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Temporal Trend of Non-Invasive Method Capacity for Early Detection of Metabolic Syndrome in Children and Adolescents: A Bayesian Multilevel Analysis of Pseudo-Panel Data

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Anthropometric · Pseudo-panel study · Serum lipid profiles · Pediatrics · Obesity

Abstract
Background: The aim of this study was to examine the ability of Noninvasive methods to early predictions of metabolic syndrome (MetS) among children and adolescents from 2003 to 2016. ***Methods:*** This was a repeated cross-sectional study based on 24,409 Iranian children and adolescents. The variables included anthropometric measures, serum lipid profiles, hypertension, and MetS. The receiver operating characteristic regression and Bayesian multilevel modeling conducted on data to comparison the power of anthropometric measures to early prediction of cardiometabolic risk factors. ***Results:*** The tri-ponderal body shape index (TBSI) in females and waist circumference (WC) percentile in males yielded a greater ability to predict lipid profiles and hypertension than the rest of anthropometric factors. The TBSI (β = 6.24, 95% credible interval [95% CrI] 3.9–8.7) followed by the WC percentile (β = 4.43, 95% CrI 3.5–5.4) were considered the better predictors of MetS compared with the body mass index (BMI), tri-ponderal mass index (TMI), WC, waist-to-height ratio, and WC to height^5 in adolescents. The TBSI with Youden index J (JI) = 0.85 was significantly more accurate than the BMI (JI = 0.73), and TMI (JI = 0.7) for classifying individuals with MetS and in healthy groups. The predictability of early MetS was consistent for both TBSI and WC components throughout the study period. ***Conclusions:*** The TBSI including, both BMI and WC components, predicts MetS and cardiometabolic risk factors more accurately than BMI or WC alone in females. The TBSI ability was higher than other anthropometric factors for screening MetS and cardiometabolic risk factors among adolescents.

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Introduction

Considering the stable nature of childhood obesity, fatness is an important risk factor of a noncommunicable disease such as metabolic syndrome (MetS). This condition can lead to diabetes and cardiovascular diseases during adulthood [1]. The body mass index (BMI), waist circumference (WC), the waist-to-height ratio (WHtR), waist-to-hip ratio factors are anthropometric measures that many studies have focused on BMI in associations with morbidity and mortality [2]. The BMI relies only on weight and height measures, and ignores the adiposity. Therefore, it cannot be a comprehensive measure to predict the mortality and morbidity associated with MetS. Several studies have recommended the BMI combined with WC assessment [2–5], but this combination could not assess adequately in screening for developing cardiometabolic risks in children and adolescents. A body shape index (ABSI) was introduced as a new anthropometric measure of abdominal obesity based on WC, BMI, and height measures, independently of BMI and height [6]. Studies have suggested ABSI as a stronger predictor of mortality and morbidity of obesity than BMI in children and adults [5]. However, little research has been conducted on the validation, comparison, and predictability of anthropometric measures for MetS, hypertension, and lipid profiles in children and adolescents. The examination of the power of prediction ability of anthropometric factors, estimating optimal cutoff points and assessing the stability of these thresholds for early predictions of MetS risks, especially over time, can play an important role for screening adverse events in the future.

Cohort studies are more relevant in the investigation of the relationship among variables than cross-sectional studies [7]. Nevertheless, longitudinal studies of cross-sectional data could yield results with similar power as cohort studies. Analyzing repeated cross-sectional (RCS) data can examine the trend, magnitude, and nature of the relationship among variables in constant population over time that the cost and individuals' dropout problems in relation to cohort studies are not question.

The probability of unbiased estimates increases in the presence of random effects, unbalanced data, non-normal distribution, and small sample size of cross-sectional data [7]. The multilevel methods have controlled the limitations of fixed effects as well as time variation, but the bias due to the low number of cross-sections remains [8]. The Bayesian multilevel methods in conjunction with applying the Hamilton sampling method could account for the variations related to age, period, and birth cohort in RCS data, better than the Gibbs sampling method [9].

The purpose of the present study was to (a) compare the predictive power of noninvasive methods for early diagnosis of MetS over time considering the random effects of age, birth, and period cohorts; (b) estimate the optimal cutoff points of noninvasive parameters to classify children with or without MetS; (c) apply Bayesian multilevel approach using Hamilton sampling for the analysis of RCS data.

Materials and Methods

Data Source

This RCS study, involved 24,409 children aged 7–18 years old from 3 national surveys, the Adolescence Surveillance and Prevention of Adult Non-communicable diseases (CASPIAN). We analyzed the data of 3 periods, CASPIAN I (2003–2004; n = 4,811), CASPIAN III (2009; n = 5,312), and CASPIAN V (2015–2016; n = 14,286).

The CASPIAN, as a school-based surveillance, study was conducted from 2003 to 2016 for screening risk factors of chronic diseases among individuals aged 7–18 years in Iran. A stratified multistage cluster sampling method was used to select individuals from urban and rural regions of 30 provinces of Iran. The size and geospatial distribution of the data are broadly representative of the Iranian children and adolescents, in which the validity of data is acceptable. The CASPIAN II (2006) and IV (2011) were ignored from the main analysis due to the lack of lipid profiles data and inconsistent variable evaluations. Detailed information on CASPIAN surveys, sampling method, and measurements are described elsewhere [10].

Variables

The data described the role of variables in the prediction of serum lipid profiles, hypertension, fasting glucose, and MetS among children in RCS data. The independent variables included in the Bayesian logistic regression model were gender, age, residential status (urban or rural), the socio-economic status quartiles, birth weight (normal or obese), family history of obesity, diabetes, and hyperlipidemia. The noninvasive measures included BMI, Triponderal mass index (TMI):

$$\text{TMI} = \frac{Weight\ (Kg)}{Height\ (m)^3},$$

tri-ponderal body shape index (TBSI), WC, WHtR, and WC to height^5 (WH.5R). The MetS, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), non-HDL (= TC-HDL), and TG/HDL ratio as response variables were classified into normal/abnormal groups according to the International Diabetes Federation definition in pediatrics [11].

Statistical Methods

The Bayesian multilevel model using Bernoulli prior family for binary response variables was used to fit the data, whereas anthropometric factors were treated as random across age, cross-sections,

and birth cohorts. The effects of other variables were considered fixed. The random effects were assumed to vary across categorical variables. Given the fact that that each cross-sectional data belonged to different samples from the same populations, different covariance matrices for each cross-section were assumed to estimate the associations of variables across each period. The model (anthropometric factors|cross-section, age cohort, birth cohort) used to account for the differences among age, birth, and cross-sections that are not related to the exposure factors. The model comparison was conducted using both Watanabe-Akaike information criterion (WAIC) [12] and leave-one-out (LOO) cross-validation parameters. The lower the WAICs and LOOs the better the model fits [13]. The interpretation of Bayesian multilevel regression model with binary response variable is the same to ordinary logistic regression, in which OR is used for declaring the associations between variables.

Following Stan parameterization, the data were nested into 3 distinct cross-sections. We assigned each cross-section to its own coefficient vector β_i that was estimated independently from the other periods. Cross-sections varied with respect to exposures, behaviors, facilities, or other aspects that induced dependency among students of the same age, birth, and cross-sectional cohort.

The receiver operating characteristic (ROC) regression model was used to estimate optimal cutoff points of noninvasive methods for early predictions of MetS. The area under ROC curve (AUC), sensitivity (Se), specificity (Sp), and optimal cutoff points based on the Youden index J (JI) were estimated from ROC regression model. The parameters of the Bayesian multilevel model were estimated using Hamiltonian Monte Carlo chains with 6,000 iterations and 1,000 warm-ups in RStan C++ library. The pROC, Stan, LOO, and Shynistan packages were used in R 3.5.1 environment [14]. Instead of random walks, the Hybrid Monte Carlo algorithm leads to most efficient estimates through the posterior distribution compared to other algorithms [14, 15]. The model convergence was checked by R-hat and Gelman-Rubin diagnostics available in Shynistan. The statistical significance was assessed by 95% credible interval (95% CrI) and p value <0.05.

Results

The underweight individuals as well as 2% of the samples were excluded from the analysis because of incomplete data. In total, 24,409 children (50.1% boy and 49.9% girl, 21.2% <10 years and 78.8% ≥10 years old) were contributed in the final analysis. The distribution of demographic and lipid profiles of participants by gender and cross-sections is shown in Table 1. The gender proportions were the same throughout the cross-sections (incidence rate ratio 0.99; 95% Crl 0.96–1.01; $p = 0.552$). Overall, 2,609 out of 24,409 (10.68%) of children (10.02% male and 11.34% female, p value = 0.001) were at the risk of MetS. The prevalence of MetS was raised significantly from 9.41 to 11.42% from 2003 to 2016 ($p = 0.0002$). Overall, 15.32 and 7.8% of children were overweight and obese respectively. The risk of obesity was 1.52 times higher among boys than girls (95% Crl 1.41–1.66), while the risk of overweight was 1.06 times higher among girls than that of boys (95% Crl 1.003–1.12).

Results of Bayesian Multilevel Model by Age Group

According to LOO and WAIC results, the model including the effects of period, age cohort, and birth cohort were considered the final model. The standardized coefficients (β) of the regression model were used to determine which anthropometric measure had a stronger association with the response variables.

The WC percentile was estimated as the only predictor of MetS among children who were aged 7–9 years old, while the risk of MetS increased 2.39 times with one unit increase in WC percentile Z score. The associations between MetS and other variables were insignificant ($p >$ 0.05).

Except LDL, the TBSI was estimated as a better predictor of serum lipid profiles compared with TMI, BMI, WC, WHtR, WH.5R, and WC percentile Z scores among children aged 10–18 years old in the adjusted model. However, the correlation between WC percentile and LDL was stronger than the remaining anthropometric factors. In addition, the TBSI (β = 4.43, 95% Crl 3.51–5.49) followed by the WC percentile (β = 6.24, 95% Crl 3.96–8.74) had the highest associations with the risk of MetS. The highest influence on hypertension was estimated for TBSI (β = 0.353, 95% Crl 0.28–0.43), whereas the risk of hypertension increased 42 and 40% with every unit of raise in TBSI and WC percentile Z scores respectively. The associations between anthropometric factors and fasting blood glucose were statistically insignificant among the participants who were aged 10–18 years ($p >$ 0.05).

Results of Bayesian Multilevel Model by Gender in 10–18-Year-Old Group

The associations of anthropometric factors with lipid profiles and hypertension by gender are shown in Figure 1. In males, the TBSI and TMI were estimated as the strongest predictors of TC (β = 0.364, 95% Crl 0.11–0.73) and TG (β = 0.306, 95% Crl 0.14–0.5) respectively. In addition, the WC percentile estimated as the strongest predictor of LDL (β = 0.195, 95% Crl 0.048–0.34), Non-HDL (β = 0.34, 95% Crl 0.05–0.33) and TG/HDL (β = 0.17, 95% Crl 0.074–0.17) compared with the rest of anthropometric measurements.

Table 1. The distribution of characteristics and laboratory parameters of participants

Variable	Category	Male, *n* (%)			Female, *n* (%)		
		CASPIAN I	CASPIAN III	CASPIAN V	CASPIAN I	CASPIAN III	CASPIAN V
Residential	Urban	2,124 (94.48)	1,835 (68.86)	5,155 (71.25)	2,405 (93.84)	1,845 (69.7)	5,049 (71.61)
	Rural	124 (5.52)	830 (31.14)	2,080 (28.75)	158 (6.16)	802 (30.3)	2,002 (28.39)
SES	Q1	703 (31.27)	749 (28.11)	2,344 (32.4)	759 (29.61)	656 (24.78)	2,139 (30.34)
	Q2	977 (43.46)	1,442 (54.11)	3,043 (42.06)	1,113 (43.43)	1,463 (55.27)	2,933 (41.6)
	Q3	568 (25.27)	474 (17.79)	1,848 (25.54)	691 (26.96)	528 (19.95)	1,979 (28.07)
MetS	No	2,039 (90.7)	2,432 (91.26)	6,459 (89.27)	2,319 (90.48)	2,359 (89.12)	6,192 (87.82)
	Yes	209 (9.3)	233 (8.74)	776 (10.73)	244 (9.52)	288 (10.88)	859 (12.18)
Fasting glucose	Normal	2,146 (95.46)	2,170 (81.43)	5,721 (79.07)	2,478 (96.68)	2,319 (87.61)	5,757 (81.65)
	Abnormal	102 (4.54)	495 (18.57)	1,514 (20.93)	85 (3.32)	328 (12.39)	1,294 (18.35)
Hypertension	Normal	1,808 (80.43)	2,069 (77.64)	6,022 (83.23)	2,286 (89.19)	2,217 (83.76)	6,014 (85.29)
	Abnormal	440 (19.57)	596 (22.36)	1,213 (16.77)	277 (10.81)	430 (16.24)	1,037 (14.71)
TC	Normal	2,129 (94.71)	2,534 (95.08)	6,875 (95.02)	2,388 (93.17)	2,489 (94.03)	6,708 (95.14)
	Abnormal	119 (5.29)	131 (4.92)	360 (4.98)	175 (6.83)	158 (5.97)	343 (4.86)
TG	Normal	1,911 (85.01)	2,306 (86.53)	6,354 (87.82)	2,113 (82.44)	2,255 (85.19)	6,027 (85.48)
	Abnormal	337 (14.99)	359 (13.47)	881 (12.18)	450 (17.56)	392 (14.81)	1,024 (14.52)
LDL	Normal	2,086 (92.79)	2,662 (99.89)	6,257 (86.48)	2,340 (91.3)	2,641 (99.77)	5,946 (84.33)
	Abnormal	162 (7.21)	3 (0.11)	978 (13.52)	223 (8.7)	6 (0.23)	1,105 (15.67)
HDL	Normal	1,310 (58.27)	2,541 (95.35)	5,024 (69.44)	1,475 (57.55)	2,548 (96.26)	4,948 (70.17)
	Abnormal	938 (41.73)	124 (4.65)	2,211 (30.56)	1,088 (42.45)	99 (3.74)	2,103 (29.83)
NON-HDL	Normal	2,009 (89.37)	2,658 (99.74)	6,746 (93.24)	2,262 (88.26)	2,456 (92.78)	6,566 (93.12)
	Abnormal	239 (10.63)	7 (0.26)	489 (6.76)	301 (11.74)	191 (7.22)	485 (6.88)
TG/HDL	Normal	1,321 (58.76)	2,451 (91.97)	5,034 (69.58)	1,459 (56.93)	2,464 (93.09)	4,764 (67.56)
	Abnormal	927 (41.24)	214 (8.03)	2,201 (30.42)	1,104 (43.07)	183 (6.91)	2,287 (32.44)
Age, years		12.14±3.26	14.61±2.26	12.39±3.15	12.08±3.19	14.5±2.33	12.18±3.17
Weight		43.83±16.55	47.82±16.35	42.36±18.24	42.67±14.56	45.99±12.97	40.41±15.83
BMI		18.34±3.76	19.25±4.4	18.43±4.3	18.78±3.97	19.61±4.09	18.54±4.45
Z BMI		–0.11±1.43	–0.45±1.57	–0.21±1.76	0.01±1.25	–0.3±1.36	–0.19±1.49
WC		66.02±10.43	69.48±11.47	67.65±12.88	64.31±9.72	67.33±9.77	65.76±11.33
WC%		43.69±28.79	41.32±28.36	47.54±31.07	38.77±27.22	40.79±27.75	44.27±29
Z WC		–0.26±1.12	–0.34±1.09	–0.18±1.27	–0.42±1.03	–0.35±1.06	–0.26±1.14
WHtR		0.1±0.3	0.17±0.38	0.21±0.41	0.1±0.29	0.14±0.35	0.2±0.4
WHtR%		36.62±27.72	34.42±27.4	49.65±29.54	31.82±25.98	33.68±26.39	44.65±28.02
WH.5R		53.55±6.63	55.65±8.02	55.5±8.71	52.73±6.51	54.58±7.26	54.58±7.95
TMI		12.15±2.36	12.4±2.81	12.54±3.62	12.65±2.34	12.89±2.53	12.8±2.81
TBSI		–0.05±0.17	–0.05±0.17	–0.041±0.2	–0.074±0.16	–0.06±0.16	–0.051±0.18

CASPIAN, Childhood and Adolescence Surveillance and Prevention of Adult Non-Communicable Diseases; MetS, metabolic syndrome; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WH.5R, WC to height^5; TMI, tri-ponderal mass index; TBSI, tri-ponderal body shape index.

The WC percentile (β = 4.28, 95% Crl 2.8–5.8), the TBSI (β = 4.017, 95% Crl 2.7–5.3), and then the WC (β = 3.02, 95% Crl 2.1–3.9) z scores were estimated as the strongest predictors of MetS risks in males aged 10–18 years old. The associations between fasting glucose and anthropometric factors were insignificant ($p > 0.05$; Fig. 2).

In females, the TBSI Z score was estimated as the strongest predictor of lipid profiles and hypertension; however, the WC percentile was estimated as the strongest predictor of MetS compared with other anthropometric measures (Fig. 2). In addition, similar to the male group, the associations between fasting glucose and anthropometric measures were insignificant.

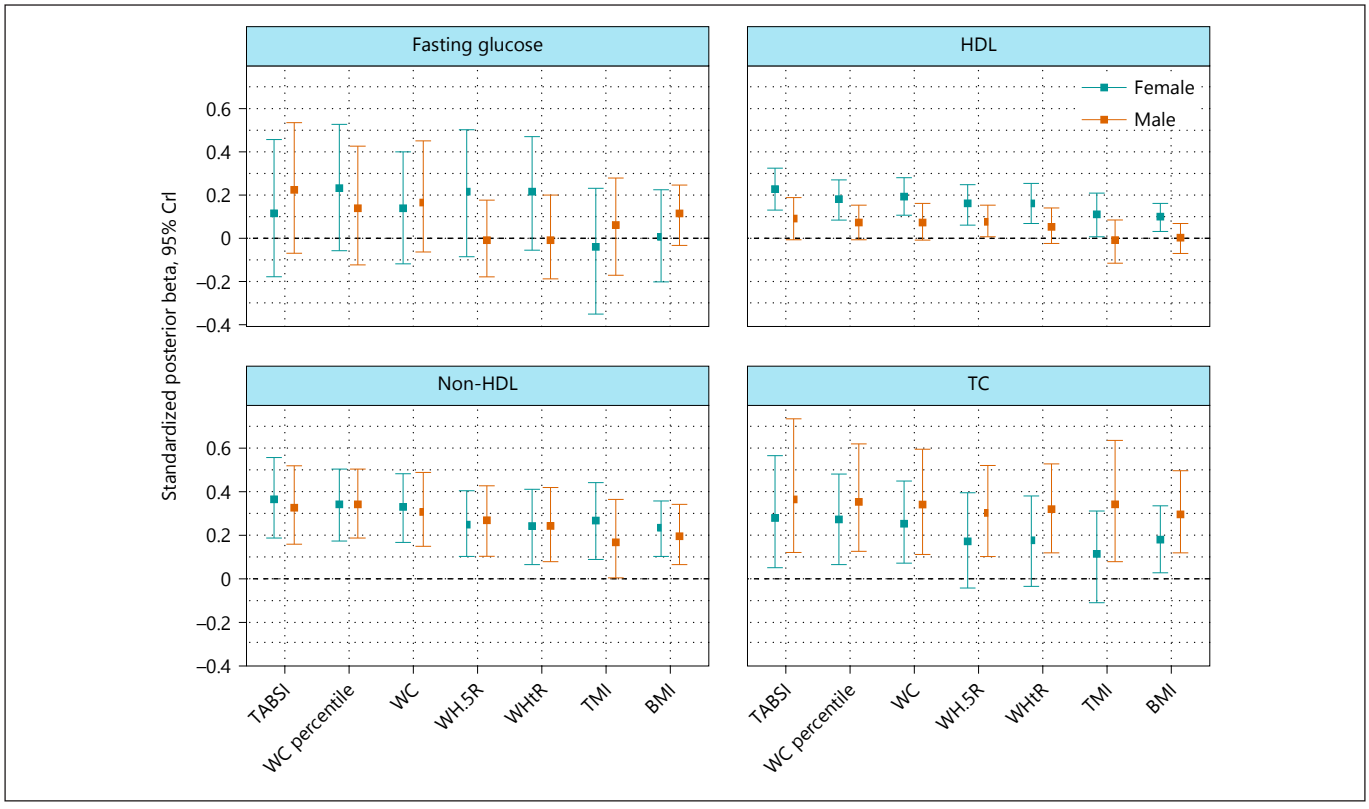

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Fig. 1. Bayesian multilevel model results of association among anthropometric factors and lipid profiles, hypertension, and fasting glucose. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; TBSI, tri-ponderal body shape index; WC, waist circumference; WH.5R, WC to height[5]; WHtR, waist-to-height ratio; TMI, tri-ponderal mass index; BMI, body mass index; CrI, credible interval.

(Figure continued on next page.)

The risk of MetS was higher in children with family history of hypertension (OR 1.31), diabetes (OR 1.29), and obesity at birth (OR 1.38), but these differences were statistically insignificant.

ROC Regression Results in 10–18 Years Old

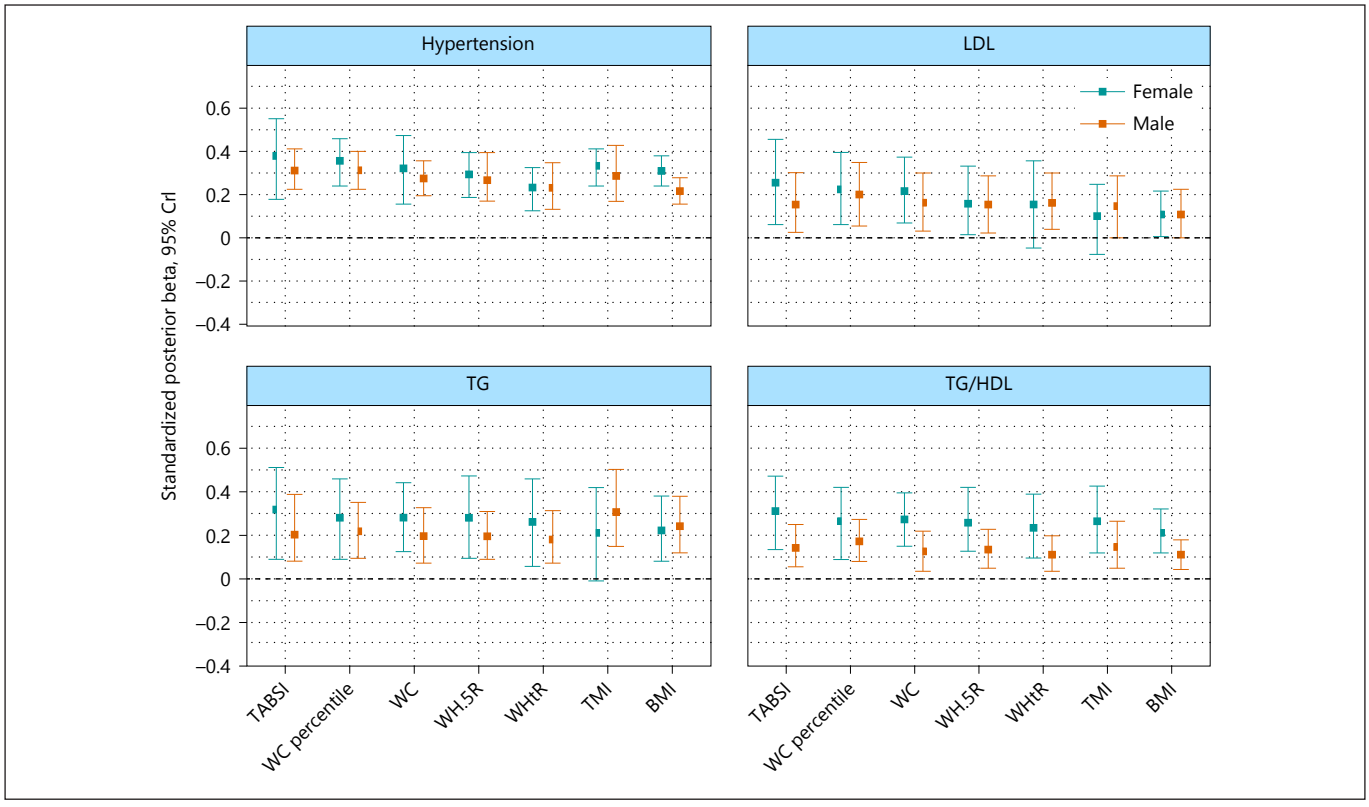
Overall, the estimated AUCs for anthropometric measures vary from 0.846 to 0.936. The WH.5R (AUC = 0.936, Se = 91.48) then the WC Z scores (AUC = 0.93, Se = 90.2) had the highest cumulative predictive ability for MetS from 2003 to 2016.

Tables 2–4 show the ROC regression results as well as the optimal cutoff points of anthropometric measures to classify children to the MetS or healthy groups. In 2003, the WH.5R had the highest predictive ability to the early diagnosis of MetS among children aged 10–18 years old. The predictive capacity of anthropometric factors decreased in both AUC and sensitivity values among the children; however, the decreases were insignificant. The WH.5R (AUC = 0.984, JI = 0.932) and WC Z score (AUC = 0.98, JI = 0.95) with the sensitivity of 100% were superior to the rest of factors for predicting the MetS among males. The WC (AUC = 0.984, JI = 0.934) and TBSI (AUC = 0.982, JI = 0.9) z scores had the highest power to predict MetS among females who were aged 10–18 years.

In 2016 cross-sections, the WH.5R was estimated as a superior predictor for the early predictions of MetS in both males (AUC = 0.95, JI = 0.89, Se = 100%) and females (AUC = 0.944, JI = 0.81, Se = 92.9%). The BMI and BMI Z scores predictive ability were insignificant for girls. In addition, the cutoff points of WHtR decreased in males from 0.52 to 0.513, but it raised in females (0.48–0.53) from 2003 to 2016.

Discussion/Conclusion

This is the first longitudinal research in children designed to evaluate the predictability of non-invasive methods for early detections of abnormal serum lipids,



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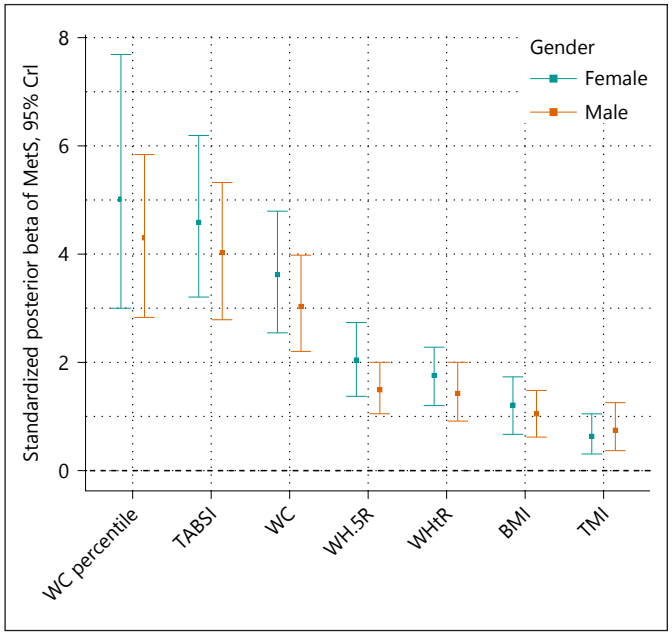

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Fig. 2. Bayesian multilevel model results of association among anthropometric factors and MetS. TBSI, tri-ponderal body shape index; WC, waist circumference; WH.5R, WC to height^5; WHtR, waist-to-height ratio; TMI, tri-ponderal mass index; BMI, body mass index.

fasting glucose, hypertension, and MetS. The results of this RCS study, involving a large sample, clearly showed the higher ability of TBSI for predicting lipid profiles, hypertension, and MetS independent of traditional measures such as WC, WHtR, and BMI z scores in Iranian children, particularly in females. Moreover, WH.5R had a better ability to make early predictions of MetS than WHtR measures.

The WC percentile was estimated as the strongest predictor of MetS in children aged 7–9 years, the MetS could not be diagnosed in children aged 6–9 years old and further measurements recommended for individuals with WC Percentile ≥90 [16]. Therefore, we suggest further cohort studies be conducted to establish the role of anthropometric measures for early predictions of MetS. For this reason, we focused on the predictive ability of the noninvasive methods among children and adolescents aged 10–18 years.

Some studies have reported a stronger positive correlation between WC and lipid profiles than with BMI [17, 18]; moreover, the WC and WHtR have been suggested as stronger predictors of cardiometabolic risks in children than BMI [19, 20]. However, the correlation of BMI with lipid profiles independently of WC is undeniable

Table 2. The Roc regression results of noninvasive method to early prediction of MetS in children aged >10 years over the 13 years of study

Group	Factor	AUC[a]	Associated criterion	Se[b]	Sp[c]	JI[d]
Male	BMI	0.899	>22.66 (20.96–22.83)	90.7	83.51	0.742
	Z BMI	0.888	>1.26 (0.79–1.73)	86.05	82.65	0.687
	WC	0.936	>81.69 (75.5–85.74)	90.7	85.66	0.763
	Z WC	0.932	>1.28 (1.27–1.3)	95.35	90.61	0.859
	WHtR	0.918	>0.513 (0.513–0.521)	93.02	85.32	0.783
	WH.5R	0.94	>6.71 (6.44–6.82)	93.02	90.32	0.833
	TMI	0.867	>14.39 (12.02–15.11)	81.4	83.5	0.649
	TBSI	0.919	>0.161 (0.124–0.166)	93.02	88.63	0.816
Female	BMI	0.852	>20.95 (20.17–22.99)	89.74	68.7	0.584
	Z BMI	0.864	>1.25 (0.49–1.54)	82.05	83.36	0.654
	WC	0.936	>76.9 (72.8–78.5)	94.87	82.03	0.769
	Z WC	0.934	>0.97 (0.97–0.98)	94.87	89.4	0.842
	WHtR	0.911	>0.487 (0.487–0.502)	94.87	78.6	0.734
	WH.5R	0.93	>6.32 (6.2–6.64)	92.31	86.41	0.787
	TMI	0.824	>13.37 (12.93–14.5)	89.74	65.07	0.548
	TBSI	0.928	>0.121 (0.106–0.155)	92.31	88.13	0.804

[a] AUC.
[b] Sensitivity.
[c] Specificity.
[d] Youden index J.

AUC, area under ROC curve; MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WH.5R, WC to height^5; TMI, tri-ponderal mass index; TBSI, tri-ponderal body shape index.

Table 3. The Roc regression results of noninvasive method to early prediction of MetS in children aged >10 years in cross-section I

Group	Factor	AUC[a]	Associated criterion	Se[b]	Sp[c]	JI[d]
Male	BMI	0.965	>22.83	100	87.52	0.875
	Z BMI	0.947	>1.26	94.7	85.8	0.8
	WC	0.987	>85	100	95.11	0.95
	Z WC	0.981	>1.3	100	95.48	0.954
	WHtR	0.967	>0.52	94.74	94.25	0.889
	WH.5R	0.984	>6.44	100	93.21	0.932
	TMI	0.918	>14.06	89.4	89.24	0.757
	TABSI	0.975	>0.155	100	92.77	0.927
Female	BMI	0.893	>20.95	95.83	69.17	0.65
	Z BMI	0.928	>1.25	91.6	84.11	0.75
	WC	0.971	>77	100	88.5	0.885
	Z WC	0.984	>0.98	100	93.41	0.934
	WHtR	0.961	>0.48	100	87.41	0.874
	WH.5R	0.971	>6.2	100	89.01	0.89
	TMI	0.875	>13.36	95.8	68.32	0.641
	TABSI	0.982	>0.116	100	89.8	0.897

[a] AUC.
[b] Sensitivity.
[c] Specificity.
[d] Youden index J.

AUC, area under ROC curve; MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WH.5R, WC to height^5; TMI, tri-ponderal mass index; TBSI, tri-ponderal body shape index.

Table 4. The Roc regression results of noninvasive method to early prediction of MetS in children aged >10 years in cross-section V

Group	Factor	AUC[a]	Associated criterion	SE[b]	SP[c]	JI[d]
Male	BMI	0.892	>22.66	91.3	82.4	0.737
	Z BMI	0.903	>1.53	86.96	86.11	0.73
	WC	0.926	>79.8	95.6	79.7	0.754
	Z WC	0.947	>1.28	100	89.3	0.89
	WHtR	0.935	>0.513	100	82.9	0.829
	WH.5R	0.945	>6.71	100	88.74	0.88
	TMI	0.888	>14.75	86.96	83.76	0.7
	TABSI	0.93	>0.16	0.98	0.89	0.87
Female	BMI	0.831	>20.55	92.86	65.3	0.58
	Z BMI	0.817	>1.28	71.4	83.8	0.55
	WC	0.938	>80.5	85.7	87.5	0.73
	Z WC	0.923	>0.97	92.8	88.04	0.809
	WHtR	0.938	>0.53	92.8	89.5	0.823
	WH.5R	0.944	>6.48	92.86	87.8	0.806
	TMI	0.817	>13.95	85.7	71.2	0.57
	TABSI	0.911	>0.121	92.8	89.5	0.82

[a] AUC.
[b] Sensitivity.
[c] Specificity.
[d] Youden index J.
AUC, area under ROC curve; MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WH.5R, WC to height[5]; TMI, tri-ponderal mass index; TBSI, tri-ponderal body shape index.

[10, 18, 21]. Therefore, in clinical practice, combining of WC and BMI could result in a better prediction of cardiometabolic risks [17, 22]. Krakauer et al. [6] suggested ABSI for the early detections of mortality and morbidity among adults. It is essential to validate and/or modify ABSI in pediatric population. Peterson et al. [23] proposed TMI to improve predictive ability of BMI among children. Moreover, crude values of anthropometric factors could cause biased results and interpretation due to dependency on age, sex, and height in children. For this reason age-sex standardization of anthropometric measures have been recommended in individuals aged <18 years. Using WC z scores instead of WC as well as TMI instated of BMI in children and adolescents can improve ABSI's predictability power. Finally, the results could be observed in the following modified equation:

$$\mathrm{TBSI} = \frac{WC\,Z\,Score}{TMI^{\frac{2}{3}} \times Height^{\frac{1}{2}}}$$

Overall, the WC percentile, TBSI, WC, WH.5R, WHtR, BMI, and TMI Z scores were found to be significant predictors of MetS in children who were aged 10–18 years. In addition, the pattern and strength of correlations between MetS and anthropometric factors were the same for both sexes. Hypertension, HDL, LDL, fasting glucose, and TG are the obvious components of MetS. Therefore, the high correlations between these factors and MetS are not unexpected. In order to clarify the most important anthropometric factors as the predictors of cardiometabolic risks, we analyzed the correlation between them and with serum lipid profiles, hypertension, and fasting glucose. The anthropometric measures with high correlations with serum lipid profiles, fasting glucose, and hypertension could be the important predictors of developing MetS risks. According to Bayesian multilevel results, the TBSI has the highest correlation with hypertension and lipid profiles compared to the remaining anthropometric factors in females. In males, the highest correlation was observed only for TBSI-TC association.

Based on the ROC regression results, the TBSI followed by WC measures have the best predictive ability of MetS compared to the remaining anthropometric factors in children and adolescents throughout the cross sections. The strong association between the WC and MetS is due to components of MetS identification. Therefore, it is very important that TBSI including both the WC and

BMI terms provide superior or even equal power for early predictions of cardiometabolic risks compared with other anthropometric measures among children and adolescents.

To the best of our knowledge, there are very few longitudinal studies that they examined the validity of noninvasive methods for early detections of MetS in children and adolescents. Mameli et al. [5] found a positive association between ABSI z score and fasting insulin, TC, LDL, TG, TG/HDL and a negative association with HDL in overweight and obese children (n = 217) aged 2–18 years. Krakauer and Krakauer [6] concluded that the ABSI was a stronger predictive measure for mortality than BMI and WC among Mexican population. Moreover, studies estimated ABSI with the same or lower accuracy compared to other measures [4, 24, 25]. The difference in population and age groups might be an explanation for the discrepant results between ABSI and serum lipid profiles by gender.

In our study, the association between anthropometric measures and serum lipid profiles varied by both gender and age. Previous studies on the association between ABSI and diseases reported the dependency of association to the age, sex, and ethnic groups [6, 20, 24]. The maturational process and body fat distribution that are connected to age and sex [26] could be an explanation for differences in the predictive ability of anthropometric factors of MetS between sex groups; however, the TBSI by considering the age and height variation of children and adolescents is robust against this fault. Chang et al. [20] defined separate formulas for computing ABSI in adult males and females. Our results did not indicate any improvement in predictability by defining a separate formula for the TBSI. Although the exact reasons for these results were unclear, after validation studies on associations between the TBSI and cardiovascular diseases, by including the TBSI in MetS definition criteria, it will be possible to increase the probability of early detections of MetS among children.

Wicklow et al. [18] examined anthropometric measures (BMI, WC, and WHtR) for MetS detections in 438 children aged 10 years in Canada. They reported the BMI Z score as a stronger predictor of MetS compared to other measures in both sex groups [18]. These differences could be explained by the longitudinal nature of the study as well as the target population. In our study, the BMI had an inferior predictive ability for MetS in both genders. Another longitudinal study has found a stronger ability of WC measure for the early predictions of MetS in girls rather than boys [27]. The mean age difference was the same in the first and last cross-sections; thus, the reduction in the predictive ability of anthropometric parameters could be due to a raise of attributable risk of other risk factors of MetS over time, whereas, the WC cutoff point, as the best predictor of MetS, decreased from 1.3 to 1.28 in males and 0.98 to 0.97 in females. This decrease could be due to the effect of other MetS risk factors that have cluster effects on the total body fat. It is possible that the exposures as well as external and environmental factors attributable to MetS influence the variability of cutoff points that clearly described the mechanism of changes in the distribution of body fat in children. Therefore, longitudinal examinations of anthropometric measures and their predictive capacities are essential in the early predictions of MetS in children and adolescents. The threshold variations of anthropometric factors were ignorable, so we can use them with a determined probability and confidence to classify children in MetS or healthy groups.

Our findings did not show a stronger association of BMI, ABSI, TMI, and WC with MetS, lipid profiles, hypertension, and fasting glucose compared with WHtR, TBSI, and WH.5R among Iranian adolescents. In line with our findings, other studies have indicated that BMI has a lower predictive power for cardiometabolic risks, and accuracy reported for TMI than BMI in children [21, 23]. These studies compared TMI with BMI, indicating that it was inferior to WC components for predicting MetS in children and adolescents, but our analysis did not show a superior predictive ability for TMI compared with other anthropometric measures.

Our findings demonstrated that children with obesity at birth and a family history of hypertension and obesity had more odds of developing MetS. However, these attributable risks were statistically insignificant but are clinically important. Therefore, it is very important to consider the effects of these factors to predict MetS risks.

This research has several limitations. First, the prevalence of MetS among children and adolescents is low; therefore, the subgroup analysis based on important independent variables was impossible. Second, the exact age of developing MetS, hypertension, abnormal lipid profiles, and the anthropometric factors are not clearly known. Therefore, we could not test the hypothesis related to the variables that would predict the MetS earlier than the other measures.

This longitudinal research is the first to demonstrate the ability of the TBSI to predict MetS and cardiometabolic risk factors among pediatrics. We compared the predictability of BMI, WC, WH.5R, WHtR, TMI, ABSI, and TBSI measures with controlling the effects of birth

weight, age-cohort, birth cohort, and time-period effects as well as the history of chronic diseases of parents that might influence serum lipid factors and MetS. In addition, we used the Bayesian multilevel model that accounts the variances related to confounding variables simultaneously compared with ordinary multilevel regression. The Fars, Turkish, Kurdish, and Arab ethnic groups participated in this analysis. Thus, it is possible to generalize the results to Iranian children from different ethnocultural backgrounds.

Overall, considering the serum lipid profiles and hypertension as the important risk factors of cardiometabolic disasters, the TBSI could have a greatest ability and role for early diagnosis of cardiometabolic risks compared with other anthropometric factors among females in adolescents. In addition, the estimated temporal consistency of optimal cutoff points to the main anthropometric factors indicated their usefulness to classify Iranian children to MetS or healthy groups.

In conclusion, the TBSI provides a superior predictive ability for abnormal hypertension and lipid profiles compared with the BMI and WC components in Iranian females aged 10–18 years old. Because of the associations of both WC and BMI with MetS, the modified ABSI could be a strong predictor of MetS than traditional anthropometric measures in Iranian children. Upon further confirmatory research and validation, the TBSI could be used as an important simple and computable predictor of obesity-related diseases in pediatric population. Our findings demonstrate the usefulness of anthropometric cutoff points to predict MetS. Furthermore, the ABSI, BMI or BMI z score should no longer be used to predict MetS and cardiometabolic risk factors in children and adolescents.

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Statement of Ethics

Since this study was retrospective in nature, this article does not contain any studies with human participants or animals performed by any of the authors. This study was approved by the Ethics Review Unit and the Committee on Human Research, and was determined to be and approved as research (IR.MUI.REC.1396.3.564).

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contribution

S.A.-J. the main investigator, performed the statistical analyses and drafted the manuscript. M.M. supervised the study and finalized the manuscript. R.K. advised the study and provided the final article. M.E.M. and R.H. advised for developing statistical model and interpretation results and provided the final article. All authors read and approved of the final manuscript.

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