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ORIGINAL ARTICLE

Estimation of the proportion of metabolic syndrome-free subjects on high cardiometabolic risk using two continuous cardiometabolic risk scores: a cross-sectional study in 16- to 20-year-old individuals

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Abstract

In contrast to the dichotomous classification of metabolic syndrome, continuous metabolic syndrome scores enable to assess cardiometabolic burden in metabolic syndrome-free individuals. Using receiver operating characteristics analysis, discrimination power of continuous metabolic syndrome score calculated from population-based Z-scores or individual measures corrected to the accepted international standards for presence/absence of metabolic syndrome was assessed. Calculated cutoff values were used to estimate the proportions of metabolic syndrome-free subjects presenting high cardiometabolic risk. Clinical data were collected from 2331 (52% females) 16- to 20-year-old subjects. Receiver operating characteristics analyses showed an acceptable performance of both scores to classify metabolic syndrome presence: area under the curve (97–98%), sensitivity (95–100%), and specificity (86–96%). Compared with the prevalence of metabolic syndrome, proportions of metabolic syndrome-free subjects on high cardiometabolic risk, e.g., presenting continuous scores ≥ cutoff points, were about 3-fold higher in males, and 4-fold higher in females. Both scores correlated significantly with markers of cardiometabolic risk.

Conclusion: Continuous cardiometabolic syndrome scores are practical tools to evaluate cardiometabolic risk in subjects not presenting metabolic syndrome. Accuracy, simplicity, and ability to classify metabolic syndrome-free subjects on high cardiometabolic risk make continuous metabolic syndrome score derived from international standards convenient for use in research and clinical practice.

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What is Known:
- *Dichotomous classification of metabolic syndrome is simple but not suitable for assessment of cardiometabolic burden in metabolic syndrome-free subjects. This prompted implementation of continuous scores, which are generally sample-specific. Score based on internationally accepted standards allows for comparison between populations and studies.*
- *The performance of different continuous metabolic syndrome scores to assess the prevalence of metabolic syndrome-free subjects presenting high cardiometabolic burden has not been compared yet.*

What is New:
- *We compared the discrimination power of sample-specific Z-score-derived continuous metabolic syndrome score and that calculated based on internationally accepted standards for presence or absence of metabolic syndrome in young subjects.*
- *The prevalence of metabolic syndrome-free subjects presenting high cardiometabolic risk was estimated using the cutoff points of continuous metabolic syndrome scores derived from the analyses of receiver operating characteristic curves.*

Keywords Metabolic syndrome · Continuous cardiometabolic risk score · Prevalence · Cardiometabolic risk

Abbreviations

AIP	Atherogenic index of plasma
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
GLM	General linear model
HDL-C	High-density lipoprotein cholesterol
hsCRP	High-sensitivity C-reactive protein
LDL-C	Low-density lipoprotein cholesterol
MS	Metabolic syndrome
OR	Odds ratio
QUICKI	Quantitative insulin sensitivity check index
RF	Risk factor
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SD	Standard deviation
siMSS	Continuous metabolic syndrome score calculated using individual measures corrected to the accepted international standards
TAG	Triacylglycerols
WHtR	Waist-to-height ratio
Z-MSS	Population-derived continuous metabolic syndrome score calculated using Z-scores

Introduction

The metabolic syndrome (MS) is a cluster of concurrently manifested conditions, e.g., abdominal obesity, elevated blood pressure (BP), impaired glucose homeostasis, and atherogenic dyslipidemia [1]. Their coexistence enhances the risk of developing type 2 diabetes and cardiovascular diseases, even in young subjects [2, 3].

Diagnosis of MS is based on dichotomous criteria, generally as the presence of 3 out of 5 criteria—central obesity, elevated BP, elevated fasting plasma glucose (FPG), elevated triacylglycerols (TAG), and low high-density lipoprotein cholesterol (HDL-C) concentrations [4–6]. Dichotomous classification enables unequivocal diagnosis of MS, but it is not suitable for assessment of cardiometabolic burden in MS-free subjects or for tracking of individual burden over time. Furthermore, there is no consensus on the classification of MS in children and adolescents. Different classification approaches may result even in 2.5-fold difference in MS prevalence [5, 6]. Continuous MS scores reflect the fact that cardiometabolic risk is a progressive function of several MS risk factor (RF); thus, they enable to overcome the above-mentioned drawbacks [7–11]. Different statistical approaches, such as Z-scores, percentile ranges, factor scores of principal component analysis, etc., are used to calculate population-based continuous MS scores. They allow for exact estimation of the individual cardiometabolic burden within the reference population but do not enable between-population comparison [7–15]. Moreover, any changes in the reference database (removal or addition of subjects) would require recalculation of the individual MS score. The recently proposed MS score authored by Soldatovic I. (siMSS) [16] normalizes the individual measures to the accepted international standards [3, 4, 17]. It represents the sum of ratios of the participant's value for each variable to that of accepted risk factor cutoff point [16], allowing for estimation of individual cardiometabolic risk even if population-based reference data are not available, as well as for comparison across different populations.

Performance of population-based continuous MS score and that of siMSS in the estimation of the proportion of MS-free subjects displaying high cardiometabolic risk has not been compared yet. Assuming that the presence of MS unequivocally indicates high cardiometabolic risk, we used the receiver operating characteristic (ROC) curve to estimate population-specific Z-score (Z-MSS) or siMSS cutoff point predicting MS. We supposed that if ROC curve analysis yields acceptable area under the curve (AUC), sensitivity, and specificity, proportion of subjects without MS displaying high

cardiometabolic risk could be reliably estimated. We hypothesized that their proportion is higher than the prevalence of subjects presenting MS. To test whether the MS scores reflect metabolic abnormalities beyond 5 components of MS, we compared the levels and the prevalence of selected cardiometabolic risk markers in individuals without MS displaying MS score either bellow or ≥ the cutoff point, and subjects manifesting MS. Due to sex differences in the prevalence of single MS components [18, 19], males and females were evaluated separately.

Subjects and methods

The data were collected from November 2011 to December 2012 in Bratislava region of Slovakia, in frames of a secondary-school-based study "Respect for Health." Protocol of this study has been explained in detail previously [20]. The exclusion criteria included any acute or chronic illness, in females pregnancy or lactation. Out of 2370 eligible White Caucasians of Central European descent aged 16 to 20 years, 39 were excluded due to missing data for classification of MS. The current analysis included 2331 individuals (52% females).

The study was approved by the Ethics Board of the Health Department of the Bratislava Self-governing Region. A written informed consent was obtained from full-aged participants. In subjects under 18 years of age, their verbal assent and written consent from a parent or legal guardian were acquired. Participation was on a voluntary basis.

Anthropometric and BP measurements were performed by trained personnel according to the standard protocol, as previously reported [20]. Briefly, height was measured in a standing position using a portable stadiometer, waist circumference using a flexible tape, and body weight using electronic scales. Body mass index (BMI) and waist-to-height ratio (WHtR) were calculated.

BP was measured on the right arm in the sitting position after 10-min rest, using a sphygmomanometer. The mean of the last 2 measurements out of 3 taken was recorded.

Blood samples were drawn from participants after overnight fasting. Blood chemistry measurements were performed at the central laboratory using standard laboratory methods. FPG, fasting plasma insulin (FPI), total cholesterol (TC), HDL-C, TAG, creatinine, uric acid, and high-sensitivity C-reactive protein (hsCRP) were analyzed using the ADVIA 2400 analyzer (Siemens, Erlangen, Germany). Low-density lipoprotein cholesterol (LDL-C) concentration [21], atherogenic index of plasma (AIP = log (TAG/HDL-C) [22], and the quantitative insulin sensitivity check index (QUICKI) were calculated [23]. The estimated glomerular filtration rate (eGRF) was calculated using the Schwartz formula (subjects up to 18 years of age), in older individuals using the Modification of Diet in Renal Disease formula [24, 25].

MS was defined as a presence of at least 3 MS components, e.g., SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, TAG ≥ 1.7 mmol/l, HDL-C; < 1.03 mmol/l in males and < 1.29 mmol/l in females, FPG ≥ 5.6 mmol/l, and WHtR ≥ 0.5 [3, 4, 17].

The concentration of FPI ≥ 20 μIU/ml, uric acid concentrations ≥ 420 mmol/l in males, and ≥ 340 mmol/l in females, and AIP ≥ 0.11 [22] were also considered as cardiometabolic risk markers.

Sex-specific Z-MSS was calculated as the sum of z-scores of WHtR, SBP, FPG, TAG, and HDL-C (inverted).

SiMSS was calculated as WHtR/0.5 + FPG/5.6 + TAG/1.7 + SBP/130 − HDL-C/1.02 (males) or 1.28 (females) [16]. A higher continuous MS score indicates a less favorable cardiometabolic profile.

Statistical analyses

Data are presented as the mean ± standard deviation (SD), mean and 95% confidence interval (CI), or as counts and percentages. Data distribution was checked by using the D'Agostino test. Skewed data were logarithmically transformed. For continuous data, between-sex differences were compared by using the two-sided Student's t test; 3 sets of data were compared using the analysis of variance (ANOVA) with post-hoc Šidák's test to correct for multiple comparisons. Effects of sex, MS component number, and their interaction on continuous MS scores were tested using the general linear model (GLM). The chi-square test (with Yates' correction where appropriate) was used to compare proportions. Spearman correlation coefficients and and odds ratios (OR) were calculated. P values < 0.05 were considered significant.

To estimate the valid cutoff value of MS score for predicting MS, the ROC curve analysis was performed. The overall performance of the ROC test was quantified with AUC; sensitivity and specificity were estimated. The maximum value of sensitivity + specificity was used as a criterion for selecting the optimum MSS cutoff point. Analyses were performed by using the GraphPad Prism software, v.6.0 (GraphPad Software, San Diego, CA, USA) and the SPSS v.16 for Windows software (SPSS Inc., Chicago, IL, USA).

Results

The general characteristics of the participants are presented in Table 1. Males differed significantly from females in all variables except for age, FPI and TAG concentrations and the prevalence of their elevated levels, QUICKI, and Z-MSS.

Table 1 General characteristics of participants

	Males	Females	*p*
n	1118	1213	
Age (years)	17.2 (1.1)	17.2 (1.1)	0.347
Height (cm)	179.2 (6.8)	165.7 (6.3)	< 0.001
Bwt (kg)	74.5 (13.8)	60.4 (10.6)	< 0.001
Waist (cm)	79.7 (9.0)	71.8 (8.0)	< 0.001
WHtR	0.44 (0.05)	0.43 (0.05)	< 0.001
BMI (kg/m^2)	23.2 (3.8)	22.0 (3.5)	< 0.001
SBP	123 (12)	107 (9)	< 0.001
DBP	73 (8)	71 (8)	< 0.001
FPG (mmol/l)	4.9 (0.5)	4.7 (0.8)	< 0.001
FPI (μIU/ml)	11.1 (6.2)	11.2 (6.6)	*0.055*
QUICKI	0.344 (0.028)	0.344 (0.026)	0.741
TC (mmol/l)	3.84 (0.70)	4.29 (0.77)	< 0.001
HDL-C (mmol/l)	1.25 (0.23)	1.53 (0.30)	< 0.001
TAG (mmol/l)	0.89 (0.47)	0.90 (0.43)	*0.092*
AIP	− 0.19 (0.23)	− 0.26 (0.20)	< 0.001
UA (mmol/l)	354 (60)	257 (50)	< 0.001
eGFR (ml/s)	1.6 (0.3)	1.7 (0.3)	< 0.001
hsCRP (mg/l)	1.0 (2.1)	1.5 (3.2)	*< 0.001*
siMSS	2.03 (0.48)	1.88 (0.43)	< 0.001
Z-MSS	0.00 (2.75)	− 0.00 (2.59)	0.997
The prevalence of cardiometabolic risk factors			
eSBP	309 (27.6%)	19 (1.6%)	< 0.001
eDBP	81 (7.2%)	57 (4.7%)	0.009
eBP	326 (29.2%)	66 (5.4%)	< 0.001
eWHtR	151 (13.5%)	116 (9.6%)	0.003
eFPG	78 (7.0%)	27 (2.2%)	< 0.001
eFPI	86 (7.7%)	80 (6.6%)	0.301
lHDL	164 (14.7%)	270 (22.3%)	< 0.001
eTAG	63 (5.6%)	70 (5.8%)	0.893
eAIP	97 (8.7%)	48 (4.0%)	< 0.001
eUA	149 (13.2%)	61 (5.0%)	< 0.001

siMSS = WHtR/0.5 + FPG/5.6 + TAG/1.7 + SBP/130 − HDL-C/1.02 (males) or 1.28 (females) [16]; data are given as mean (standard deviation), in case on frequencies as number (percentage); *p* was calculated using 2-sided Student's *t* test (in case of calculations performed on logarithmically transformed data results are given in Italics)

n number of subjects, *Bwt* body weight, *WHtR* waist-to-height ratio, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *FPI* fasting plasma insulin, *QUICKI* quantitative insulin sensitivity check index, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TAG* triacylglycerols, *AIP* atherogenic index of plasma, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *hsCRP* high-sensitivity C-reactive protein, *MS* metabolic syndrome, *e* elevated, *l* low, *Z-MSS* population-based continuous metabolic syndrome score (sum of WHtR, FPG, TAG, SBP, and HDL-C (inverted) Z-scores)

Males presented more frequently 1 ($p = 0.007$), 2, and ≥ 3 ($p < 0.001$, both) components of MS, while a higher proportion of females was MS components free ($p < 0.001$) (Table 2). SiMSS as well as Z-MSS increased significantly with the rising number of MS components (Table 2). The GLM indicated a significant effect of MS component number ($p < 0.001$), sex ($p = 0.002$), and their interaction ($p < 0.001$) on siMSS. The model explained 46% in siMSS variability. Regarding the Z-MSS, the model explained 49% in its variability, with *p* values of 0.001, < 0.001, and 0.011, respectively.

Spearman correlations between siMSS and body weight, waist circumference, BMI, DBP, FPI, QUICKI, TC, LDL-C, AIP, uric acid, and hsCRP ranged 0.246 to 0.880 ($p < 0.001$, all) in males, and 0.099 to 0.816 ($p \leq 0.001$, all) in females; correlations between Z-MSS and mentioned variables ranged 0.256 to 0.697 ($p < 0.001$, all) in males, and 0.109 to 0.602 ($p \leq 0.001$, all) in females (Online resource).

Males

Among males not presenting MS, about 53% were free from any component of MS, 34% presented one, and 12% manifested 2 components. Eighty-three percent of males displaying MS presented 3 MS RFs; all others displayed 4 RFs (Table 2).

SiMSS value predicting MS was 2.369 (sensitivity 95%, specificity 86%, AUC 97% (95% CI 95%–98%)). The ROC curves of siMSS and Z-MSS corresponding to MS are given in Fig. 1a.

Among males not presenting MS, 15% displayed siMSS ≥ 2.369, thus could be considered as subjects on increased cardiometabolic risk (Table 3); 9% out of them did not present a single MS RF, 43% displayed 1, and 49% presented 2 RFs. Among those with siMSS below the cutoff point, the prevalence reached 61%, 33%, and 6%, respectively ($p < 0.001$). In both groups of males without MS, siMSS increased significantly ($p < 0.001$) by rising number of MS components (Online resource). MS-free males on high cardiometabolic risk displayed worse cardiometabolic characteristics compared with their counterparts presenting siMSS < 2.369 and higher prevalence of cardiometabolic RFs (Table 3).

Compared with males presenting MS, those without MS on high cardiometabolic risk showed significantly better cardiometabolic characteristics and lower prevalence of cardiometabolic RFs (Table 3). Two males with MS presented siMSS below the MS cutoff point.

Z-MSS predicting MS was 2.149 (sensitivity 100%, specificity 86%, AUC 98% (95% CI 97%–99%)).

Based on Z-MSS cutoff point, 14% of MS-free males displayed high cardiometabolic risk (Table 3). Among them, 3% did not display a single MS RF, 38% presented 1, and 59% presented 2 components. The prevalence in subjects presenting Z-MSS < 2.149 reached 61%, 34%, and 5%, respectively ($p < 0.001$). In both subgroups of males not presenting MS, Z-MSS showed an increased trend with rising number of MS components ($p < 0.005$, both; Online resource). MS-free

Table 2 Number of presented components of metabolic syndrome, continuous metabolic syndrome score based on international standards and continuous metabolic syndrome score calculated from population-derived Z-scores according to the number of presented components in males and females

Number of MS components	Males			Females		
	N (%)	siMSS Mean (SD)	Z-MSS Mean (SD)	*N* (%)	siMSS Mean (SD)	Z-MSS Mean (SD)
0	571 (51.1)	1.80 (0.30)	− 1.55 (1.65)	781 (64.4)	1.70 (0.29)	− 1.05 (1.76)
1	366 (32.7)	2.08 (0.32)	0.48 (1.67)	335 (27.6)	2.10 (0.31)	1.10 (1.83)
2	133 (11.9)	2.46 (0.41)	2.95 (2.40)	78 (6.4)	2.55 (0.60)	4.24 (3.83)
3	40 (3.6)	3.09 (0.72)	6.30 (2.97)	18 (1.5)	2.82 (0.29)	6.08 (1.62)
4	8 (0.7)	3.57 (0.70)	8.02 (2.79)	1 (0.1)	3.20	7.78
≥ 3	48 (4.3)	3.17 (0.73)	6.59 (2.98)	19 (1.6)	2.84 (0.30)	6.17 (1.63)

MS metabolic syndrome, *N* number, *siMSS* continuous metabolic syndrome score based on international standards (= WHtR/0.5 + FPG/5.6 + TAG/1.7 + SBP/130 − HDL-C/1.02 (males) or 1.28 (females)) [16], *Z-MSS* continuous metabolic syndrome score calculated from population-derived Z-scores (sum of WHtR, FPG, TAG, SBP, and HDL-C (inverted) Z-scores), *SD* standard deviation

males on high cardiometabolic risk displayed worse cardiometabolic characteristics and a higher prevalence of cardiometabolic RFs compared with their counterparts presenting Z-MSS < 2.149 (Table 3).

Among MS-free males, the OR of presenting the score ≥ cutoff value using siMSS vs. Z-MSS was insignificant (OR 1.15, 95% CI 0.90–1.46, $p = 0.269$).

Females

The prevalence according to the number of presented MS components is given in Table 2. Sixty-five percent of MS-free females were MS RF-free, 28% presented 1, and 7% displayed 2 RFs. Among females displaying MS, 95% presented 3 MS RFs, 1 girl displayed 4 RFs.

SiMSS value for predicting MS was 2.431 (sensitivity 95%, specificity 93%, AUC 97% (95% CI 96%–99%)). ROC curves of siMSS and Z-MSS corresponding to MS are given in Fig. 1b.

Among MS-free females, 7% presented siMSS ≥ 2.431, e.g., were on high cardiometabolic risk (Table 4). Six percent out of them did not present any MS RF, 49% displayed 1, and 44% presented 2 RFs, while in those with siMSS < 2.431, the prevalence reached70%, 26%, and 4%, respectively ($p < 0.001$). In both groups of females without MS, siMSS increased significantly ($p < 0.001$) by rising number of MS RFs (Online resources). Females without MS presenting high cardiometabolic risk displayed significantly worse cardiometabolic characteristics compared with their counterparts presenting siMSS < 2.431, and a higher prevalence of cardiometabolic RFs, except for those of BP (Table 4).

In comparison with females manifesting MS, MS-free subjects on the high cardiometabolic risk presented lower WHtR, BP measures, FPI and uric acid levels, and lower prevalence of elevated DBP, BP, WHtR, and low HDL-C levels (Table 4).

One out of 19 females with MS presented siMSS below the cutoff point for MS prediction.

Z-MSS predicting MS was 3.823 (sensitivity 100%, specificity 96%, AUC 98% (95% CI 97%–99%)).

About 5% of MS-free females presented Z-MSS ≥ cutoff point (Table 4). Among them, 3% did not display a single MS RF, 30% presented 1, and 67% presented 2 components. The prevalence in subjects on low cardiometabolic risk reached 68%, 28%, and 4%, respectively ($p < 0.001$). In MS-free females on low cardiometabolic risk, Z-MSS showed an increasing trend ($p < 0.001$) with rising number of MS components, while in those displaying high cardiometabolic risk significance has not been reached ($p_{ANOVA} = 0.466$; Online resources). Females on high cardiometabolic risk displayed worse cardiometabolic characteristics, and a higher prevalence of cardiometabolic RFs (except for DBP) compared with their counterparts on low risk (Table 4).

Among MS-free females, the OR of being classified on high cardiometabolic risk using siMSS vs. Z-MSS was significant (OR 1.54, 95% CI 1.08–2.19, $p = 0.018$).

Discussion

Both siMSS and Z-MSS have good construct and predictive validity for MS in 16- to 20-year-old subjects. Our data confirm that dichotomic classification of MS underestimates cardiometabolic burden: compared with the prevalence of individuals presenting MS, the proportion of MS-free subjects presenting siMSS in range displayed by subjects with MS was about 3.4-fold higher in males, and 4.2-fold higher in females, while using Z-MSS, it was 3-fold and 2.8-fold higher, respectively.

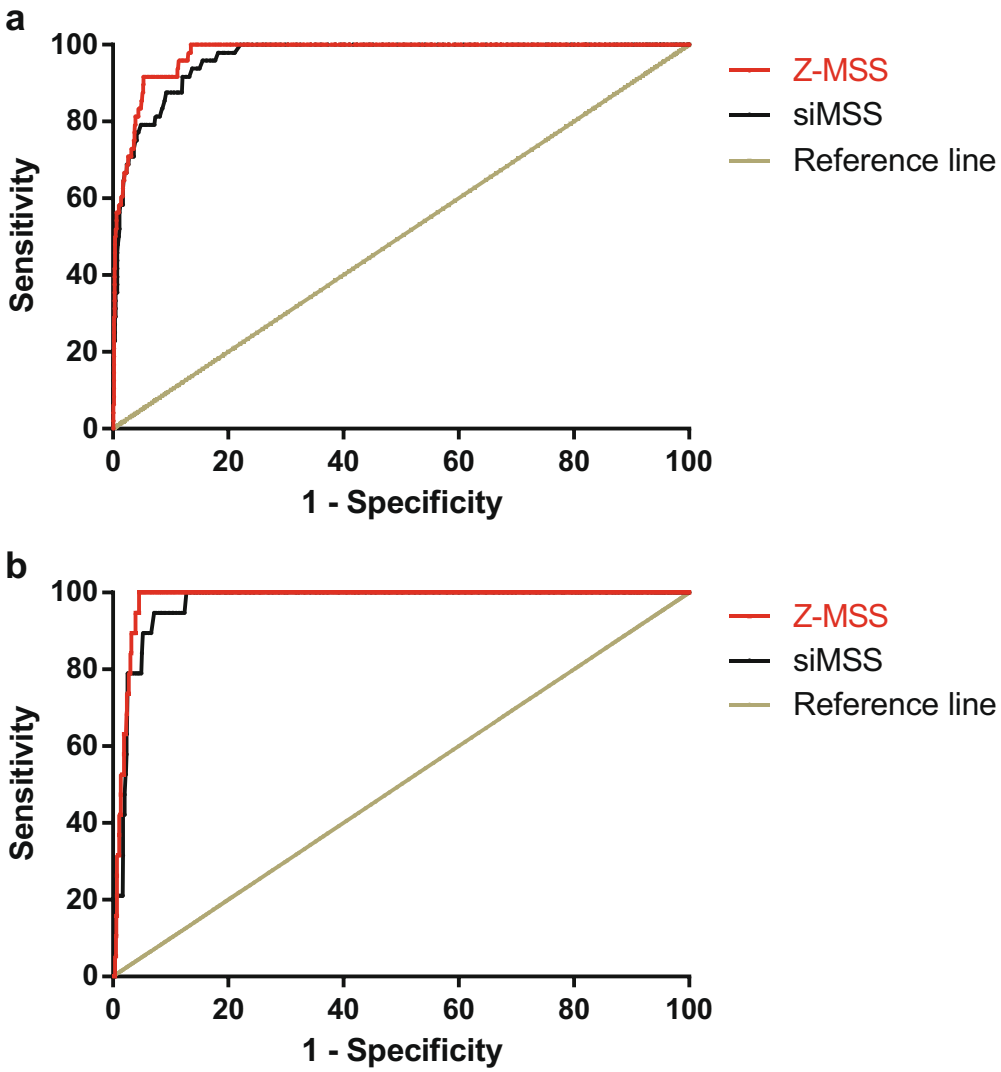

Fig. 1 The receiver operating characteristic curves of continuous metabolic syndrome score derived from sample-specific Z-scores (Z-MSS) and continuous metabolic syndrome score based on international standards (siMSS) corresponding to metabolic syndrome **a** in males and **b** in females

Dichotomous classification of MS is easy, quick, and the presence of MS is predictive regarding increased cardiometabolic risk [1, 2, 4]. However, due to different definitions of MS and criteria employed, the same subjects are not always classified concordantly as presenting MS, thus prevalence of MS in the same cohort may vary substantially [5, 6]. The low agreement among the existing classifications led to the elaboration of alternative approaches, e.g., continuous scores of the syndrome [7–15], allowing for estimation of cardiometabolic risk even in subjects not presenting MS yet. In our study, continuous MS scores performed similarly in both sexes: Z-MSS and siMSS identified the subjects presenting MS with 100% and 95% sensitivity, respectively. Specificity of both scores was also similar. Considering that Z-MSS exactly reflects the metabolic burden of an individual within a specific population, while siMSS captures it in relation to internationally accepted standards, the difference in their performance is minimal. This was mirrored only by a small difference in MS prevalence: 4.3% vs. 4.1% in males, and 1.6% vs. 1.5% in females. For both scores, the optimal cutoff points for identification of MS were higher in females than males. This is an interesting finding, since Z-MSS is calculated using sex-specific values, while denominator for HDL-C is the single sex-specific constant in the siMSS equation. Optimal cutoff points seem to be indicative of sex differences, since also the GLM indicated a significant impact of sex on both score values in relation to MS components number. Sex differences in optimal continuous MS score cutoff points were also reported in other studies [10, 26]. Reasons remain unclear, but they might reflect the different prevalence of single MS components in males and females, as well as more common clustering of the components in males. The latter fact might impose a higher cardiometabolic risk in presence

Table 3 Characteristics of males without metabolic syndrome presenting continuous metabolic syndrome score based on international standards and continuous metabolic syndrome score calculated from population-derived Z-score value either under or equal to and above the cutoff point, and those presenting metabolic syndrome

	Without MS		MS	*p*	Without MS		MS	*p*
	siMSS < 2.369	siMSS ≥ 2.369			Z-MSS < 2.149	Z-MSS ≥ 2.149		
n	906	164	48		924	146	48	
WHtR	0.43 (0.04)	0.48 (0.06)***	0.54 (0.06)$^{***,+++}$	< 0.001	0.43 (0.04)	0.50 (0.06)***	0.54 (0.06)$^{***,+++}$	< 0.001
SBP (mm Hg)	122 (11)	128 (13)***	135 (12)$^{***,++}$	< 0.001	121 (11)	132 (14)***	135 (12)***	< 0.001
DBP (mm Hg)	72 (7)	76 (8)***	81 (10)$^{***,++}$	< 0.001	72 (7)	78 (8)***	81 (10)***	< 0.001
FPG (mmol/l)	4.8 (0.4)	5.1 (0.9)***	5.2 (0.6)***	< 0.001	4.9 (0.4)	5.2 (0.9)***	5.2 (0.6)***	< 0.001
FPI (μIU/ml)	9.6 (5.2)	15.8 (11.6)***	24.3 (17.3)$^{***,+++}$	*< 0.001*	9.5 (5.2)	16.5 (11.7)***	24.3 (17.3)$^{***,+++}$	*< 0.001*
QUICKI	0.349 (0.025)	0.326 (0.027)***	0.308 (0.029)$^{***,+++}$	< 0.001	0.349 (0.025)	0.322 (0.025)***	0.308 (0.029)$^{***,++}$	< 0.001
TC (mmol/l)	3.74 (0.63)	4.18 (0.79)***	4.39 (1.04)***	< 0.001	3.75 (0.63)	4.23 (0.78)***	4.39 (1.04)***	< 0.001
HDL-C (mmol/l)	1.29 (0.21)	1.08 (0.17)***	0.98 (0.21)$^{***,+}$	< 0.001	1.28 (0.22)	1.12 (0.17)***	0.98 (0.21)$^{***,+++}$	< 0.001
TAG (mmol/l)	0.75 (0.25)	1.37 (0.45)***	1.83 (1.14)$^{***,+}$	*< 0.001*	0.78 (0.29)	1.27 (0.50)***	1.83 (1.14)$^{***,+++}$	*< 0.001*
AIP	− 0.26 (0.17)	0.09 (0.14)***	0.21 (0.30)$^{***,++}$	< 0.001	− 0.24 (0.17)	0.03 (0.19)***	0.21 (0.30)$^{***,+++}$	< 0.001
UA (mmol/l)	348 (57)	376 (59)***	411 (67)$^{***,++}$	< 0.001	348 (57)	376 (59)***	411 (67)$^{***,++}$	< 0.001
eGFR (ml/s)	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	0.351	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	0.274
hsCRP (mg/l)	0.9 (1.8)	1.4 (1.9)***	2.7 (5.2)***	*< 0.001*	0.9 (1.8)	1.4 (1.9)***	2.7 (5.2)***	*< 0.001*
siMSS	1.86 (0.29)	2.62 (0.25)***	3.17 (0.73)$^{***,+++}$	< 0.001	1.88 (0.31)	2.60 (0.29)***	3.17 (0.73)$^{***,+++}$	< 0.001
Z-MSS	− 0.94 (1.76)	3.27 (1.97)***	6.59 (2.98)$^{***,+++}$	< 0.001	− 0.93 (1.70)	3.72 (1.78)***	6.59 (2.98)$^{***,+++}$	< 0.001
Prevalence								
eSBP	207 (22.8)	65 (39.6)***	37 (77.1)$^{***,+++}$	< 0.001	190 (20.6)	82 (56.2)***	37 (77.1)$^{***,+++}$	< 0.001
eDBP	47 (5.2)	18 (11.0)**	16 (33.3)$^{***,+++}$	< 0.001	41 (4.4)	24 (16.4)***	16 (33.3)$^{***,+}$	< 0.001
eBP	222 (24.5)	66 (40.2)***	38 (79.2)$^{***,+++}$	< 0.001	206 (22.3)	82 (56.2)***	38 (79.2)$^{***,++}$	< 0.001
eWHtR	57 (6.3)	52 (31.7)***	42 (87.5)$^{***,+++}$	< 0.001	46 (5.0)	63 (33.2)***	42 (87.5)$^{***,+++}$	< 0.001
eFPG	47 (5.2)	17 (10.4)**	14 (29.2)$^{***,++}$	< 0.001	45 (4.9)	19 (13.0)***	14 (29.2)$^{***,++}$	< 0.001
eFPI	33 (3.6)	33 (20.1)***	20 (41.7)$^{***,++}$	< 0.001	34 (3.7)	32 (21.9)***	20 (41.7)$^{***,++}$	< 0.001
lHDL	74 (8.2)	58 (35.4)***	32 (66.7)$^{***,+++}$	< 0.001	96 (10.4)	36 (24.7)***	32 (66.7)$^{***,+++}$	< 0.001
eTAG	2 (0.2)	37 (22.6)***	24 (50.0)$^{***,++}$	< 0.001	12 (1.3)	27 (18.5)***	24 (50.0)$^{***,+++}$	< 0.001
eAIP	4 (0.4)	62 (37.8)***	31 (64.6)$^{***,++}$	< 0.001	25 (2.7)	41 (28.1)***	31 (64.6)$^{***,++}$	< 0.001
eUA	89 (9.8)	36 (22.0)***	24 (50.0)$^{***,+++}$	< 0.001	92 (10.0)	33 (22.6)***	24 (50.0)$^{***,++}$	< 0.001

Data are given as mean (standard deviation), for prevalence as counts (percentages); *p* was calculated using analysis of variance with post hoc Šidak's test (in case of calculations performed on logarithmically transformed data, results are given in italics), prevalence was compared using chi-square test; $^{*}p < 0.05$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score below the indicated cutoff point; $^{**}p < 0.01$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score below the indicated cutoff point;$^{***}p < 0.001$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score below the indicated cutoff point; $^{+}p < 0.05$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score ≥ the cutoff point; $^{++}p < 0.01$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score ≥ the cutoff point; $^{+++}p < 0.001$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score ≥ the cutoff point

MS metabolic syndrome, *siMSS* continuous metabolic syndrome score based on international standards (= WHtR/0.5 + FPG/5.6 + TAG/1.7 + SBP/130 – HDL-C/1.02) [16], *Z-MSS* continuous metabolic syndrome score calculated from population-derived Z-scores (= sum of WHtR, FPG, TAG, SBP, and HDL-C (inverted) Z-scores)), *n* number of subjects, *WHtR* waist-to-height ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *FPI* fasting plasma insulin, *QUICKI* quantitative insulin sensitivity check index, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TAG* triacylglycerols, *AIP* atherogenic index of plasma, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *hsCRP* high-sensitivity C-reactive protein, *e* elevated, *l* low, *WHtR* waist-to-height ratio

of mild increase of multiple RFs. In line with other data employing population-specific continuous MS scores [7, 10, 12, 26, 27], we observed a graded relationship between either siMSS or Z-MSS and having 0 to 4 components of MS, with the highest values in subjects presenting MS.

Our data confirm the former statements that continuous MS score is particularly suitable for detecting increased cardiometabolic risk prior to the manifestation of MS [7–9, 11, 16, 28], and extend the current knowledge by estimation of the prevalence of MS-free subjects presenting high

Table 4 Characteristics of females without metabolic syndrome presenting continuous metabolic syndrome score based on international standards and continuous metabolic syndrome score calculated from population-derived Z-score value either under or equal to and above the cutoff point, and those presenting metabolic syndrome

	Without MS		MS	*p*	Without MS		MS	*p*
	siMSS < 2.431	siMSS ≥ 2.431			Z-MSS < 3.823	Z-MSS ≥ 3.823		
n	1113	81	19		1140	54	19	
WHtR	0.43 (0.04)	0.49 (0.08)***	0.53 (0.06)$^{***,+++}$	< 0.001	0.43 (0.04)	0.53 (0.08)***	0.53 (0.06)***	< 0.001
SBP (mm Hg)	107 (9)	111 (8)***	120 (9)$^{***,++}$	< 0.001	107 (9)	116 (8)***	120 (9)***	< 0.001
DBP (mm Hg)	70 (7)	72 (7)*	85 (9)$^{***,+++}$	< 0.001	70 (7)	75 (7)***	85 (9)$^{***,+++}$	< 0.001
FPG (mmol/l)	4.6 (0.4)	5.3 (0.5)***	4.9 (0.7)	< 0.001	4.6 (0.4)	5.6 (3.1)***	4.9 (0.7)$^{++}$	< 0.001
FPI (μIU/ml)	10.5 (5.5)	17.0 (9.2)***	23.8 (17.3)$^{***,+}$	*< 0.001*	10.6 (5.6)	18.0 (10.3)***	23.8 (17.3)***	*< 0.001*
QUICKI	0.346 (0.025)	0.320 (0.024)***	0.313 (0.034)***	< 0.001	0.346 (0.025)	0.317 (0.026)***	0.313 (0.034)***	< 0.001
TC (mmol/l)	4.26 (0.75)	4.73 (0.87)***	4.59 (0.98)	< 0.001	4.27 (0.76)	4.58 (0.90)*	4.59 (0.98)	0.004
HDL-C (mmol/l)	1.55 (0.30)	1.29 (0.27)***	1.17 (0.11)***	< 0.001	1.55 (0.30)	1.27 (0.24)***	1.17 (0.11)***	< 0.001
TAG (mmol/l)	0.84 (0.33)	1.70 (0.67)***	1.50 (0.53)***	*< 0.001*	0.86 (0.37)	1.53 (0.76)***	1.50 (0.53)***	*< 0.001*
AIP	− 0.29 (0.18)	0.10 (0.13)***	0.08 (0.16)***	< 0.001	− 0.28 (0.19)	0.04 (0.19)***	0.08 (0.16)***	< 0.001
UA (mmol/l)	255 (49)	275 (60)***	304 (46)$^{***,+}$	< 0.001	254 (49)	284 (68)***	304 (46)***	< 0.001
eGFR (ml/s)	1.7 (0.2)	1.8 (0.3)	1.8 (0.3)	0.076	1.7 (0.2)	1.7 (0.3)	1.8 (0.3)	0.135
hsCRP (mg/l)	1.3 (2.7)	4.7 (2.5)***	2.8 (2.8)***	*< 0.001*	1.4 (3.1)	4.4 (4.8)***	2.8 (2.8)**	*< 0.001*
siMSS	1.80 (0.31)	2.78 (0.51)***	2.84 (0.30)***	< 0.001	1.82 (0.33)	2.85 (0.62)***	2.84 (0.30)***	< 0.001
Z-MSS	− 0.47 (1.90)	4.98 (3.63)***	6.17 (1.63)***	< 0.001	− 0.40 (1.93)	6.28 (3.86)***	6.17 (1.63)***	< 0.001
Prevalence								
eSBP	14 (1.3)	2 (2.5)	3 (15.8)$^{***,+}$	< 0.001	11 (1.0)	5 (9.3)***	3 (15.8)***	< 0.001
eDBP	41 (3.7)	2 (2.5)	14 (73.7)$^{***,+++}$	< 0.001	38 (3.3)	5 (9.3)	14 (73.7)$^{***,+++}$	< 0.001
eBP	48 (4.3)	3 (3.7)	15 (78.9)$^{***,+++}$	< 0.001	44 (3.9)	7 (13.0)**	15 (78.9)$^{***,+++}$	< 0.001
eWHtR	74 (6.6)	27 (33.3)***	15 (78.9)$^{***,+++}$	< 0.001	71 (6.2)	30 (55.6)***	15 (78.9)***	< 0.001
eFPG	16 (1.4)	7 (8.6)***	4 (21.1)***	< 0.001	18 (1.6)	5 (9.3)***	4 (21.1)***	< 0.001
eFPI	50 (4.5)	22 (27.2)***	8 (42.1)***	< 0.001	55 (4.8)	17 (31.5)***	8 (42.1)***	< 0.001
lHDL	214(19.2)	38 (46.9)***	18 (94.7)$^{***,+++}$	< 0.001	224(19.6)	28 (51.9)***	18 (94.7)$^{***,+++}$	< 0.001
eTAG	27 (2.4)	37 (45.7)***	6 (31.6)***	< 0.001	46 (4.0)	18 (33.3)***	6 (31.6)***	< 0.001
eAIP	5 (0.4)	34 (42.0)***	9 (47.4)***	< 0.001	21 (1.8)	18 (33.3)***	9 (47.4)***	< 0.001
eUA	47 (4.2)	10 (12.3)***	4 (21.1)***	< 0.001	45 (3.9)	12 (22.2)***	4 (21.1)***	< 0.001

Data are given as mean (standard deviation), for prevalence as counts (percentages); *p* was calculated using analysis of variance with post hoc Šidak's test (in case of calculations performed on logarithmically transformed data, results are given in italics), prevalence was compared using chi-square test; $^{*}p < 0.05$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score below the indicated cutoff point; $^{**}p < 0.01$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score below the indicated cutoff point;$^{***}p < 0.001$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score below the indicated cutoff point; $^{+}p < 0.05$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score ≥ the cutoff point; $^{++}p < 0.01$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score ≥ the cutoff point; $^{+++}p < 0.001$ vs. subjects without metabolic syndrome presenting continuous metabolic syndrome score ≥ the cutoff point

MS metabolic syndrome, *siMSS* continuous metabolic syndrome score based on international standards (= WHtR/0.5 + FPG/5.6 + TAG/1.7 + SBP/130 − HDL-C/1.28) [16], *Z-MSS* continuous metabolic syndrome score calculated from population-derived Z-scores (=sum of WHtR, FPG, TAG, SBP, and HDL-C (inverted) Z-scores)), *n* number of subjects, *WHtR* waist-to-height ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *FPI* fasting plasma insulin, *QUICKI* quantitative insulin sensitivity check index, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TAG* triacylglycerols, *AIP* atherogenic index of plasma, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *hsCRP* high-sensitivity C-reactive protein, *e* elevated, *l* low, *WHtR* waist-to-height ratio

cardiometabolic burden. They account for 14.7% of all males and 6.7% of females using the siMSS cutoff value, and 13.1% and 4.5%, respectively, employing the Z-MSS cutoffs. Thus, among 16- to 20-year-old MS-free subjects, about 15 out of 100 males and about 7 per 100 females present high cardiometabolic risk employing siMSS, while using Z-MSS cutoff point, about 14 males and about 5 females out of 100 fall into this category. From a clinical point of view, the difference in proportions between the 2 continuous MS scores is negligible. Among MS-free subjects presenting high

cardiometabolic burden, about 3 to 8% did not manifest a single MS component. This underlines the importance of the continuous rise in different risk markers, rather than reaching or not the defined dichotomous cutoff point [7–14, 16]. Since the prevalence of MS rises with aging [1], the proportion of MS-free subjects displaying high cardiometabolic risk is probably even higher in older adults.

Population-based MS scores document a significant relationship between childhood MS scores and a risk of cardiometabolic diseases in adulthood [29, 30], and in adults, they predict long-term risk of development of cardiometabolic disease, cardiovascular and overall mortality [31–35]. At present, it is neither clear whether the longitudinal prognosis of subjects presenting MS and MS-free individuals presenting high cardiometabolic burden differs, nor whether siMSS is inferior or not to population-based continuous MS scores regarding the predictive value of longitudinal risks.

Continuous MS scores reflect cardiometabolic burden imposed by factors beyond the components included into their calculation [11]. Association between population-derived MS scores and different markers of cardiometabolic risk has been affirmed in several studies [12, 13, 15, 36], and herein both scores displayed significant relationship with RFs not incorporated into their calculations. In contrast to adults, in whom MS associated with a mild reduction of eGFR [37], our data suggest that deterioration of renal function is not an early sign of increased cardiometabolic burden in young subjects.

The advantage of this study was the sample size, and a concurrent evaluation using either an approach normalizing the individual measures to the accepted international standards [3, 4, 16, 17], which allows for a comparison across different studies and populations, or the population-specific Z-score-based approach. Limitations include a relatively low prevalence of MS, particularly in females; the fact that none of our subjects presented 5 MS components, and that our data do not reflect a representative sample of 16 to 20-year-old Slovak subjects. Having in mind the importance of a straightforward application in clinical and epidemiological practice, the inclusion of RFs beyond the traditional MS components has not been considered. However, this might have improved the performance of continuous MS scores [11]. The weights of individual components of MS scores were considered equal. The cross-sectional nature of our study allows only for description of associations.

Conclusions

Both continuous MS scores capture the risk of metabolic abnormalities adequately. Continuous MS scores enable to identify individuals on high cardiometabolic risk prior to manifestation of MS, e.g., subjects requiring early intervention to counteract developing pathological processes, and evidence that their proportion exceeds that of individuals manifesting MS. SiMSS is easy to calculate (Excel and Android applications are available [16]) and represents a practical approach to quantify cardiometabolic burden in clinical and epidemiological practice.

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Authors' contributions Conceived and designed the study: KS. Performed the measurements: RG, IK, MSc. Analyzed the data: JS. Wrote the first draft: KS. All coauthors read and approved the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and later amendments thereto or the comparable ethical standards.

Informed consent A written informed consent was obtained from full-aged participants. In subjects under 18 years of age, their verbal assent and written consent from a parent or legal guardian were acquired.

References

1. Papakonstantinou E, Lambadiari V, Dimitriadis G, Zampelas A (2013) Metabolic syndrome and cardiometabolic risk factors. Curr Vasc Pharmacol 11:858–879. https://doi.org/10.2174/15701611113116660176
2. Ford ES (2005) Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome. Diabetes Care 28:1769–1778. https://doi.org/10.2337/diacare.28.7.1769
3. Zimmet P, George K, Alberti MM, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S, Grp IDFC (2007) The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 8:299–306. https://doi.org/10.1111/j.1399-5448.2007.00271.x
4. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WPT, Loria CM, Smith SC (2009) Harmonizing the metabolic syndrome a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120:1640–1645. https://doi.org/10.1161/circulationaha.109.192644

5. Vanlancker T, Schaubroeck E, Vyncke K, Cadenas-Sanchez C, Breidenassel C, Gonzalez-Gross M, Gottrand F, Moreno LA, Beghin L, Molnar D, Manios Y, Gunter MJ, Widhalm K, Leclercq C, Dallongeville J, Ascension M, Kafatos A, Castillo MJ, De Henauw S, Ortega FB, Huybrechts I, Grp HP (2017) Comparison of definitions for the metabolic syndrome in adolescents. The HELENA study. Eur J Pediatr 176:241–252. https://doi.org/10.1007/s00431-016-2831-6
6. Reuter CP, Burgos M, Barbian C, Renner J, Franke S, de Mello ED (2018) Comparison between different criteria for metabolic syndrome in schoolchildren from southern Brazil. Eur J Pediatr 177:1471–1477. https://doi.org/10.1007/s00431-018-3202-2
7. Wijndaele K, Beunen G, Duvigneaud N, Matton L, Duquet W, Thomis M, Lefevre J, Philippaerts RM (2006) A continuous metabolic syndrome risk score - utility for epidemiological analyses. Diabetes Care 29:2329–2329. https://doi.org/10.2337/dc06-1341
8. Eisenmann JC (2008) On the use of a continuous metabolic syndrome score in pediatric research. Cardiovasc Diabetol 7:17. https://doi.org/10.1186/1475-2840-7-17
9. DeBoer MD, Gurka MJ (2017) Clinical utility of metabolic syndrome severity scores: considerations for practitioners. Diabetes Metab Syndr Obes 10:65–72. https://doi.org/10.2147/dmso.s101624
10. Heshmat R, Heidari M, Ejtahed HS, Motlagh ME, Mahdavi-Gorab A, Ziaodini H, Taheri M, Shafiee G, Beshtar S, Qorbani M, Kelishadi R (2017) Validity of a continuous metabolic syndrome score as an index for modeling metabolic syndrome in children and adolescents: the CASPIAN-V study. Diabetol Metab Syndr 9:89. https://doi.org/10.1186/s13098-017-0291-4
11. Andersen LB, Lauersen JB, Brond JC, Anderssen SA, Sardinha LB, Steene-Johannessen J, McMurray RG, Barros MVG, Kriemler S, Moller NC, Bugge A, Kristensen PL, Ried-Larsen M, Grontved A, Ekelund U (2015) A new approach to define and diagnose cardiometabolic disorder in children. J Diabetes Res 2015:539835. https://doi.org/10.1155/2015/539835
12. Pandit D, Chiplonkar S, Khadilkar A, Kinare A, Khadilkar V (2011) Efficacy of a continuous metabolic syndrome score in Indian children for detecting subclinical atherosclerotic risk. Int J Obes 35:1318–1324. https://doi.org/10.1038/ijo.2011.138
13. Olza J, Aguilera CM, Gil-Campos M, Leis R, Bueno G, Valle M, Canete R, Tojo R, Moreno LA, Gil A (2015) A continuous metabolic syndrome score is associated with specific biomarkers of inflammation and CVD risk in prepubertal children. Ann Nutr Metab 66:72–79. https://doi.org/10.1159/000369981
14. Hesse MB, Young G, Murray RD (2016) Evaluating health risk using a continuous metabolic syndrome score in obese children. J Pediatr Endocrinol Metab 29:451–458. https://doi.org/10.1515/jpem-2015-0271
15. Prochotska K, Kovacs L, Vitariusova E, Feber J (2016) Is arterial stiffness predicted by continuous metabolic syndrome score in obese children? J Am Soc Hypertens 10:47–54. https://doi.org/10.1016/j.jash.2015.10.011
16. Soldatovic I, Vukovic R, Culafic D, Gajic M, Dimitrijevic-Sreckovic V (2016) siMS score: simple method for quantifying metabolic syndrome. PLoS One 11:e0146143. https://doi.org/10.1371/journal.pone.0146143
17. Ashwell M, Gibson S (2014) A proposal for a primary screening tool: 'Keep your waist circumference to less than half your height'. BMC Med 12:207. https://doi.org/10.1186/s12916-014-0207-1
18. Rochlani Y, Pothineni NV, Mehta JL (2015) Metabolic syndrome: does it differ between women and men? Cardiovasc Drugs Ther 29:329–338. https://doi.org/10.1007/s10557-015-6593-6
19. Pradhan AD (2014) Sex differences in the metabolic syndrome: implications for cardiovascular health in women. Clin Chem 60:44–52. https://doi.org/10.1373/clinchem.2013.202549
20. Gurecka R, Koborova I, Sebek J, Sebekova K (2015) Presence of cardiometabolic risk factors is not associated with microalbuminuria in 14-to-20-years old Slovak adolescents: a cross-sectional, population study. PLoS One 10:e0129311. https://doi.org/10.1371/journal.pone.0129311
21. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
22. Dobiasova M, Frohlich J (2001) The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER (HDL)). Clin Biochem 34:583–588. https://doi.org/10.1016/S0009-9120(01)00263-6
23. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ (2000) Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 85:2402–2410. https://doi.org/10.1210/jcem.85.7.6661
24. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637. https://doi.org/10.1681/asn.2008030287
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, Modification Diet Renal Dis Study G (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–470. https://doi.org/10.7326/0003-4819-130-6-199903160-00002
26. Okosun IS, Lyn R, Davis-Smith M, Eriksen M, Seale P (2010) Validity of a continuous metabolic risk score as an index for modeling metabolic syndrome in adolescents. Ann Epidemiol 20:843–851. https://doi.org/10.1016/j.annepidem.2010.08.001
27. Eisenmann JC, Laurson KR, DuBose KD, Smith BK, Donnelly JE (2010) Construct validity of a continuous metabolic syndrome score in children. Diabetol Metab Syndr 2:8. https://doi.org/10.1186/1758-5996-2-8
28. Vukovic R, Milenkovic T, Stojan G, Vukovic A, Mitrovic K, Todorovic S, Soldatovic I (2017) Pediatric siMS score: a new, simple and accurate continuous metabolic syndrome score for everyday use in pediatrics. PLoS One 12:e0189232. https://doi.org/10.1371/journal.pone.0189232
29. Kelly AS, Steinberger J, Jacobs DR, Hong CP, Moran A, Sinaiko AR (2011) Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. Int J Pediatr Obes 6:e283–e289. https://doi.org/10.3109/17477166.2010.528765
30. Viitasalo A, Lakka TA, Laaksonen DE, Savonen K, Lakka H-M, Hassinen M, Komulainen P, Tompuri T, Kurl S, Laukkanen JA, Rauramaa R (2014) Validation of metabolic syndrome score by confirmatory factor analysis in children and adults and prediction of cardiometabolic outcomes in adults. Diabetologia 57:940–949. https://doi.org/10.1007/s00125-014-3172-5
31. DeBoer MD, Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Pearson TA (2017) Independent associations between metabolic syndrome severity & future coronary heart disease by sex and race. J Am Coll Cardiol 69:1204–1205. https://doi.org/10.1016/j.jacc.2016.10.088
32. Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD (2017) Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk in Communities Study and Jackson Heart Study. Diabetologia 60:1261–1270. https://doi.org/10.1007/s00125-017-4267-6
33. Jung KJ, Jee YH, Jee SH (2017) Metabolic risk score and vascular mortality among Korean adults. Asia Pac J Public Health 29:122–131. https://doi.org/10.1177/1010539516688082

34. Gurka MJ, Guo Y, Filipp SL, DeBoer MD (2018) Metabolic syndrome severity is significantly associated with future coronary heart disease in type 2 diabetes. Cardiovasc Diabetol 17:17. https://doi.org/10.1186/s12933-017-0647-y
35. Hillier TA, Rousseau A, Lange C, Lepinay P, Cailleau M, Novak M, Calliez E, Ducimetiere P, Balkau B (2006) Practical way to assess metabolic syndrome using a continuous score obtained from principal components analysis. Diabetologia 49:1528–1535. https://doi.org/10.1007/s00125-006-0266-8
36. Okosun IS, Boltri JM, Lyn R, Davis-Smith M (2010) Continuous metabolic syndrome risk score, body mass index percentile, and leisure time physical activity in American children. J Clin Hypertens 12:636–644. https://doi.org/10.1111/j.1751-7176.2010.00338.x
37. Hu W, Wu XJ, Ni YJ, Hao HR, Yu WN, Zhou HW (2017) Metabolic syndrome is independently associated with a mildly reduced estimated glomerular filtration rate: a cross-sectional study. BMC Nephrol 18:192. https://doi.org/10.1186/s12882-017-0597-3