)	0.003
TyG	7.8 (7.5, 8.1)	8.1 (7.8, 8.3)	0.003	8.0 (7.7, 8.3)	8.4 (8.2, 8.7)	<0.0001
VAI	1.2 (0.8, 1.9)	1.7 (1.2, 2.3)	0.004	1.5 (1.0, 2.1)	2.3 (1.7, 3.1)	<0.0001
LAP	−98.3 (−403.0, 381.3)	1357.8 (872.7, 1785.6)	<0.0001	152.3 (−94.8, 444.4)	867.5 (389.3, 1558.4)	<0.0001
TyG-BMI	136.1 (118.4, 162.2)	205.7 (176.8, 225.8)	<0.0001	156.9 (145.4, 169.4)	187.3 (173.2, 200.5)	<0.0001
TyG-WC	462.3 (408.3, 528.9)	661.6 (605.7, 714.1)	<0.0001	515.9 (481.8, 557.6)	599.8 (552.9, 632.3)	<0.0001
TyG-WHtR	3.3 (3.0, 3.7)	4.4 (4.2, 4.7)	<0.0001	3.9 (3.6, 4.1)	4.5 (4.1, 4.6)	<0.0001
Weight status by WHO criterion, n (%)			<0.0001			<0.0001
NW	386 (68)	0 (0)		39 (10)	0 (0)	
OW	85 (15)	3 (12)		179 (47)	8 (18)	
OB	99 (17)	23 (88)		160 (42)	36 (82)	
Weight status by Chinese criterion, n (%)			<0.0001			0.0003
NW	384 (67)	0 (0)		27 (7)	0 (0)	
OW	105 (19)	4 (15)		152 (40)	7 (16)	
OB	81 (14)	22 (85)		199 (53)	37 (84)	

[a]Displayed as the median and interquartile range (IQR). [b]Displayed by mean and standard deviation (SD). BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; BFP, body fat percentage; FPG, fasting plasma glucose; TG, serum triglyceride; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride-glucose; VAI, visceral adiposity index; LAP, lipid accumulation product; WHO, World Health Organization; NW, normal weight; OW, overweight; OB, obese.

Table 1: **General characteristics and indices of the children in the training and validation sets.**

from those two values, in the first category, where the obesity prevalence was lower than the 40th percentile, only one out of 12 provinces had MASLD prevalence above zero. For the second category, where the obesity prevalence was higher than the 40th percentile but lower than the 80th percentile, one province was still not applicable to our MASLD screening model, and the prevalence of MASLD for the remaining 11 provinces ranged from 0.2% (−3.4%, 7.9%) to 6.7% (4.1%, 15.0%). For the last category, where the obesity prevalence was higher than the 80th percentile, the prediction model could be applied in all six provinces, and the MASLD prevalence ranged from 5.0% (2.2%, 12.9%) to 21.5% (20.0%, 30.8%).

The 40th percentile and 80th percentile of the obesity prevalence for thirty provinces were 10.6% and 14.4% in the Chinese criterion, respectively. The results were consistent with those of the main analysis (Appendix 4 Figures S6 and S7). Two tertiles of OB prevalence were 7.4% and 10.5%, respectively. Only one out of ten provinces had a MASLD prevalence above zero in the first tertile, while seven out of ten did in the second tertile, and all had a prevalence above zero in the last tertile (Appendix 4 Figure S8).

The trends of recommendations categories for 200 countries in the past three decades

Similarly, countries with an obesity prevalence ≥12.0% were classified as "Population-screening-recommended", representing the necessity for screening. Those with an obesity prevalence between 8.4% and 12.0% were classified as "Resources-permitted", meaning screening should be conducted if resources are permitted. Those with an obesity prevalence <8.4% were classified as "Population screening-not-recommended", displaying the unnecessity of screening. Fig. 3 shows the recommendations for 200 countries in the past three decades. An increasing number of countries were classified into "Population-screening-recommended" and "Resources-permitted" groups, reflecting a growing burden of pediatric MASLD. In 2022, 95 countries, including the United States, United Kingdom, Brazil, Argentina, China, Australia, and Iran; and countries located in the Mediterranean region (such as Algeria, Egypt, and Libya) were classified as "Population-screening-recommended"; and 28 countries, including Canada, and countries located in Europe (such as the Ireland, Germany, and Sweden) were classified as "Resources-permitted", while the number of countries classified into "Population-screening-recommended"; and

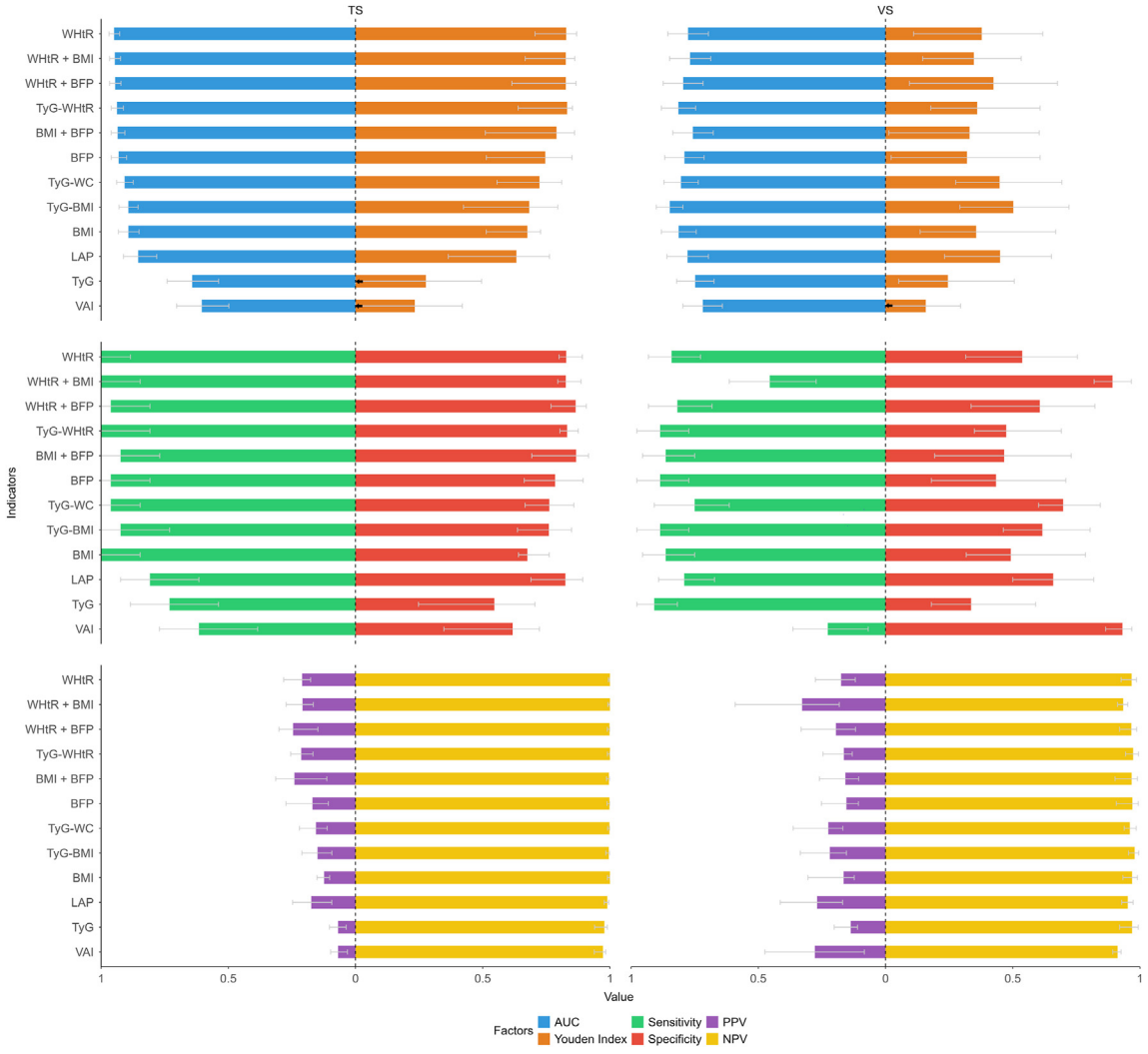

Fig. 1: Comparison of different indices of the LR model in the training set (TS, left) and validation set (VS, right) for all children. LR, logistic regression; WHtR, waist-to-height ratio; BFP, body fat percentage; BMI, body mass index; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value. The arrow indicates the value out of range to show.

"Resources-permitted" were only one and 11 in 1990, respectively.

Discussion

In the present study, multicenter school-based data were utilized to develop predictors for pediatric MASLD, encompassing both training and validation sets. Given its global availability and practicality, WHtR was chosen as the pediatric MASLD predictor, with a suggested cutoff value of ≥0.48 for individual-level screening. Based on obesity prevalence classification, we propose a "Population-screening-recommended" status for areas with a high prevalence (12.0% by WHO criterion, 14.4% by Chinese criterion). We provided country-year specific recommendations, revealing the rising global burden of MASLD. This suggests a proactive approach to address obesity-related health concerns through targeted screening in regions with elevated obesity prevalence.

Based on easily measurable parameters, we implemented both commonly used indices (LAP, VAI, TyG, TyG-BMI, TyG-WC, and TyG-WHtR) and six new noninvasive indices (BMI, WHtR, BFP, WHtR + BFP, BMI + BFP, and WHtR + BMI) to construct screening models for MASLD. Consistent with the findings of prior research,[18,37] we observed strong predictive performance for both invasive and noninvasive indices in the Beijing data, validated against the Ningbo data, applicable to both the general and OWOB population. Remarkably, the WHtR, a noninvasive index, consistently demonstrated satisfactory performance in both the training and validation sets, consistent with previous

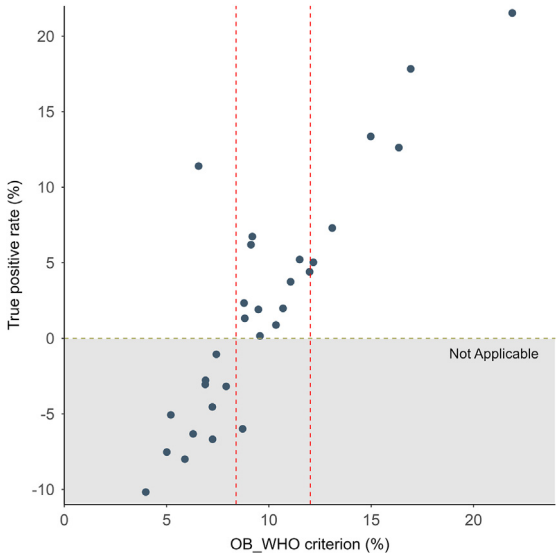

Fig. 2: Prediction of the MASLD prevalence and its association with the prevalence of OB based on the WHO criterion. The 40th and 80th percentiles of the OB rate for thirty provinces were 8.4% and 12.0%, respectively. OB, obese.

findings.[7,8,41–43] Due to its noninvasive nature and the widespread availability of WC and height measurements, WHtR has emerged as a child-friendly option, particularly beneficial in regions with limited access to blood testing. Furthermore, unlike BMI and WC, WHtR overcomes the limitations of age and sex in children and adolescents.[44] Globally, pediatric societies endorse the use of the term MASLD.[45] However, this nomenclature might also overlook the issue of lean NAFLD population. For instance, PNPLA3 I148M carriers may develop steatosis at a lower BMI with or without a cardiometabolic risk factor. Notably, these carriers might also exhibit higher WC,[46] reinforcing the utility of as a useful indicator for screening pediatric MASLD. These compelling findings underscore the potential of the WHtR as a primary screening tool for pediatric MASLD, supported by its practicality and diagnostic superiority.

The WHtR's robust predictive capability for MASLD could be attributed to several hypothetical mechanisms under current consideration: 1) Central adiposity: The WHtR provides a more accurate reflection of central adiposity compared to other measures, such as BMI and WC, indicating the distribution of visceral fat.[44,47] Elevated visceral fat is associated with metabolic abnormalities and closely linked to liver fat accumulation, making the WHtR a reliable predictor.[48] 2) Insulin resistance (IR): Elevated WHtR often correlates with IR, a pivotal factor in the development of MASLD.[48] According to the 'multiple parallel hits hypothesis', IR serves as the primary trigger for MASLD.[49,50] IR induces an increase in free fatty acids within hepatocytes, rendering the liver more susceptible to additional insults and amplifying its vulnerability to other damaging factors.[51,52] 3) Chronic inflammation: Abdominal obesity, as indicated by WHtR, is associated metabolically active visceral fat that releases inflammatory cytokines. This chronic low-grade inflammation is implicated in MASLD progression.[53] Additionally, chronic inflammation contributes to hepatocyte stress

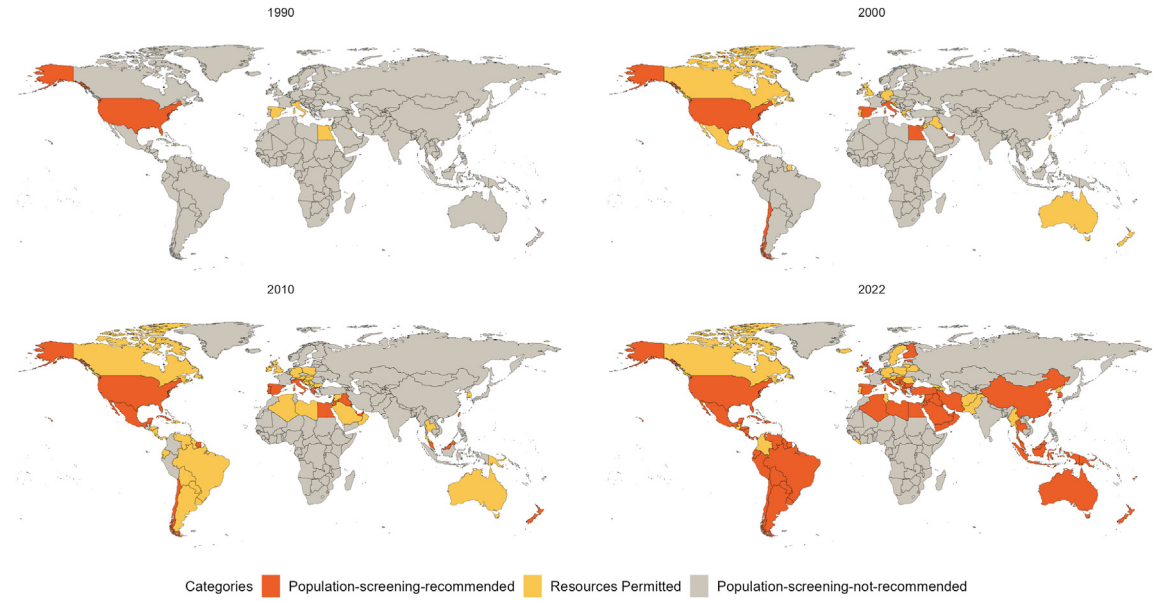

Fig. 3: Recommendations for screening MASLD burden among children according to the country-year specific prevalence of OB on WHO criterion in 1990, 2000, 2010, and 2022. OB, obese.

and IR, creating a detrimental cycle that promotes lipid accumulation and heightens the risk of MASLD.[54,55] 4) Other factors: WHtR may also reflect hormonal imbalances[56] linked to abdominal adiposity. These hormonal dysregulations contribute to the metabolic abnormalities observed in MASLD patients. Each of these mechanisms contributes to the predictive validity of the WHtR as a predictor of MASLD, making it a valuable tool for assessing MASLD-associated metabolic health.

Given the burden of OWOB among children worldwide and that MASLD is an obesity-related disease,[57] MASLD screening is highly recommended. Still, specific recommendations for individual screening based on different WHtR conditions or for population screening are lacking especially in areas with different prevalences of childhood obesity. In this study, we used the noninvasive WHtR to provide personal recommendations, advocating for MASLD screening in children with WHtR ≥0.48. In addition, we predicted the MASLD prevalence in each province in China. The model proved effective in provinces with high childhood OWOB prevalence, and *vice versa*. Three recommendations were proposed based on the obesity prevalence >80th percentile or <40th percentile or in between. In industrialized nations, obesity prevalence imposes a significant social and economic burden,[58] necessitating swift policy actions and monitoring efforts. Our findings highlight a global trend, designating more countries as "Population-screening-recommended" and "Resources-permitted". This emphasizes the worldwide demand for screening MASLD in young populations. It underscores the imperative of addressing MASLD globally, including in China and developing economies, to address the metabolic burden stemming from overweight and obesity throughout the life course. Given the threshold for both individuals and populations and the results of serial tests, we proposed the following recommendations: 1) in areas with obesity prevalence ≥12.0%, children with WHtR ≥0.48 were recommended to conduct further screening such as ultrasound; 2) in areas where the prevalence of obesity is unknown, children with WHtR ≥0.48 accompanying with LAP ≥668.22 cm × mg/dL were recommended to conduct further screening; 3) further screening is unnecessary for children with WHtR <0.48 when no abnormal liver enzymes were detected. Implementation of these recommendations could facilitate noninvasive MASLD screening for children in large populations, aligning with the research priority outlined in the recent consensus statement of "defining and implementing models of care" for fatty liver disease.[27]

Several merits warrant acknowledgment in our study: First, we encompassed children across a wide age range in the training set and validated our predictor externally, ensuring the reliability of the MASLD predictor, including those with OWOB. Second, we developed a practical MASLD screening strategy and recommendation based on local children's obesity prevalence. Third, sensitivity analyses revealed the consistency of result and the robustness and generalizability of our findings. However, several limitations need to be addressed. First, the diagnosis of hepatic steatosis was based on abdominal ultrasound or FibroScan®, which are not the gold standards for diagnosis and are not consistent across different populations. Ultrasound imaging enables a subjective estimation of the fatty infiltration in the liver but is only of limited suitability for detecting mild steatosis,[57] which might underestimate the prevalence in our population. However, both methods were widely used in previous studies.[37,57] Second, data constraints precluded inclusion of several common indices, such as alanine aminotransferase (ALT) and AST; however, they have only moderate diagnostic accuracy in children.[59–61] Instead, we included several complex indices with better performance, such as the TyG and modified TyG indices.[18] Nonetheless, the comparison with frequently used indices such as ALT and AST should be conducted in the future studies in terms of performance and benefits. Third, although we used the WHO criterion for defining weight status, our recommendations were based on the Chinese population, predominantly encompasses individuals of East Asian descent, and additional supranational data encompassing a more diverse range of ethnics are needed to ensure the generalizability and applicability of our findings. Fourth, due to limitations in data sources, the sex ratio provided pertains to children aged 5–14 years, which differs from the age range (6–14 years) used for assessing obesity prevalence. Additionally, while population and sex ratio data are available for the years 1950–2021, using 2021 data to estimate the aggregate obesity prevalence for children aged 6–14 years in 2022. This approach may result in slight discrepancies.

Conclusion

Our findings underscore the utility of WHtR as a practical and accessible index for predicting pediatric MASLD. Our findings emphasize the importance of considering local obesity prevalence when applying the screening tool. In areas where obesity prevalence is ≥12.0%, a WHtR ≥0.48 may warrant further screening. In areas where obesity prevalence is unknown, a serial test combining WHtR ≥0.48 and LAP ≥668.22 cm × mg/dL could also indicate a need for additional screening. Although the cost-effectiveness and performance of WHtR need to be validated in other populations/ethnics with more sensitive diagnostics methods, with the growing global burden of pediatric obesity and MASLD, the implementation of this screening model might allow for the early detection and management of pediatric MASLD, contributing to a reduction in MASLD burden during childhood and later in life.

Contributors

YL, YW, HW and YS conceived and designed the study. YL and YW did the systematic search of the literature, did the statistical analyses, and drafted the initial manuscript. YL, YW, YX, DS, PZ, JD, ZC, SC, YW, JL, XW, LG, MX, YL, JS, JL, YD, YC, PH, JM, LL, and YS acquired the data. HJW, JM, YY, HW, and YS were responsible for the general supervision. HJW, LL, JM, YY, HW, and YS contributed to the interpretation of the data. MW, HZ, AH, HJW, LL, JM, YY, HW, and YS significantly edited and critically reviewed the manuscript. All authors reviewed and revised the article. All authors read the final manuscript and approved submission.

Data sharing statement

All the data in this article could be shared with researchers. The request from researchers with appropriate ethics board approvals and study protocols will be assessed by the Institute of Child and Adolescent Health, Peking University. To request access please contact the corresponding authors by email: huiwang@bjmu.edu.cn or songyi@bjmu.edu.cn.

Editor note

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Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101150.

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