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Screening accuracy of Single-Point Insulin Sensitivity Estimator (SPISE) for metabolic syndrome: a systematic review and meta-analysis

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Abstract

Background Metabolic syndrome (MetS) is a multifactorial condition linked to increased risk of cardiovascular disease and type 2 diabetes. The Single-Point Insulin Sensitivity Estimator (SPISE), a non-invasive index calculated via 600 × HDL-C^0.185 / (TG^0.2 × BMI^1.338), offers a practical alternative. This systematic review and meta-analysis aim to evaluate the accuracy of SPISE as an indicator for MetS.

Methods We conducted a systematic review and meta-analysis following PRISMA guidelines. We searched databases such as MEDLINE, Scopus, Web of Science, and Embase, focusing on studies evaluating SPISE's screening accuracy for MetS. Eligible studies were observational, reporting mean SPISE values and its predictive performance. Meta-analyses were performed using Hedges' g standardized mean differences (SMD) and pooled area under the curve (AUC) estimates.

Results Seven studies comprising 12,919 participants were included, with an age range of 9.2 ± 2.1 to 52.4 ± 11.0. Individuals with MetS had significantly lower SPISE scores than controls (SMD = -0.94, 95% CI: -1.25 to -0.63). The pooled AUC for SPISE as a predictor of MetS was 0.86 (95% CI: 0.83 to 0.90), surpassing other insulin resistance indices like HOMA-IR and the triglyceride/HDL-C ratio. Meta-regression showed that systolic and diastolic blood pressure were potential sources of heterogeneity and age, gender, BMI, waist circumference, fasting blood glucose, triglyceride, and HDL did not contribute to heterogeneity.

Conclusions SPISE is a highly accurate and non-invasive tool for predicting MetS, potentially outperforming traditional indices like HOMA-IR. Its ease of use and precision make it a valuable clinical screening tool, especially in diverse populations.

Keywords Metabolic syndrome, Single-Point Insulin Sensitivity Estimator, Insulin resistance, Meta-analysis

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Introduction

Metabolic syndrome (MetS) is a clinical entity defined by the coexistence of multiple cardiometabolic risk factors, including abdominal obesity, hypertension, dyslipidemia, and insulin resistance, which collectively increase the risk for cardiovascular disease, type 2 diabetes mellitus, and overall mortality [1, 2], with varying global prevalence ranging from 12.5% to 31.4% depending on the diagnostic criteria [3]. MetS is diagnosed using different criteria, including the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III), the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), and the International Diabetes Federation (IDF) [4–6]. The global prevalence of MetS has risen alarmingly, necessitating effective screening and early intervention strategies to mitigate associated health risks [7].

Insulin resistance is known as a pivotal mechanism underlying the pathophysiology of MetS, impairing glucose metabolism and leading to a cascade of metabolic dysregulations [8]. While the hyperinsulinemic-euglycemic clamp remains the gold standard for assessing insulin resistance, its invasive nature, high cost, and complexity limit its application [8]. Therefore, there is an emerging need for reliable, non-invasive, and accessible tools to evaluate insulin sensitivity and insulin resistance, which are related but distinct conditions: insulin sensitivity refers to the body's effective response to insulin, whereas insulin resistance reflects a diminished response. Several surrogate measures such as homeostatic model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI), and the triglyceride-to-HDL cholesterol (TG/HDL-C) ratio have been developed to facilitate more accessible assessments [9–11].

The TG/HDL-C ratio is a lipid-based index that provides a straightforward marker for insulin resistance, making it suitable for routine clinical use. However, significant variability in the proposed cut-off values has been observed [12]. To improve its reliability, Paulmichl et al. developed the Single Point Insulin Sensitivity Estimator (SPISE) as an easily accessible marker of insulin resistance, using BMI, TG, and HDL-C without requiring insulin measurements using computer-assisted mathematical modeling [13]. Various studies have shown that SPISE correlates with MetS, highlighting its potential as a practical screening tool [14–16]. However, no pooled analysis has yet been conducted. To address this gap, our study undertakes a comprehensive systematic review and meta-analysis, to evaluate the diagnostic accuracy of the SPISE index for detecting MetS and to compare its performance with other commonly used indices. We hypothesize that the SPISE index is a highly accurate, non-invasive predictor of MetS, outperforming traditional markers.

Materials and methods

This meta-analysis adhered to the"Preferred Reporting Items for Systematic Reviews and Meta-Analyses"(PRISMA) guidelines [17]. The review protocol was also registered in the prospective register of systematic reviews (PROSPERO) (CRD42024591129).

Search strategy and screening

Comprehensive searches were performed across multiple electronic databases, including MEDLINE/PubMed, Scopus, Web of Science, and Embase. Additionally, Google Scholar was manually searched for relevant citations and publications. The most recent update to the search occurred in September 2024, just before the final analysis. The keywords used in the search focused on ("Single Point Insulin Sensitivity Estimator"[Title/Abstract] OR"SPISE"[Title/Abstract]) AND ("Metabolic Syndrome"[Title/Abstract] OR"Metabolic Syndrome X"[MeSH Terms]). Rayyan (https://rayyan.ai) was used to assist in the screening process. After eliminating duplicates, two reviewers (R.A. and S.J.) independently reviewed the titles and abstracts of all studies. Full-text screenings were then conducted based on the predefined inclusion and exclusion criteria. Any disagreements between reviewers were resolved through consensus meetings mediated by the third author, A.G.R.

Inclusion and exclusion criteria

To be eligible for inclusion, studies had to meet the following criteria: 1) Participants: Human subjects, including adults and/or adolescents, with or without metabolic syndrome, as defined by each individual study; 2) Exposure: SPISE measurement; 3) Comparison: Non-metabolic syndrome groups; 4) Outcome: Comparison of mean SPISE between metabolic syndrome patients and controls, and the predictive power of SPISE; 5) Study Design: Observational studies (cross-sectional, case–control, or cohort). Exclusion criteria included: 1) Articles such as letters to editors, technical papers, conference abstracts, pilot studies, reviews, commentaries, animal studies, and cadaver research; 2) non-English articles; 3) Studies that involved participants other than those with metabolic syndrome.

Data extraction and quality assessment

Two researchers (S.J. and P.F.) independently extracted data and compiled them into a pre-designed Excel sheet. Information collected included mean SPISE in metabolic syndrome patients and controls, SPISE's area under the curve (AUC) values in predicting metabolic syndrome, and the related lab data including Fasting Blood Sugar (FBS), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Triglycerides (TG), Total Cholesterol

(TC), TG/HDL-C, Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP), Hemoglobin A1c (HbA1c), insulin, HOMA-IR, and C-Reactive Protein (CRP). Additional data included demographic factors like publication year, study design, sample size, mean age, BMI, Waist Circumference (WC), and gender distribution. Any disagreements were reviewed and resolved by A.A. Table 1 outlines widely used surrogate markers for insulin resistance by our included studies along with their mathematical formulas.

To evaluate the methodological quality of the included studies, we used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. This tool comprises eight domains that assess the risk of bias in key methodological areas, including the clarity of inclusion criteria, the reliability of measurement methods, identification and management of confounding factors, and appropriateness of statistical analyses. Each study was independently assessed by two reviewers (R.A. and A.S.). Disagreements were resolved through discussion or consultation with a third reviewer when necessary (A.A.). For each item, a score of "Yes," "No," "Unclear," or "Not Applicable" was assigned based on the information provided in the study [20].

Data analyses

The meta-analysis was conducted using the"meta"package in R software, employing Hedges'g standardized mean differences (SMD) with 95% confidence intervals (CI) for assessing the relationship between SPISE in MetS vs. non-MetS groups. Another analysis was done by pooling the AUC [95%CI] of SPISE for MetS and computing the overall AUC. The choice between a fixed-effects or random-effects model was based on the level of heterogeneity. The Q-test and I^2 statistic were used to measure heterogeneity, where I^2 values of 0%−25%, 26%−50%, and above 50% indicated low, moderate, and high heterogeneity, respectively. A fixed-effects model was applied if $P > 0.1$ and $I^2 < 50\%$; otherwise, a random-effects model was used [21]. Sensitivity analysis was conducted by backward elimination of studies one at a time and assessing the sensitivity of the eliminated study. A meta-regression analysis was also performed to explore potential sources of heterogeneity, considering factors such as age, gender, BMI, blood pressure, and lipid profile markers like FBS, TG, HDL, and WC. Publication bias was assessed using Begg's test, and statistical significance was set at $P < 0.05$ for all analyses except for heterogeneity [22].

Results

Study selection

The first systematic search of databases, including PubMed, Web of Science, Scopus, and Embase, found 146 studies. Following the removal of duplicates, 78 entries underwent screening based on title and abstract, with 60 studies being excluded for irrelevance. After reviewing the citations in the relevant papers through Google Scholar, it was found that none satisfied the eligibility criteria. An evaluation of the full text was carried out for the other 18 research projects. Seven of these research studies were finally considered suitable for inclusion in the systematic review [Fig. 1]. Four of these studies had adequate data to enter meta-analysis [14, 23–25], with the rest being ineligible for quantitative synthesis due to involving adolescents and children as well as insufficient data [15, 16, 26].

Baseline characteristics and risk of bias assessment

Our comprehensive analysis involved research conducted in different parts of the world, including the United States [23], India [14, 24], Saudi Arabia [26], Chile [16, 27], and Korea [25]. All of the included studies employed cross-sectional methodologies [13, 14, 16, 23–27]. A number of 12,919 individuals were enrolled in the research, with a mean age spanning from 9.2 ± 2.1 [27] to 52.4 ± 11.0 [24]. Participants had BMIs ranging from 21.4 ± 5.7 [26] to 35.1 ± 8.1 [23] kg/m^2 and waist circumferences ranging from 75 ± 16 [26] to 113.2 ± 13.5 cm [23]. Additional information is provided in Table 2. Also, laboratory tests and cardiovascular data are extracted in Table 3.

In the quality assessment, most studies met all the criteria, achieving a perfect score across all eight quality

Table 1 Summary of insulin resistance surrogate indices used by the included studies and their formulas

Marker	Definition	Formula	Reference
TG/HDL-C ratio	A lipid-derived index used as a simple marker of insulin resistance, especially in dyslipidemia	TG (mg/dL)/HDL-C (mg/dL)	[18]
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance; reflects hepatic insulin resistance	[Fasting Insulin (μU/L) × Fasting Glucose (mmol/L)]/22.5	[9]
TyG index	Triglyceride-Glucose Index; a reliable surrogate for IR	ln [TG (mg/dL) × Fasting Glucose (mg/dL)/2]	[19]
SPISE	Single Point Insulin Sensitivity Estimator; a newer insulin sensitivity index using lipids and BMI	600 × HDL-C (mg/dL) ^0.185/[TG (mg/dL) ^0.2 × BMI (kg/m^2) ^1.338]	[13]

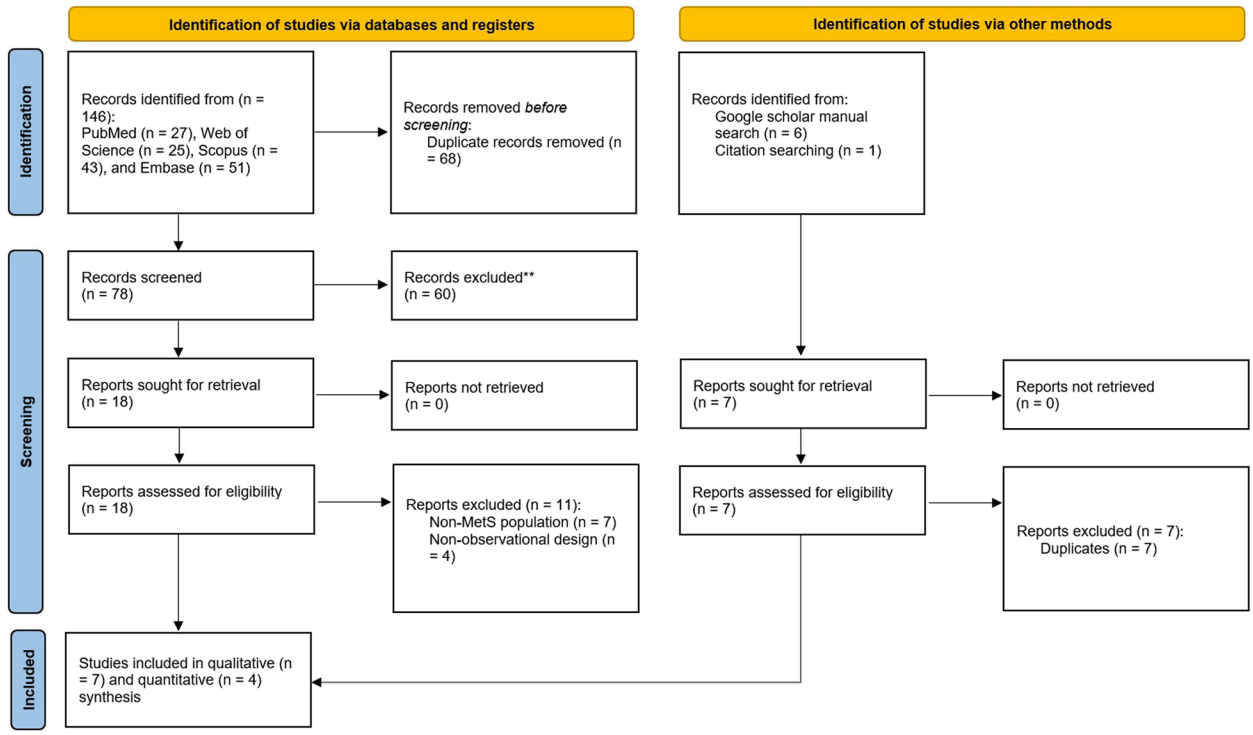

Fig. 1 PRISMA diagram flowchart

indicators [23, 24, 26]. Some studies lacked appropriate statistical measures [14, 25]. Notably, Correa-Burrows et al. [16, 27] exhibited some deficiencies, failing to identify confounding factors and employing strategies to address them (Supplemental file 1: Table S1).

Summary of results of individual studies

We present a summary of the individual studies evaluating the performance of the SPISE index across diverse populations. In a large U.S. adult cohort [23], SPISE values varied significantly by ethnicity, with the lowest values among Hispanic individuals and the highest predictive performance for metabolic syndrome noted in White adults (ROC-AUC = 88%). Similarly, in Chilean adolescents [16], SPISE showed strong discrimination for both metabolic syndrome and insulin resistance, particularly among males (AUC = 0.97). This was reaffirmed in a later study on obese Chilean youth [15], where SPISE maintained high predictive accuracy across pubertal stages. North Indian adults [14] demonstrated a significant SPISE reduction in metabolic syndrome cases, with a ROC-AUC of 0.83, while in another Indian cohort [24], SPISE outperformed HOMA-IR and TG/HDL-C in identifying metabolic syndrome (AUC = 0.88). In South Korea [25], SPISE yielded excellent predictive performance (AUC = 0.90) and large effect sizes distinguishing obese vs. non-obese individuals. Lastly, among Arab adolescents [26], sex-specific SPISE cutoffs robustly predicted metabolic syndrome, with AUCs of 84.1% for boys and 90.3% for girls.

SPISE in metabolic syndrome

The meta-analysis pooling data from three studies [14, 23, 24] showed that individuals with MetS have a significantly lower SPISE index compared to those without MetS (SMD [95%CI] = −0.94 [−1.25, −0.63]; I2 = 85%; *P*-value < 0.01) [Fig. 2]. A sensitivity analysis was conducted and revealed that removing any of the studies did not have a significant impact on the overall effect size; however, by removing Dudi et al. [14] heterogeneity was substantially reduced (SMD [95%CI] = −0.83 [−0.92, −0.74]; I2 = 0%) [Fig. 3]. Meta-regression indicated statistically significant results for both SBP (Estimate = −0.02; *P*-value = 0.0005) [Fig. 4] and DBP (Estimate = −0.035; *P*-value = 0.01) [Fig. 5], showing that studies with elevated SBP and DBP exhibited lower SMD of SPISE in MetS vs. non-MetS patients. However, meta regression revealed that age, gender, BMI, WC, FBS, TG, and HDL did not contribute to heterogeneity (*P*-values > 0.05).

Predictive value of SPISE for metabolic syndrome

By pooling the AUC and 95%CI of SPISE for metabolic syndrome from four studies [14, 23–25], we assessed the predictive value and found that SPISE is an excellent

Table 2 Baseline characteristics of the studies

Study	Type of Population	Country	Study Design	MetS diagnosis criteria	Groups	Sample size	Female, N (%)	Age, mean ± SD	BMI, mean ± SD	WC, mean ± SD
Cho 2024 [28]	Community	USA	Cross-sectional	American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria [29]	MetS	727	411 (56.5)	47.5 ± 13.5	35.1 ± 8.1	113.2 ± 13.5
					Non-MetS	1441	695 (48.2)	40.2 ± 15.2	28.4 ± 7.6	95.5 ± 15.2
Rabari 2022 [24]	Hospital	India	Cross-sectional	South Asian Modified National Cholesterol Education Program-ATP-III (SAM-NCEP-ATP-III) criteria [30]	MetS	56	32 (57)	52.4 ± 11.0	26.7 ± 6.0	92.5 ± 16.3
					Non-MetS	27	4 (15)	48.9 ± 13.7	21.8 ± 3.3	77.7 ± 20.2
Wani 2023 [31]	Arab Adolescents	Saudi Arabia	Cross-sectional	Cook et al. [32]	MetS	82	28 (34.1)	14.9 ± 1.9	28.9 ± 7.8	75 ± 16
					Non-MetS	869	420 (48.3)	13.7 ± 2.3	21.4 ± 5.7	
Correa-Burrows 2020 (Male) [16]	16–17-year-old post-pubertal adolescents of low-to-middle socioeconomic status (Santiago Longitudinal Study)	Chile	Cross-sectional	AHA/NHLBI/ IDF Joint Interim Statement for individuals 16y and older [30]	MetS (SPISE > 5.0)	307	0 (0)	16.8 ± 0.2	BMI (z score) = 0.57 ± 0.2	78.1 ± 7.5
					MetS (SPISE ≤ 5.0)	49	0 (0)			100.4 ± 10.1
Correa-Burrows 2020 (Female) [16]	16–17-year-old post-pubertal adolescents of low-to-middle socioeconomic status (Santiago Longitudinal Study)	Chile	Cross-sectional	AHA/NHLBI/ IDF Joint Interim Statement for individuals 16y and older [30]	MetS (SPISE > 6.0)	243	243 (100)	16.8 ± 0.3	BMI (z score) = 0.74 ± 1.1	76.9 ± 8.1
					MetS (SPISE ≤ 6.0)	79	79 (100)			94.8 ± 11.0
Correa-Burrows 2023 [33]	Adolescents with Obesity	Chile	Cross-sectional	Cook et al. [30]	MetS (Children)	432	353 (81.6)	9.2 ± 2.1	BMI (z score) = 4.5 ± 1.8	83.5 ± 10.5
					MetS (Adolescents)	293	126 (43.1)	12.6 ± 1.8	BMI (z score) = 3.8 ± 1.7	93.8 ± 11.7
Dudi 2019 [14]	Community	India	Cross-sectional	South Asian Modified NCEP criteria [30]	MetS	229	102 (44.5)	46.9 ± 12.5	27.2 ± 4.3	92.5 ± 16.8
					Non-MetS	248	56 (22.6)	38.4 ± 14.7	23.3 ± 4.1	84.6 ± 16.5

Table 2 (continued)

Study	Type of Population	Country	Study Design	MetS diagnosis criteria	Groups	Sample size	Female, N (%)	Age, mean ± SD	BMI, mean ± SD	WC, mean ± SD
Seo 2023 [25]	Community (KNHANES)	Korea	Cross-sectional	American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) [29], with a WC cut-off based on the Korean Society for the Study of Obesity (KSSO) [34]	Obese	2974	1270 (42.7)	45.5 ± 10.9	28.0 ± 5.5	93.5 ± 5.5
					Non-Obese	4863	2971 (61.1)	43.9 ± 13.9	22.1 ± 0.7	78.3 ± 7.0

Abbreviations: *BMI* Body Mass Index, *KNHANES* Korea National Health and Nutrition Examination Survey, *MetS* Metabolic Syndrome, *N* Number, *SD* Standard Deviation, SPISE, Single Point Insulin Sensitivity Estimator; WC, Waist Circumference

Table 3 Baseline characteristics of the studies

Study	Groups	FBS (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	TG (mg/dL)	TC (mg/dL)	TG/HDL-C	DBP (mmHg)	SBP (mmHg)	HbA1c (%)	Insulin (μIU/mL)	HOMA-IR	CRP (mg/L)	SPISE
Cho 2024 [28]	Metabolic Syndrome	128.2 ± 51.2	44.3 ± 10.8	113.2 ± 35.1	160.2 ± 156.4	188.2 ± 43.1	4.1 ± 5.4	80.6 ± 10.8	128 ± 18.9	6.3 ± 2.7	23.7 ± 32.4	7.9 ± 13.5	NA	4.10 ± 0.27
	Non-Metabolic Syndrome	101.7 ± 22.8	56.9 ± 15.2	108.4 ± 34.2	79.1 ± 41.8	181.2 ± 37.96	1.5 ± 0.38	72.7 ± 11.4	117.2 ± 15.2	5.5 ± 3.8	10.6 ± 11.4	2.8 ± 0.38	NA	6.70 ± 3.80
Rabari 2022 [24]	Metabolic Syndrome	174.98 ± 93.09	39.32 ± 6.93	NA	210.18 ± 117.59	186.26 ± 53.81	6.34 ± 7.83	82 ± 12	132 ± 22	NA	NA	4.83 ± 7.53	5.56 ± 8.87	6.38 ± 2.81
	Non-Metabolic Syndrome	137.64 ± 82.29	44.43 ± 10.03	NA	127.75 ± 58.57	173.93 ± 53.09	4.51 ± 4.75	74 ± 14	116 ± 20	NA	NA	3.92 ± 5.07	4.16 ± 6.46	8.60 ± 4.16
Wani 2023 [31]	Metabolic Syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	29.1 ± 24.4	7.7 ± 7.8	4.7 ± 7.3	5.17 ± 2.3
	Non-Metabolic Syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	12.5 ± 9.7	2.8 ± 2.3	1.7 ± 2.6	9.04 ± 3.2
Correa-Burrows 2020 (Male) [16]	Metabolic syndrome (SPISE > 5.0)	89.9 ± 8.5	39.1 ± 9.9	88.9 ± 16.3	67.5 ± 27.26	144.2 ± 21.7	1.8 ± 0.89	69.8 ± 6.7	113.4 ± 10.3	NA	5.6 ± 2.98	1.27 ± 1.19	0.32 ± 0.52	N/A
	Metabolic syndrome (SPISE ≤ 5.0)	94.7 ± 13.7	30.7 ± 6.4	106.3 ± 18.4	133.5 ± 77.8	167.5 ± 29.1	4.15 ± 2.6	75.0 ± 7.5	122.5 ± 9.8	NA	14 ± 6.3	3.27 ± 1.8	0.91 ± 1.45	N/A
Correa-Burrows 2020 (Female) [16]	Metabolic syndrome (SPISE > 6.0)	85.8 ± 8.7	44.5 ± 10.8	94.9 ± 16.4	71.6 ± 25.4	154.2 ± 27.4	1.65 ± 0.67	66.5 ± 6.5	106.0 ± 8.3	NA	6.59 ± 2.9	1.39 ± 0.67	0.34 ± 0.6	N/A
	Metabolic syndrome (SPISE ≤ 6.0)	88.4 ± 9.3	37.0 ± 8.4	102 ± 18.95	103.3 ± 54.97	163.1 ± 24.7	2.66 ± 1.66	70.3 ± 6.7	115.2 ± 10.2	NA	10.8 ± 6.6	2.27 ± 1.43	1.16 ± 1.36	N/A
Correa-Burrows 2023 [33]	Metabolic syndrome (Children)	86.5 ± 9.3	47.5 ± 10.2	104.2 ± 29.6	85.4 ± 61.0	171.7 ± 32.9	2.38 ± 1.8	66 ± 9	105 ± 12	NA	9 ± 7.44	1.93 ± 1.56	NA	6.81 ± 1.6
	Metabolic syndrome (Adolescents)	86.9 ± 9.3	44.9 ± 9.8	99.7 ± 30.7	100.0 ± 72.9	166.1 ± 35.2	2.68 ± 1.8	72 ± 9	114 ± 14	NA	14.4 ± 8.4	3.04 ± 1.86	NA	5.71 ± 1.5
Dudi 2019 [14]	Metabolic Syndrome	111 ± 38	43 ± 11	NA	194 ± 119	NA	NA	91 ± 11	148 ± 22	NA	NA	NA	NA	5.35 ± 1.35
	Non-Metabolic Syndrome	94 ± 31	43 ± 8	NA	117 ± 78	NA	NA	82 ± 13	130 ± 22	NA	NA	NA	NA	7.45 ± 2.00

Table 3 (continued)

Study	Groups	FBS (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	TG (mg/dL)	TC (mg/dL)	TG/HDL-C	DBP (mmHg)	SBP (mmHg)	HbA1c (%)	Insulin (μIU/mL)	HOMA-IR	CRP (mg/L)	SPISE
Seo 2023 [25]	Obese	105.6 ± 27.3	48.2 ± 10.9	NA	166.3 ± 130.88	197.3 ± 38.2	3.9 ± 5.45	80.3 ± 10.9	121.3 ± 16.4	6.0 ± 0.5	13.0 ± 10.9	3.5 ± 5.45	NA	5.4 ± 1.7
	Non-Obese	96.3 ± 20.9	55.6 ± 13.9	NA	116.2 ± 97.6	194.2 ± 34.9	2.4 ± 0.7	74.8 ± 6.97	113.4 ± 13.9	5.6 ± 0.7	7.3 ± 6.97	1.8 ± 0.7	NA	8.2 ± 1.8

Abbreviations: *FBS* Fasting Blood Sugar, *HDL* High-Density Lipoprotein, *LDL* Low-Density Lipoprotein, *TG* Triglycerides, *TC* Total Cholesterol, *TG/HDL-C* Triglycerides to HDL Cholesterol Ratio, *DBP* Diastolic Blood Pressure, *SBP* Systolic Blood Pressure, *HbA1c* Hemoglobin A1c (Glycated Hemoglobin), *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *CRP* C-Reactive Protein, *SPISE* Single Point Insulin Sensitivity Estimator

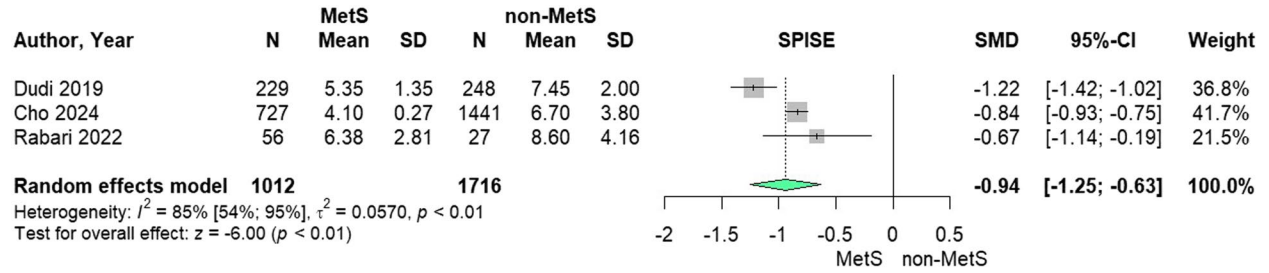

Fig. 2 Forest plot of the mean SPISE in MetS vs. non-MetS patients

predictor [35] of metabolic syndrome (AUC [95%CI] = 0.86 [0.83, 0.90]) [Fig. 6]. By conducting meta-regression on the cut-off values of SPISE, we found that the determination of different cut-offs by studies had no impact on our AUC meta-analysis ($P = 0.38$).

Comparing the AUC of SPISE with other insulin sensitivity indices

Two studies drew comparisons between the predictive power of SPISE vs. other indices [23, 25]. SPISE was discovered to be a more effective predictor of MetS compared to other indices. When compared with HOMA-IR (AUC $_{Cho}$ = 0.82; AUC $_{Seo}$ = 0.81), SPISE (AUC $_{Cho}$ = 0.85; AUC $_{Seo}$ = 0.90) was found to have a higher predictive value for MetS (P-values < 0.001). When compared with TG-HDL ratio (AUC $_{Cho}$ = 0.82; AUC $_{Seo}$ = 0.87), SPISE (AUC $_{Cho}$ = 0.85; AUC $_{Seo}$ = 0.90) was found to have a better predictive value for MetS (P-values < 0.001). Additionally, a comparison between SPISE (AUC $_{Cho}$ = 0.851; AUC $_{Seo}$ = 0.90) and TyG index (AUC $_{Cho}$ = 0.827; AUC $_{Seo}$ = 0.88), showed that SPISE is a superior predictor of MetS (P-value $_{Cho}$ = 0.013, P-value $_{Seo}$ < 0.001). Furthermore, SPISE (AUC $_{Cho}$ = 0.851; AUC $_{Seo}$ = 0.90) was shown to be a more accurate predictor of MetS compared to inverse insulin (1/fasting insulin) (AUC $_{Cho}$ = 0.786; AUC $_{Seo}$ = 0.76; P-values < 0.001) [Table 4].

Screening accuracy of SPISE among children and adolescents

Three studies assessed the predictive power of SPISE in non-adult populations [15, 16, 26]. Wani et al. illustrated that the SPISE index showed a marked decrease in participants with MetS compared to those without MetS in both boys and girls (5.5 ± 2.5 vs. 9.4 ± 3.2, p < 0.001 for boys and 4.4 ± 1.4 vs. 8.6 ± 3.2, p < 0.001 for girls). AUC showed decent and strong accuracy in predicting MetS, with rates of 84.1% [80%, 87%] for boys and 90.3% [87%,

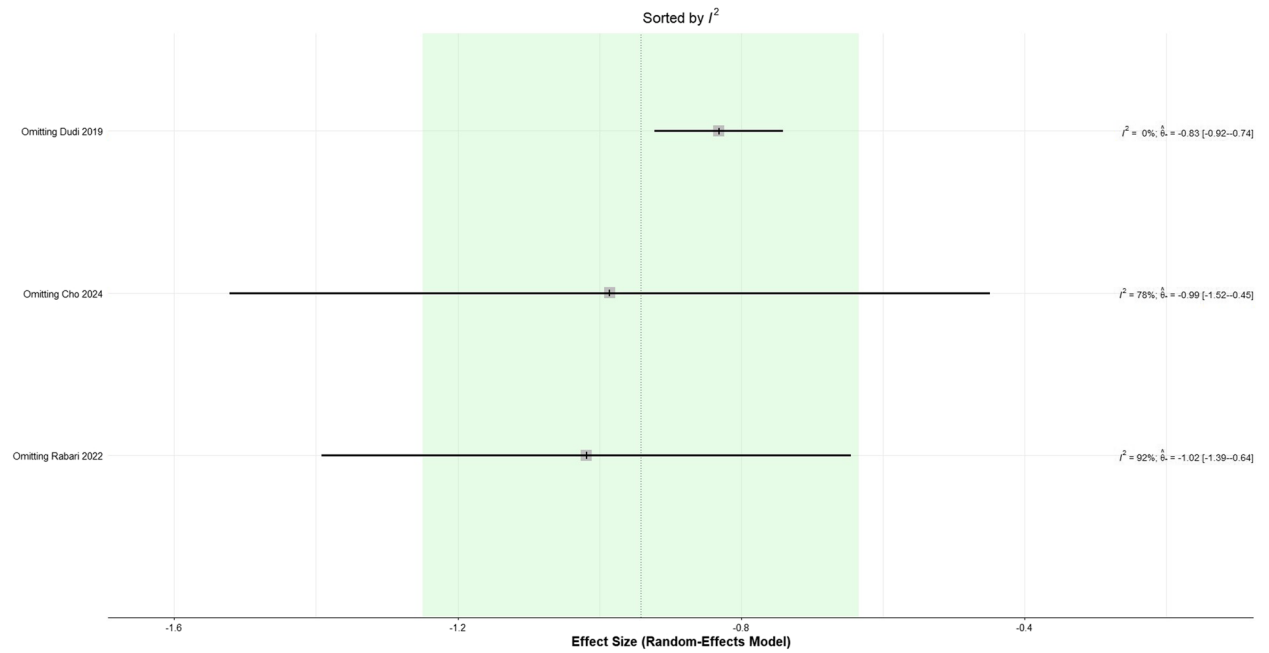

Fig. 3 Sensitivity analysis of the mean SPISE in MetS vs. non-MetS patients

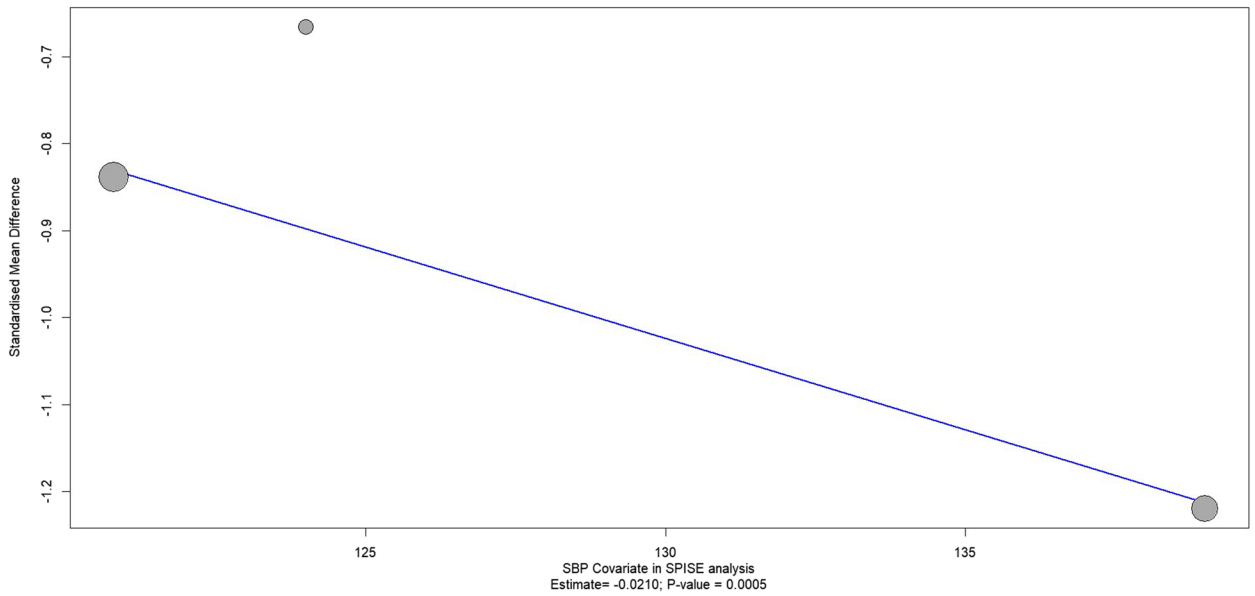

Fig. 4 Bubble plot of the meta regression with FBS as covariate in the analysis of mean SPISE in MetS vs. non-MetS patients

93%] for girls. The suggested cutoff for boys was SPISE index ≤6.1 (with sensitivity 72.2% and specificity 83.9%) and for girls it was ≤6.46 (with sensitivity 96.3% and specificity 73.4%) [26]. In the study by Correa-Burrows et al., the AUC of SPISE for metabolic syndrome was 0.873 (Cut-off = 5.7) in children and 0.895 (Cut-off = 5.4) in adolescents [27]. In another study, it was found that SPISE had an AUC of 0.97 (Cut-off = 5) for metabolic syndrome in post-pubertal adolescent males and 0.9 (Cut-off = 6) in females [16]. Additionally, SPISE was discovered to be a more effective predictor of MetS compared to HOMA-IR, with significantly higher AUC values for both genders according to Correa-Burrows et al. (male = 0.968; female = 0.029 for SPISE vs. male = 0.816; female = 0.751 for HOMA-IR) [16].

Publication bias

Begg's test was used to evaluate publication bias in the analyses of SPISE in MetS vs. non-MetS and there was no

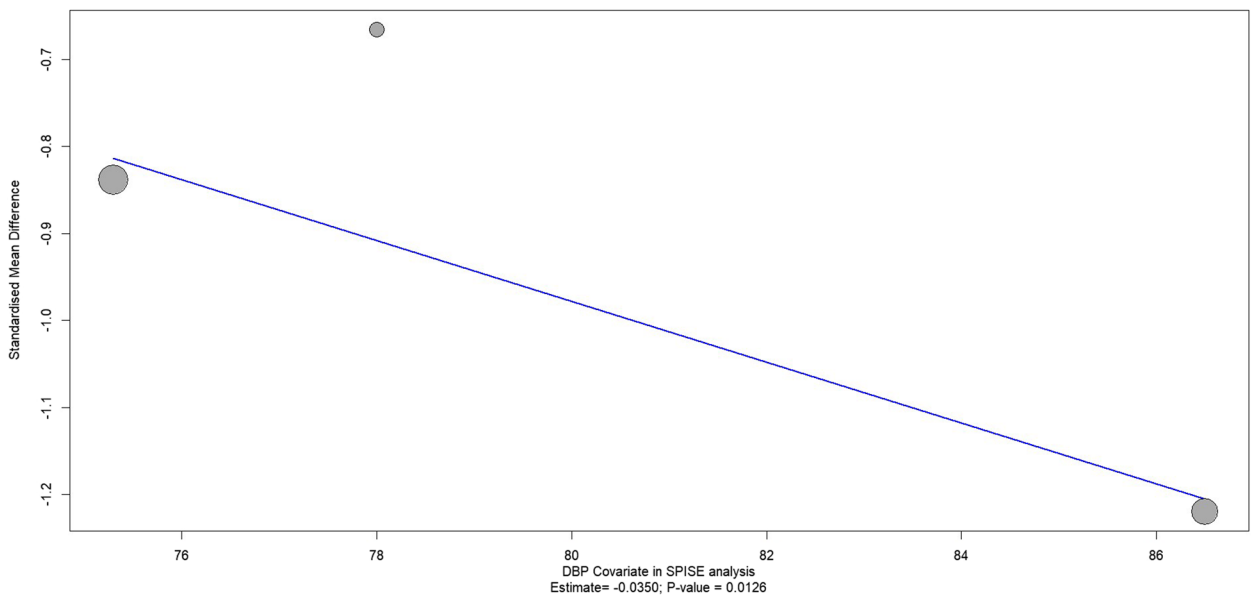

Fig. 5 Bubble plot of the meta regression with WC as covariate in the analysis of mean SPISE in MetS vs. non-MetS patients

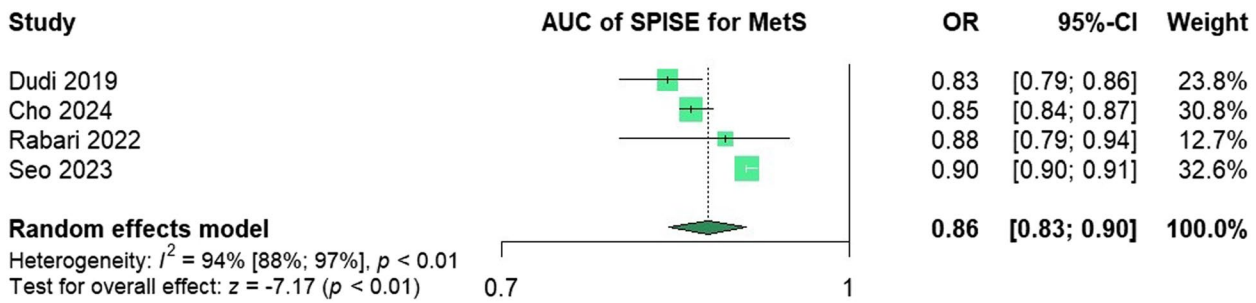

Fig. 6 Forest plot of the pooled AUC of SPISE in the prediction of MetS

Table 4 Comparative predictive accuracy of SPISE versus other insulin resistance indices for metabolic syndrome

Index	AUC (Cho (23))	AUC (Seo (25))	*P*-Value vs SPISE (Cho (23))	*P*-Value vs SPISE (Seo (25))	Interpretation
SPISE	0.851	0.90	—	—	Strong predictive value for MetS
HOMA-IR	0.82	0.81	< 0.001	< 0.001	SPISE significantly outperforms HOMA-IR
TG-HDL Ratio	0.82	0.87	< 0.001	< 0.001	SPISE significantly better than TG-HDL ratio
TyG Index	0.827	0.88	0.013	< 0.001	SPISE modestly but significantly better than TyG index
Inverse Insulin	0.786	0.76	< 0.001	< 0.001	SPISE clearly superior to inverse insulin

sign of publication bias (P = 0.60). Funnel plot was visualized for asymmetry assessment [Fig. 7].

Discussion

Our systematic review and meta-analysis revealed that individuals with MetS had a significantly lower SPISE index compared to those without, with a SMD of −0.94. The meta-regression revealed significant relationships between SPISE and both SBP and DBP. Importantly, SPISE demonstrated excellent predictive value for MetS, with an AUC of 0.86, outperforming other indices like HOMA-IR, the TG/HDL-C ratio, and the TyG index. The screening accuracy of SPISE was particularly strong among children and adolescents.

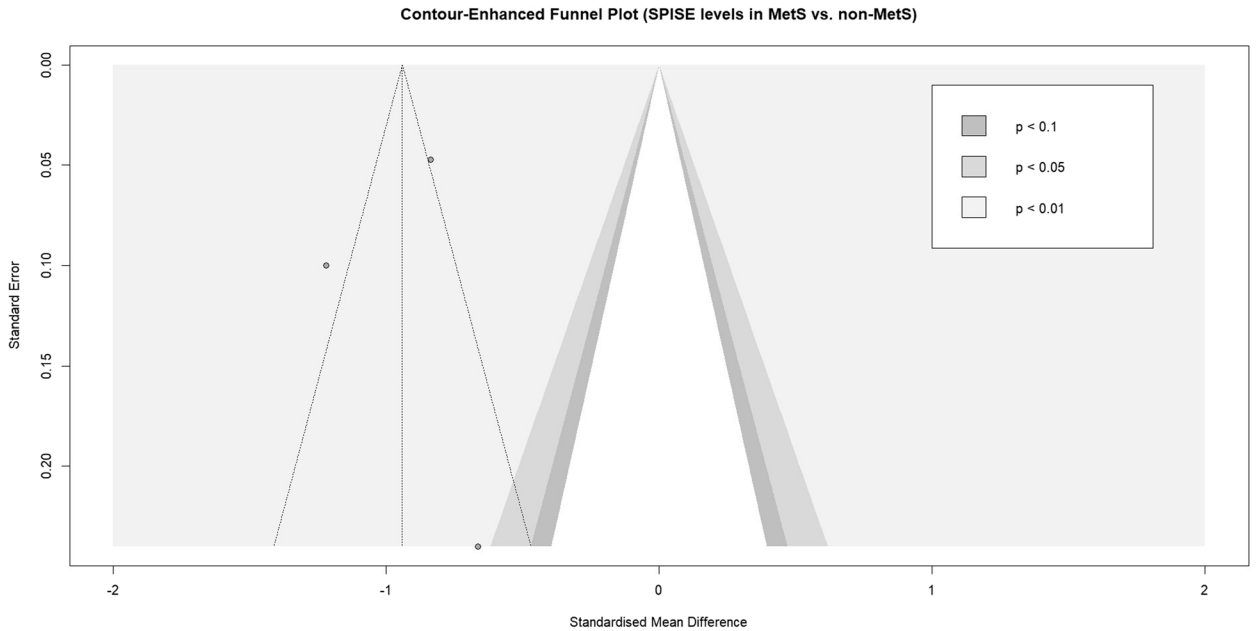

Fig. 7 Funnel plot of the meta-analysis of the mean SPISE in MetS vs. non-MetS patients

The SPISE index was initially derived from two European cohorts with obesity: the β-cell Function in Juvenile Diabetes and Obesity (Beta JUDO) study cohort [36] and the Relationship between Insulin Sensitivity and Cardiovascular Disease (RISC) study cohort [37]. In these cohorts, insulin sensitivity was assessed using oral glucose tolerance tests and hyperinsulinemic-euglycemic clamps, followed by the calculation of insulin resistance indices. Mathematical models incorporating BMI, fasting TG, and HDL-C were used to estimate SPISE values, which were compared to clamp-derived M-values via ROC analysis [13]. SPISE integrates easily accessible biomarkers—BMI, TG, and HDL-C—which are pivotal in the development of insulin resistance and MetS. Elevated BMI, particularly excess visceral fat, disrupts insulin signaling in peripheral tissues, contributing to increased circulating free fatty acids and inflammatory cytokines, both of which impair glucose metabolism [38]. Increased TG levels and altered lipoprotein profiles are also characteristic of insulin resistance [39, 40]. SPISE incorporates these markers to estimate insulin resistance in a simple, non-invasive manner.

SPISE has demonstrated superior predictive performance compared to traditional measures like HOMA-IR, the TG/HDL-C ratio, and TyG index [16, 25]. HOMA-IR, which measures insulin resistance, requires fasting insulin levels, making it less practical. Furthermore, TyG index, while useful in reflecting insulin resistance, is less reliable across all ethnic groups [41]. In contrast, SPISE provides a more comprehensive and integrated approach, offering superior predictive power, particularly in large epidemiological studies. Additionally, The SPISE index has proven particularly useful in pediatric populations, where traditional indices like HOMA-IR may not be as reliable. By incorporating widely available markers SPISE enables early detection of insulin resistance and MetS in children, offering a non-invasive, cost-effective tool for pediatric screening [13, 25, 42, 43].

Subsequent validation studies have affirmed SPISE's ability to predict cardiometabolic risk. SPISE-IR (calculated as 10/SPISE) has been shown to robustly predict both diabetes and coronary heart disease (CHD), outperforming traditional indices like QUICKI-IR and Log HOMA-IR [44]. In another study a higher SPISE index was independently linked to a reduced risk of future cardiovascular events in patients with type 2 diabetes, even after adjusting for established metabolic risk factors [45]. This reinforces the notion that early insulin resistance can lead to metabolic dysfunction, including lipid metabolism impairment and the development of a pro-atherogenic phenotype, which ultimately increases cardiovascular risk [46, 47]. Our analysis revealed significant relationships between SPISE and both SBP and DBP, suggesting that lower SPISE values may be associated with an increased risk of hypertension, a key component of MetS. This highlights the utility of SPISE as a potential early marker for cardiovascular risk in individuals with MetS.

Cutoff values for the SPISE differ significantly across populations, reflecting variations in insulin resistance. For example, in North India, a cutoff value of 5.82 effectively distinguished MetS cases from controls, while in European populations, the cutoff is higher, at 6.61 [13, 14]. In a study conducted in Chile, in adolescents, a SPISE cutoff of 5.4 was identified as optimal for predicting insulin resistance and MetS [15]. Additionally, sex-specific cutoffs were proposed, with values of ≤ 6.1 for boys and ≤ 6.46 for girls, reflecting the varying diagnostic performance across different demographics [26]. In another study, SPISE has shown notable sex differences in its predictive accuracy, performing significantly better in males than females for identifying MetS and insulin resistance. While it was highly accurate in males, its effectiveness in females was slightly reduced but still within a fair-to-good range [16].

A key advantage of SPISE is its reliance on routine lipid profiles and BMI, which are widely available and cost-effective compared to insulin-based indices. Insulin assays are often not recommended for screening in pediatric and adolescent populations, making SPISE an appealing alternative [48, 49]. SPISE's simplicity, requiring only a single blood sample, makes it highly suitable for large-scale epidemiological studies and clinical applications. Moreover, SPISE is especially useful for detecting insulin resistance during puberty, a critical developmental stage when individuals are particularly susceptible to metabolic disturbances [50].

Limitations

This study is not without limitations. First, the number of studies included in the meta-analysis was limited, which may affect the robustness and generalizability of the findings. Including studies with cross-sectional designs limits the causal inference. Additionally, the observed high heterogeneity among the studies may reflect variability in methodologies or populations, complicating result interpretation. Some studies lacked adequate reporting of statistical measures, potentially introducing bias. Small-study effects, where smaller studies may report more favorable outcomes, could also contribute to publication bias, potentially influencing the pooled estimates. Furthermore, we could not perform a meta-analysis on cut-off values due to the inconsistency in the reporting of these thresholds across studies. Lastly, several studies did not sufficiently address confounding factors, which could impact the validity of the observed associations.

Conclusion

In conclusion, our systematic review and meta-analysis revealed that individuals with MetS exhibit a significantly lower SPISE index than those without. The predictive value of SPISE for MetS was notably high, with an AUC of 0.86, outperforming traditional insulin resistance indices, indicating its potential utility for screening MetS. The accuracy of SPISE was particularly robust in children and adolescents. Further longitudinal research is essential to validate these findings and refine SPISE's application in clinical settings.

Supplementary Information

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Supplementary Material 1

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Authors' contributions
A.A. = Conceptualization, formal analysis, investigation, methodology, project administration, supervision, validation, writing-review & editing P.F. = Conceptualization, formal analysis, validation, writing-original draft, writing-review & editing S.J. = data curation, writing-original draft, methodology A.S. = writing-original draft, methodology R.A. = data curation, writing-original draft, methodology A.G.R. = writing-original draft, writing-review & editing, investigation.

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Declarations

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Consent for publication
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Competing interests
The authors declare no competing interests.

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