Jalali *et al.*
Reproductive Biology and Endocrinology (2024) 22:148
https://doi.org/10.1186/s12958-024-01317-4

Reproductive Biology and Endocrinology

REVIEW

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Association of insulin resistance surrogate indices and erectile dysfunction: a systematic review and meta-analysis

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Abstract

Background Erectile dysfunction (ED) has been linked to insulin resistance (IR), with various surrogate indices being used to assess this association. This systematic review and meta-analysis aimed to evaluate the relationship between IR indices and the incidence and severity of ED.

Methods A comprehensive search across PubMed, Embase, Web of Science, and Scopus was carried out. Required data were extracted and meta-analyzed. The Newcastle–Ottawa Scale (NOS) was employed to evaluate the studies' risk of bias. Sensitivity analyses and meta-regressions were conducted to explore heterogeneity and the impact of confounding variables.

Results Seventeen studies with a total of 3810 patients with ED and 8252 without ED were included. Meta-analysis revealed that males with ED had significantly higher levels of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (SMD = 0.59, 95% CI [0.15, 1.03], $I^2 = 82\%$, $P < 0.01$), Triglyceride-Glucose Index (TyG) (SMD = 0.53, 95% CI [0.31, 0.75], $I^2 = 69\%$, $P < 0.01$), and Visceral Adiposity Index (VAI) (SMD = 0.45, 95% CI [0.25, 0.64], $I^2 = 76\%$, $P < 0.01$) compared to those without ED. However, there was no significant correlation between a one-unit increase in HOMA-IR (OR = 0.63, 95% CI [0.03, 13.69], $I^2 = 91\%$, $P = 0.77$) or TyG (OR = 0.53, 95% CI [0.02, 11.53], $I^2 = 88\%$, $P = 0.68$) and the odds of ED. Additionally, a one-unit increase in VAI was associated with more severe ED (SMD = 0.34, 95% CI [0.03, 0.64], $I^2 = 16\%$, $P = 0.03$). The diagnostic accuracy of these indices varied.

Conclusions The results indicate a significant connection between insulin resistance and erectile dysfunction, as shown by HOMA-IR, TyG, and VAI. Yet, their usefulness in predicting ED is restricted because of significant differences and inconsistencies in diagnostic precision. More research is required to determine the clinical importance of these indices in treating ED.

Keywords Erectile dysfunction, Insulin resistance, Surrogate indices, HOMA-IR, Triglyceride-glucose index, Metabolic syndrome, Systematic review, Meta-analysis, Male sexual health

Introduction

Erectile dysfunction (ED), characterized by the persistent inability to achieve and maintain a penile erection sufficient for satisfactory sexual intercourse, is a prevalent condition with significant implications for men's physical and psychological well-being [1]. According to an estimate of the incidence rate of ED, about 20% to 30% of adult men have at least one sexual dysfunction [2]. It is

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predicted that by 2025, over 300 million men worldwide will suffer from ED [3].The prevalence of ED increases with age, and it is closely associated with various lifestyle factors and chronic diseases, including type 2 diabetes mellitus (DM), obesity, and/or metabolic syndrome [1, 4].

The onset of ED has been linked to insulin resistance (IR), a metabolic disorder marked by reduced tissue sensitivity to insulin [5]. A common feature of both IR and ED is endothelial dysfunction, which is characterized by decreased vasodilation and increased vasoconstriction [6]. Recognizing the connection between insulin resistance and erectile dysfunction could be crucial in identifying and treating men at risk of ED early on, especially in cases of metabolic syndrome and type 2 DM. This is why several simple and cost-effective tools, such as the homeostasis model assessment index for insulin resistance (HOMA-IR) and the triglyceride-glucose (TyG) index, have been utilized to investigate this link in the population [7].

Several studies have investigated the relationship between various insulin resistance indices and erectile dysfunction, yet the consistency of these findings remains controversial. To address this gap in knowledge, this systematic review and meta-analysis aims to comprehensively pool available data to not only clarify the association of insulin resistance in patients with and without erectile dysfunction but also the severity of erectile dysfunction.

Materials and methods

The PRISMA statement guidelines were followed during the execution of this meta-analysis [8]. The analysis was conducted using a pre-established approach outlined in the systematic review registration (PROSPERO) (CRD42024571940).

Search strategy and screening

Two authors (S.J., N.Z.) individually conducted searches on electronic databases PubMed, Embase, Web of Science, and Scopus until July 2024 with no filters on publication year or any factor. The following keywords were employed: (“erectile dysfunction”[tiab] OR “impotence”[tiab] OR “sexual dysfunction”[tiab] OR erect*[tiab] OR “sexual disorder”[tiab] OR "Erectile Dysfunction"[Mesh]) AND ("visceral adiposity index" [Title/Abstract] OR VAI [Title/Abstract] OR "lipid accumulation product" [Title/Abstract] OR LAP [Title/Abstract] OR "triglyceride glucose index" [Title/Abstract] OR TyG [Title/Abstract] OR "triglyceride-glucose index" [Title/Abstract] OR "TyG-body mass index" [Title/Abstract] OR "TyG-BMI" [Title/Abstract] OR "TyG-waist circumference" [Title/Abstract] OR "TyG-WC" [Title/Abstract] OR "Homeostatic Model Assessment for Insulin Resistance" [Title/Abstract] OR "HOMA-IR" [Title/Abstract] OR "Metabolic Syndrome Insulin Resistance" [Title/Abstract] OR "MetS-IR" [Title/Abstract] OR "Lipoprotein Insulin Resistance Index" [Title/Abstract] OR "LP-IR" [Title/Abstract] OR "TyG-NC" [Title/Abstract] OR "TyG-NHtR" [Title/Abstract] OR "triglycerides to HDL cholesterol ratio" [Title/Abstract] OR "TG/HDL-C" [Title/Abstract] OR "Adipose insulin resistance index" [Title/Abstract] OR "Adipo-IR" [Title/Abstract] OR "lipid indices" [Title/Abstract] OR "Insulin Resistance index" [Title/Abstract] OR "Insulin Resistance indices" [Title/Abstract]). Further screening of additional articles was conducted using the reference list of the included studies. The research was filtered using Rayyan, an online tool for reviewing, accessible at https://www.rayyan.ai. Two reviewers (S.J. and A.A.) independently assessed each research study and thoroughly examined the complete text to remove any repeated information. Studies meeting the inclusion–exclusion criteria were chosen. Meetings headed by the third author (A.H.B.) were used to reach agreement and address any potential disagreements between reviewers.

Inclusion and exclusion criteria

Population (P): Men diagnosed with ED; Exposure (E): Insulin resistance surrogate indices; Comparison (C): Men without ED or with lower levels of insulin resistance surrogate indices; Outcomes: Association between insulin resistance surrogate indices and prevalence/severity of ED; Type of design (T): Observational studies were included.

Regarding exclusion criteria, studies that included patients with other sexual dysfunctions like premature ejaculation, non-English studies, case reports, reviews, editorials, commentaries, and conference abstracts lacking original research data or detailed methodologies were excluded.

Data extraction and quality assessment

After completing the full-text screening, two researchers (S.Y.H., A.S.) separately entered the provided data into an Excel spreadsheet that already existed, including 1- demographic information such as, authors, year of publication, location of study, study design, sample size, mean age of patients, BMI, co-morbidities and 2- outcomes such as number of patients with Diabetes Meletus (DM), Hypertension (HTN), Metabolic Syndrome (MetS), Blood Glucose (BG), insulin, Waist Circumference (WC), Hemoglobin A1c (HbA1c), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Total Cholesterol (TC), Triglycerides (TG), testosterone, International Index of Erectile Function-5 (IIEF-5), and levels of different insulin resistance surrogates including

Triglyceride-Glucose Index (TyG), Visceral Adiposity Index (VAI), Lipid Accumulation Product (LAP), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and Metabolic Score for Insulin Resistance (METS-IR). The conflicts were evaluated by the third reviewer (A.G.R.). ED is the consistent or recurrent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual intercourse [9]. Here are the formulas of the aforementioned indices:

$$\text{HOMA-IR} = \frac{\text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Glucose (mg/dL)}}{405}$$

$$\text{TyG} = \ln\left(\text{Fasting Triglycerides (mg/dL)} \times \text{Fasting Glucose (mg/dL)}\right)$$

$$\text{CRP-TyG index} = \log\left(\frac{\text{Triglycerides} \times \text{Fasting Glucose}}{2}\right) + \text{CRP level}$$

$$\text{METS-IR} = \ln\left(\text{Fasting Glucose (mg/dL)} \times \text{Fasting Triglycerides (mg/dL)} \times \text{BMI (kg/m}^2\text{)}\right)$$

$$\text{VAI (Men)} = \frac{\text{WC (cm)}}{39.68 + (1.88 \times \text{BMI})} \times \frac{\text{TG (mmol/L)}}{1.03} \times \frac{1.31}{\text{HDL (mmol/L)}}$$

$$\text{VAI (Women)} = \frac{\text{WC (cm)}}{36.58 + (1.89 \times \text{BMI})} \times \frac{\text{TG (mmol/L)}}{0.81} \times \frac{1.52}{\text{HDL (mmol/L)}}$$

Men:

$$\text{LAP} = (\text{Waist circumference (cm)} - 65) \times \text{Triglycerides (mmol/L)}$$

Women:

$$\text{LAP} = (\text{Waist circumference (cm)} - 58) \times \text{Triglycerides (mmol/L)}$$

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the studies included. The Cochrane Handbook has recommended and created this tool for examining the quality of observational studies [10]. Three key factors to evaluate: selection, comparability, and outcome, with ratings ranging from four, two, and three stars, respectively. A rating of 7 or higher is deemed outstanding on this scale. Attributes were evaluated by two authors (S.J., N.Z.), and any disagreements were settled by a third writer (A.H.B.).

Statistical analysis

The researchers reviewed two studies, at minimum, while conducting the meta-analysis pooling process. The data was evaluated with the "meta" package in the R software. The standardized mean difference (SMD) and its 95% confidence intervals (CI) were calculated using the Hedge's g method as the effect measure for all continuous data. The odds ratios (ORs) representing the risk for each one-unit increase in the IR index were combined when treating the IR index as a continuous variable. Restricted maximum likelihood (REML) random-effect meta-analysis was employed to combine the ORs for ED occurrence from each study for a one-unit increment in the IR index.

The decision of whether to use a fixed-effect model or a random-effects model for combining study-specific effect estimates was based on the level of heterogeneity observed. Statistical diversity was assessed using the Q-test and I^2. The I^2 statistic was used to evaluate differences between studies, where I2 values of 0% to 25% indicate low heterogeneity, 26% to 50% suggest moderate heterogeneity, and over 50% show high heterogeneity. If P is above 0.1 and I^2 is less than 50%, a fixed-effect model was used; otherwise, a random-effect model was applied. One study was removed at a time in a sensitivity analysis to assess the individual impact of each study. Meta regression based on the available demographic and lab data was conducted to find the potential sources of heterogeneity. The publication bias was evaluated using Egger's test. A two-sided *P* value less than 0.05 was

considered statistically significant in all data analyses, except for heterogeneity and publication bias.

Results

Study selection

The initial systematic search of databases identified 434 studies. Following the elimination of 156 duplicates, the title and abstract of 278 studies were reviewed, of which 255 were deemed irrelevant and excluded. A full-text assessment was conducted for the remaining 23 studies. 17 studies met the inclusion criteria and were included in the systematic review and meta-analysis (Fig. 1).

Baseline characteristics and quality assessment

This systematic review included research from multiple countries, including the USA [11–14], China [15–17], Turkey [18–22], Italy [23, 24], Argentina [25], Korea [26], and Poland [27]. The research mainly used cross-sectional [11–17, 19–24, 27, 28] as well as prospective [25] and retrospective [18] cohort study designs. A total of 3810 males with ED and 8252 with no ED as the control group were included in this study, with a mean age ranging from 29.44 ± 5.67 [17] to 65.48 ± 4.28 [27] and a BMI of 27.88 ± 4.1 kg/m2 in ED and 27.93 ± 5.4 kg/m2 in non-ED populations. Studies reported the levels of IR indices, including HOMA-IR, TyG, VAI, METS-IR, and LAP, in different ED and non-ED groups (Table 1). Comorbidities and metabolic markers across study groups are also summarized in Table 2.

The NOS scores ranged from 7 to 9, indicating that the studies included were of good to very good quality. Eight studies [11–14, 16, 20, 26, 27] received a score of 9, categorizing them as "Very Good," whereas nine studies [15, 17–19, 21–25] scored slightly lower but still maintained a "Good" quality rating (Supplementary File 1: Table S1).

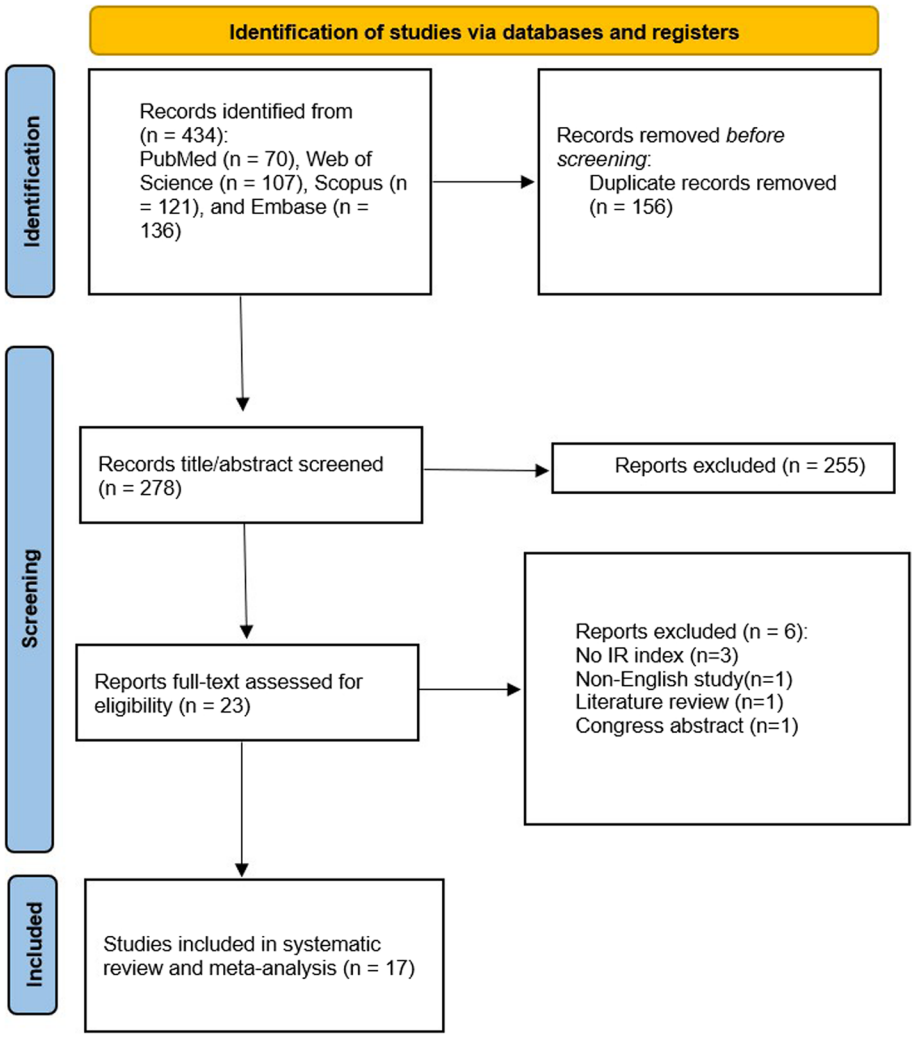

Fig. 1 PRISMA flowchart

Table 1 Baseline characteristics

Study	Groups	Population	Country	Study Design	Age	BMI	IR index
Yilmaz 2021 [22]	ED	91	Turkey	Cross-sectional	51.6 ± 10.4	28.5 ± 3.6	TyG = 9.22 ± 0.72 HOMA-IR = 4.82 ± 4.54
	non-ED	51			47.6 ± 10.4	27.5 ± 3.4	TyG = 8.68 ± 0.49 HOMA-IR = 2.74 ± 3.84
Yao 2013 [17]	ED	192	China	Cross-sectional	29.4 ± 5.7	23.3 ± 4.6	HOMA-IR = 1.5 ± 0.8
	non-ED	33			29.8 ± 3.6	22.2 ± 1.9	HOMA-IR = 0.95 ± 0.44
Yang 2022 [16]	DMED	30	China	Cross-sectional	49.8 ± 6.1	25.2 ± 3.0	HOMA-IR = 3.44 ± 0.91
	DM	31			48.3 ± 6.7	24.6 ± 3.7	HOMA-IR = 3.07 ± 0.63
	Healthy	32			48.3 ± 4.9	24.3 ± 2.3	HOMA-IR = 1.8 ± 0.25
Xu 2023 [14]	ED	900	USA	Cross-sectional	68.0 ± 13.4	N/A	VAI = 1.8 ± 1.4
	non-ED	2480			42.0 ± 16.3	N/A	VAI = 1.5 ± 1.3
Sun 2024 [13]	ED	512	USA	Cross-sectional	65.3 ± 14.7	N/A	METS-IR = 45.22 ± 11.41
	non-ED	1247			43.6 ± 15.5	N/A	METS-IR = 43.09 ± 10.51
Sambel 2023 [21]	ED	199	Turkey	Cross-sectional	49.6 ± 9.0	28.4 ± 4.2	TyG = 9.16 ± 0.71
	non-ED	51			47.6 ± 9.2	26.7 ± 2.6	TyG = 8.77 ± 0.52
Peng 2022 [15]	Severe DMED	18	China	Cross-sectional	41.9 ± 7.4	24.6 ± 3.1	TyG = 7.66 ± 0.76
	Moderate DMED	26			45.9 ± 10.7	24.7 ± 4.6	TyG = 9.16 ± 0.71
	Mild DMED	91			43.6 ± 8.6	24.8 ± 2.7	TyG = 7.77 ± 0.57
	Severe non-DMED	24			35.0 ± 10.1	22.7 ± 2.9	TyG = 7.07 ± 0.61
	Moderate non-DMED	60			33.3 ± 7.9	24.1 ± 2.9	TyG = 7.09 ± 0.51
	Mild non-DMED	146			33.3 ± 7.6	23.2 ± 2.9	TyG = 7.07 ± 0.52
Mei 2024 [12]	ED	302	USA	Cross-sectional	53.9 ± 0.8	30.0 ± 0.6	TyG = 9.14 ± 0.2
	non-ED	1200			40.3 ± 0.4	28.0 ± 0.2	TyG = 8.75 ± 0.70
Li 2022 [11]	ED	606	USA	Cross-sectional	53.9 ± 1.4	N/A	TyG = 9.00 ± 0.63
	non-ED	2560			40.4 ± 0.8	N/A	TyG = 8.6 ± 1.3
Knoblovits 2010 [25]	ED	74	Argentina	Prospective Cohort	60.0 ± 9.3	29.7 ± 4.4	HOMA-IR = 5.0 ± 2.9
	non-ED	17			55.8 ± 8.2	26.2 ± 2.9	HOMA-IR = 3.5 ± 2.5
Kim 2019 [26]	ED	44	Korea	Cross-sectional	55.0 ± 2.3	N/A	HOMA-IR = 2.3 ± 1.0
	non-ED	36			48.0 ± 3.3	N/A	HOMA-IR = 1.7 ± 1.0
Gatti 2009 [24]	ED	17	Italy	Cross-sectional	43.0 ± 12.4	42.5 ± 7.2	HOMA-IR = 6.5 ± 3.8
	non-ED	33			41.6 ± 10.9	44.8 ± 11.2	HOMA-IR = 7.3 ± 4.9
Dursun 2018 [20]	ED	95	Turkey	Cross-sectional	53.5 ± 6.3	29.1 ± 2.9	VAI = 5.18 ± 2.5
	non-ED	82			52.9 ± 7.2	27.3 ± 3.0	VAI = 3.47 ± 1.76
Derosa 2015 [23]	ED	109	Italy	Cross-sectional	63.8 ± 8.6	29.6 ± 4.7	HOMA-IR = 3.4 ± 2.8
	non-ED	97			58.5 ± 9.3	28.8 ± 4.2	HOMA-IR = 2.7 ± 2.0
Bolat 2020 [19]	Severe ED	59	Turkey	Cross-sectional	53.2 ± 9.0	29.3 ± 4.0	VAI = 13.9 ± 23.1
	Moderate ED	59			53.4 ± 9.1	28.9 ± 3.7	VAI = 11.4 ± 17.8
	Mild ED	54			50.0 ± 10.9	27.4 ± 3.4	VAI = 5.6 ± 10.0
Aleksandra 2022 [27]	ED	72	Poland	Cross-sectional	65.5 ± 4.3	29.5 ± 4.4	VAI = 3.07 ± 1.69 LAP = 84.03 ± 43.18 HOMA-IR = 3.76 ± 7.36
	non-ED	34			64.7 ± 4.5	29.5 ± 3.7	VAI = 2.32 ± 1.22 LAP = 63.96 ± 25.59 HOMA-IR = 2.79 ± 3.59
Akdemir 2019 [18]	ED	176	Turkey	Retrospective Cohort	58.7 ± 8.4	27.6 ± 4.2	VAI = 5.32 ± 2.77
	non-ED	122			57.1 ± 7.6	26.6 ± 3.5	VAI = 4.11 ± 1.93

Abbreviations: *BMI* Body Mass Index, *DM* Diabetes Mellitus, *DMED* Diabetes Mellitus Erectile Dysfunction, *ED* Erectile Dysfunction, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *IR* Insulin Resistance, *LAP* Lipid Accumulation Product, *METS-IR* Metabolic Score for Insulin Resistance, *N/A* Not Applicable, *TyG* Triglyceride Glucose Index, *VAI* Visceral Adiposity Index

Table 2 Comorbidities and metabolic markers across study groups

Study	Groups	Population	WC (cm)	DM (n)	HTN (n)	MetS (n)	Current Smoking (n)	Testostrone (ng/ml)	Insulin (μU/mL)	TG (mg/dl)	BG (mg/dL)	HbA1c (%)	HDL (mg/dl)	LDL (mg/dl)	TC (mg/dl)	IIEF-5
Yilmaz 2021 [22]	ED	91	103.8 ± 8.8	21	30	8	N/A	3.9 ± 1.5	15.9 ± 11.4	204.5 ± 153.2	127.1 ± 61.1	6.6 ± 1.9	42.8 ± 9.4	109.5 ± 40.0	185.4 ± 44.7	14.7 ± 0.5
	non-ED	51	99.5 ± 11.9	3	5	47	N/A	4.1 ± 1.3	11.4 ± 16.0	138.9 ± 74.3	96.2 ± 10.8	5.5 ± 0.4	48.8 ± 9.7	112.3 ± 30.8	180.4 ± 38.4	23.4 ± 0.2
Yao 2013 [17]	ED	192	N/A	N/A	N/A	N/A	N/A	6.8 ± 2.1 (ng/dl)	7.1 ± 3.8	97.4 ± 53.1	85.1 ± 10.1	N/A	54.1 ± 10.8	120.7 ± 32.1	184.8 ± 28.6	11.5 ± 5.0
	non-ED	33	N/A	N/A	N/A	N/A	N/A	6.7 ± 2.1 (ng/dl)	6.0 ± 1.9	85.0 ± 15.9	81.7 ± 9.0	N/A	50.3 ± 8.9	121.1 ± 29.0	176.6 ± 20.9	23.8 ± 0.9
Yang 2022 [16]	DMED	30	N/A	N/A	N/A	N/A	11	5.0 ± 0.6	N/A	188.8 ± 34.5	153.2 ± 20.7	8.1 ± 1.0	43.7 ± 8.9	114.4 ± 16.6	192.4 ± 20.5	11.9 ± 6.4
	DM	31	N/A	N/A	N/A	N/A	11	5.3 ± 0.6	N/A	173.5 ± 28.4	144.4 ± 18.4	8.0 ± 1.4	42.9 ± 9.7	109.5 ± 12.0	183.8 ± 20.1	22.6 ± 0.8
	Healthy	32	N/A	N/A	N/A	N/A	12	6.3 ± 0.4	N/A	119.5 ± 25.7	92.3 ± 6.7	5.3 ± 0.3	50.2 ± 9.7	86.5 ± 13.1	158.9 ± 11.6	23.6 ± 0.8
Xu 2023 [14]	ED	900	N/A	208	571	N/A	187	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	non-ED	2480	N/A	126	792	N/A	731	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sun 2024 [13]	ED	512	N/A	121	269	N/A	368	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	non-ED	1247	N/A	62	292	N/A	683	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sambel 2023 [21]	ED	199	N/A	50	44	N/A	N/A	3.8 ± 1.7	N/A	197.2 ± 110.1	121.3 ± 29.5	6.2 ± 1.7	41.3 ± 9.7	129.1 ± 32.7	206.4 ± 40.1	N/A
	non-ED	51	N/A	3	9	N/A	N/A	4.0 ± 1.3	N/A	161.7 ± 95.3	92.0 ± 11.9	5.4 ± 0.4	42.7 ± 8.2	116.1 ± 23.2	193.3 ± 40.3	N/A
Peng 2022 [15]	Severe DMED	18	N/A	N/A	N/A	N/A	N/A	12.1 ± 5.0 (mmol/l)	N/A	215.8 ± 101.8	135.9 ± 37.8	N/A	N/A	N/A	4.7 ± 1.9	13.6 ± 4.8
	Moderate DMED	26	N/A	N/A	N/A	N/A	N/A	15.5 ± 4.4 (mmol/l)	N/A	173.5 ± 101.8	153.4 ± 59.6	N/A	N/A	N/A	5.7 ± 3.3	
	Mild DMED	91	N/A	N/A	N/A	N/A	N/A	14.5 ± 5.3 (mmol/l)	N/A	208.6 ± 136.4	134.8 ± 29.7	N/A	N/A	N/A	4.5 ± 1.2	
	Severe non-DMED	24	N/A	N/A	N/A	N/A	N/A	16.9 ± 5.1 (mmol/l)	N/A	143.4 ± 80.6	91.6 ± 10.3	N/A	N/A	N/A	4.9 ± 1.5	14.1 ± 4.7
	Moderate non-DMED	60	N/A	N/A	N/A	N/A	N/A	18.3 ± 7.6 (mmol/l)	N/A	149.2 ± 85.7	93.4 ± 6.1	N/A	N/A	N/A	4.8 ± 0.9	
	Mild non-DMED	146	N/A	N/A	N/A	N/A	N/A	19.2 ± 6.4 (mmol/l)	N/A	146.3 ± 81.5	93.2 ± 7.0	N/A	N/A	N/A	4.8 ± 1.1	
Mei 2024 [12]	ED	302	N/A	98	163	N/A	90	N/A	N/A	215.8 ± 20.2	119.8 ± 2.9	N/A	N/A	N/A	N/A	N/A
	non-ED	1200	N/A	70	342	N/A	354	N/A	N/A	158.3 ± 4.7	100.5 ± 0.7	N/A	N/A	N/A	N/A	N/A
Li 2022 [11]	ED	606	N/A	138	290	N/A	422	N/A	N/A	N/A	N/A	N/A	45.8 ± 1.6	N/A	202.9 ± 7.3	N/A
	non-ED	2560	N/A	99	526	N/A	1384	N/A	N/A	N/A	N/A	N/A	47.1 ± 1.0	N/A	201.9 ± 2.9	N/A
Knoblovits 2010 [25]	ED	74	105.5 ± 10.6	N/A	N/A	N/A	N/A	4.2 ± 1.2	21.9 ± 11.1	N/A	90.0 ± 13.3	N/A	N/A	N/A	N/A	13.7 ± 4.4
	non-ED	17	98.1 ± 7.5	N/A	N/A	N/A	N/A	5.5 ± 1.9	16.8 ± 11.0	N/A	85.9 ± 10.5	N/A	N/A	N/A	N/A	16.2 ± 3.2
Kim 2019 [26]	ED	44	87.4 ± 2.3	N/A	N/A	N/A	N/A	3.9 ± 0.4	9.0 ± 1.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	non-ED	36	86.0 ± 2.2	N/A	N/A	N/A	N/A	4.2 ± 0.4	7.2 ± 1.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 2 (continued)

Study	Groups	Population	WC (cm)	DM (n)	HTN (n)	MetS (n)	Current Smoking (n)	Testostrone (ng/ml)	Insulin (μU/mL)	TG (mg/dl)	BG (mg/dL)	HbA1c (%)	HDL (mg/dl)	LDL (mg/dl)	TC (mg/dl)	IIEF-5
Gatti 2009 [24]	ED	17	N/A	N/A	15	12	8	1.5 ± 0.3	N/A	150.5 ± 78.0	92.5 ± 11.1	N/A	46.2 ± 8.0	N/A	205.2 ± 43.5	17.5 ± 4.0
	non-ED	33	N/A	N/A	25	23	12	1.4 ± 0.7	N/A	164.1 ± 77.7	90.1 ± 11.5	N/A	44.0 ± 6.2	N/A	198.9 ± 32.6	23.7 ± 1.1
Dursun 2018 [20]	ED	95	93.8 ± 8.3	N/A	N/A	N/A	N/A	N/A	N/A	167.7 ± 73.7	N/A	N/A	43.0 ± 7.4	N/A	N/A	N/A
	non-ED	82	91.0 ± 8.5	N/A	N/A	N/A	N/A	N/A	N/A	130.3 ± 70.8	N/A	N/A	49.5 ± 4.5	N/A	N/A	N/A
Derosa 2015 [23]	ED	109	102.6 ± 10.1	N/A	82	N/A	N/A	198.9 ± 36.3 (pg/ml)	10.0 ± 2.0	151.4 ± 90.3	135.4 ± 44.6	7.0 ± 1.1	43.5 ± 10.6	86.7 ± 27.0	161.2 ± 29.0	N/A
	non-ED	97	100.6 ± 9.8	N/A	56	N/A	N/A	226.6 ± 59.6 (pg/ml)	8.2 ± 1.6	123.5 ± 71.3	134.0 ± 37.6	7.2 ± 1.2	43.2 ± 10.0	87.2 ± 26.3	155.1 ± 30.0	N/A
Bolat 2020 [19]	Severe ED	59	107.8 ± 11.7	19	19	N/A	N/A	3.6 ± 1.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4.9 ± 4.2
	Moderate ED	59	104.1 ± 9.6	16	19	N/A	N/A	3.9 ± 1.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	13.6 ± 1.7
	Mild ED	54	96.0 ± 8.3	3	7	N/A	N/A	4.4 ± 0.9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	23.7 ± 1.3
Aleksandra 2022 [27]	ED	72	105.6 ± 11.5	N/A	N/A	N/A	N/A	4.8 ± 2.1	N/A	196.0 ± 157.5	86.8 ± 29.3	N/A	39.4 ± 9.8	113.2 ± 82.1	180.5 ± 49.6	N/A
	non-ED	34	103.1 ± 9.5	N/A	N/A	N/A	N/A	5.8 ± 2.3	N/A	176.0 ± 105.6	80.7 ± 18.2	N/A	41.8 ± 9.9	103.6 ± 45.2	179.9 ± 47.0	N/A
Akdemir 2019 [18]	ED	176	N/A	32	27	N/A	80	4.1 ± 1.2	N/A	161.6 ± 58.0	107.8 ± 29.5	N/A	41.2 ± 9.0	116.2 ± 30.2	190.5 ± 35.9	N/A
	non-ED	122	N/A	25	12	N/A	56	4.5 ± 1.6	N/A	140.0 ± 45.0	102.3 ± 26.0	N/A	45.7 ± 9.2	109.8 ± 30.8	190.9 ± 36.7	N/A

Abbreviations: *BG* Blood Glucose; cm, Centimeters, *DM* Diabetes Mellitus, *DMED* Diabetes Mellitus Erectile Dysfunction, *ED* Erectile Dysfunction; HbA1c, Hemoglobin A1c, *HDL* High-Density Lipoprotein, *HTN* Hypertension, *IIEF-5* International Index of Erectile Function-5, *LDL* Low-Density Lipoprotein, *MetS* Metabolic Syndrome, *mg/dL* Milligrams per Deciliter, *mmol/l* Millimoles per Liter, *N/A* Not Available, *ng/dl* Nanograms per Deciliter, *ng/ml* Nanograms per Milliliter; pg/ml, Picograms per Milliliter, *TC* Total Cholesterol, *TG* Triglycerides, *μU/mL* Micro Units per Milliliter, *WC* Waist Circumference

HOMA-IR index and ED

Meta-analysis showed that males with ED had higher levels of HOMA-IR (SMD [95%CI] = 0.59 [0.15, 1.03], I^2 = 82%, *P*-value < 0.01) when compared with those without ED (Fig. 2A). Subgroup analysis based on the NOS of the studies revealed that with high-quality studies (NOS > 7) the association between HOMA-IR levels and ED remained (SMD [95%CI] = 0.71 [0.07, 1.35], I^2 = 87%, *P*-value = 0.03), while studies with NOS ≤ 7 showed no statistically significant association (SMD [95%CI] = 0.39 [-0.12, 0.91], I^2 = 69%, *P*-value = 0.14) (Fig. 2B). By omitting Yang et al. [16], the association of the HOMA-IR and ED remained significant, while heterogeneity substantially reduced (SMD [95%CI] = 0.40 [0.23, 0.57], I^2 = 29%, *P*-value < 0.01) (Fig. 3). Meta-regression with age, BMI, BG, TG, and TT as covariates demonstrated no statistically significant sign that these factors may be a possible source of heterogeneity (*P*-values > 0.05).

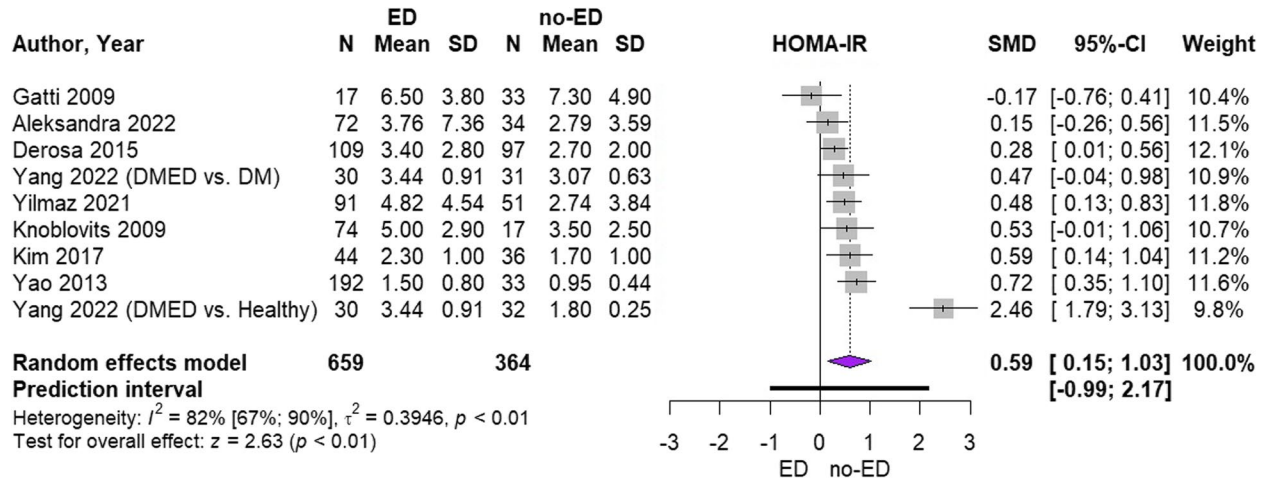

Fig. 2 **A** Forest plot of the HOMA-IR index levels in ED vs. no ED patients; (**B**) Subgroup analysis based on NOS of the HOMA-IR index levels in ED vs. no ED patients

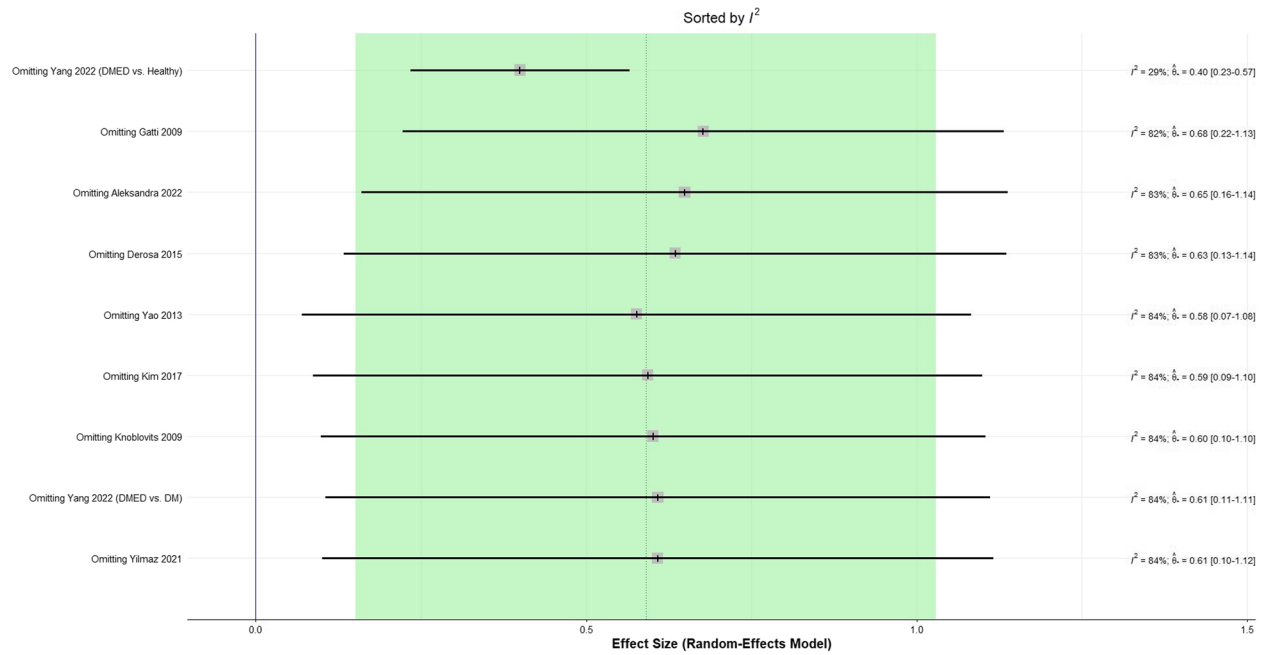

Fig. 3 Sensitivity analysis of the HOMA-IR index levels in ED vs. no ED patients

Also, meta-analysis demonstrated that a one-unit increase in HOMA-IR was not significantly associated with the odds of ED (OR [95%Cl] = 0.63 [0.03, 13.69, $I^2 = 91\%$, *P*-value = 0.77) (Fig. 4A). The sensitivity analysis revealed that the overall effect remained the same, regardless of which study was omitted (Fig. 4B).

TyG index and ED

The meta-analysis also revealed that males suffering from ED had elevated TyG levels compared to those without the condition (SMD [95% CI] = 0.53 [0.31, 0.75], I2 = 69%, *P*-value < 0.01) (Fig. 5A). Excluding Li et al. [11] decreased heterogeneity substantially, but the relationship between TyG and ED remained significant (SMD

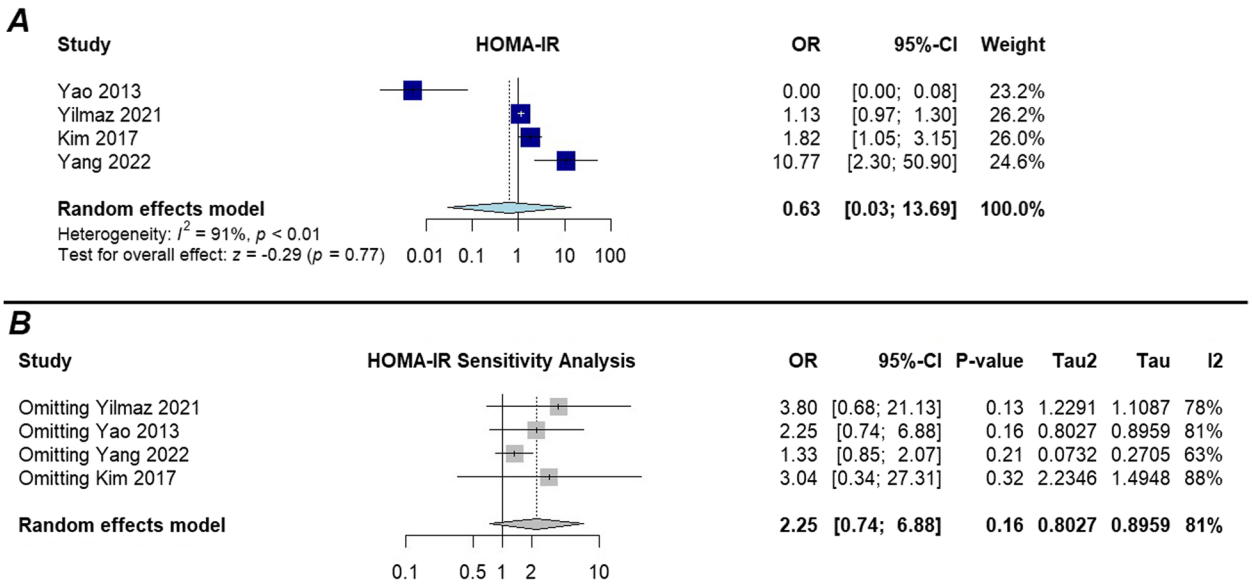

Fig. 4 **A** Forest plot of ED incidence using the HOMA-IR index as a continuous variable (1-unit increase); (**B**) Sensitivity analysis of ED incidence using the HOMA-IR index as a continuous variable (1-unit increase)

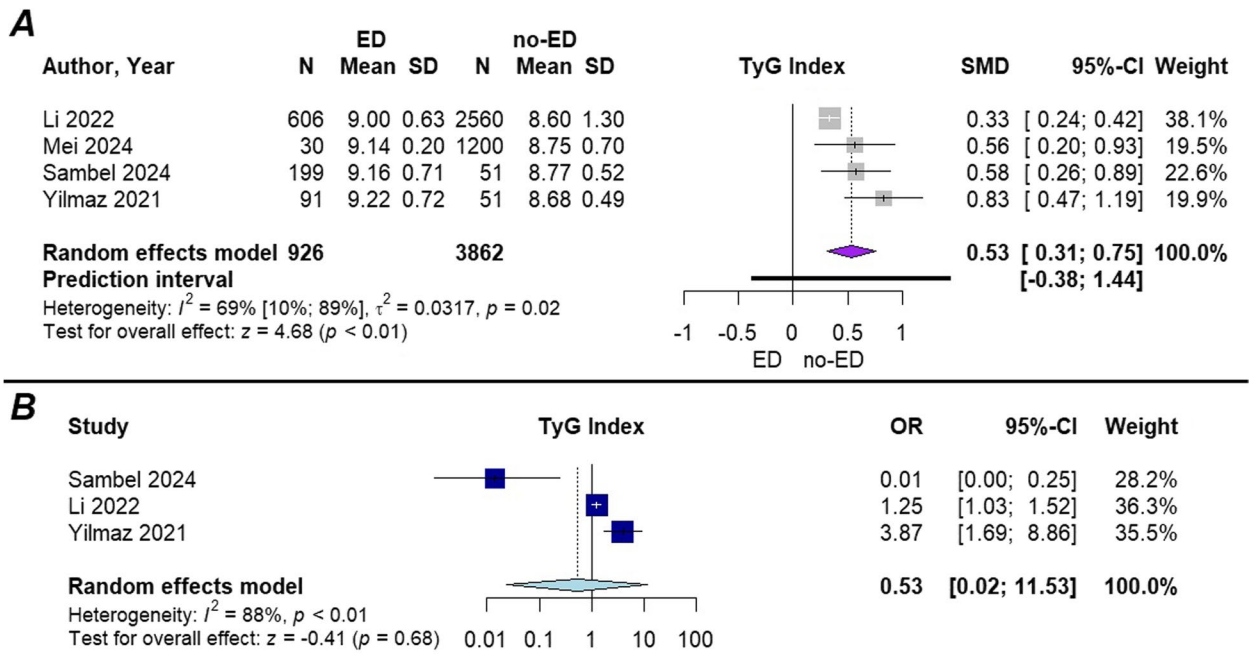

Fig. 5 **A** Forest plot of the TyG index levels in ED vs. no ED patients; (**B**) Forest plot of ED incidence using the TyG index as a continuous variable (1-unit increase)

[95%CI] = 0.65 [0.45, 0.85], I2 = 0%, *P*-value < 0.01) (Supplementary File 1: Figure S1). Moreover, statistically significant findings were observed in the meta-regression involving age (*P* = 0.01) (Supplementary File 1: Figure S2), DM (*P* = 0.003) (Supplementary File 1: Figure S3), and HTN (*P* = 0.004) (Supplementary File 1: Figure S4). Studies involving men with a higher mean age showed a greater prevalence of DM and HTN in their populations.

Additionally, meta-analysis found that there was no significant correlation between a one-unit increase in TyG and the odds of ED (OR [95%Cl] = 0.53 [0.02, 11.53], I^2 = 88%, *P*-value = 0.68) (Fig. 5B). The sensitivity analysis showed that the overall result remained statistically insignificant regardless of excluding any specific study.

VAI index and ED

The meta-analysis revealed that men with ED had increased VAI levels (SMD [95%CI] = 0.45 [0.25, 0.64], I2 = 76%, *P*-value < 0.01) compared to those without (Fig. 6). By excluding Xu et al. [14], the relationship between VAI and ED remained significant, but a notable decrease in heterogeneity was noticed (SMD [95%CI] = 0.54 [0.38, 0.70], I^2 = 10%, *P*-value < 0.01) (Supplementary File 1: Figure S5).

Insulin surrogate indices and severity of ED

Studies also reported the levels of insulin surrogate indices in cases of mild, moderate, and severe ED. Aleksandra et al. [27] reported that a one-unit increase in TyG had a notable correlation with the severity of ED (OR [95%CI] = 1.58 [1.16, 2.16]). Furthermore, men with severe erectile dysfunction exhibited increased levels of VAI in comparison to those with mild ED (SMD [95%CI] = 0.34 [0.03, 0.64], I^2 = 16%, *P*-value = 0.03) (Supplementary File 1: Figure S6). Nevertheless, no distinguishable difference was observed in the comparison between severe vs. moderate ED (SMD [95%CI] = 0.03 [-0.22, 0.28], I2 = 0%, *P* = 0.81) (Supplementary File 1: Figure S7), as well as moderate vs. mild ED (SMD [95%CI] = 0.30 [0.00, 0.59], I^2 = 0%, *P*-value = 0.05) (Supplementary File 1: Figure S8).

Qualitative synthesis

The following outcomes were only reported by one study; therefore, a systematic review of the data will suffice. Weinberg et al. [29] categorized the participants into three groups according to their HOMA-IR tertiles and discovered that in the 2nd tertile vs. the 1st tertile (reference), HOMA-IR was significantly linked to the likelihood of experiencing ED (OR [95%CI] = 2.14 [1.1, 4.2]). No difference was found in the 3rd tertile vs. the 1st (OR [95%CI] = 1.8 [0.8, 3.8]).

Mei et al. [12] assessed the link between CRP-TyG and ED, revealing a significant correlation with ED per one unit increase (OR [95%CI] = 1.56 [1.27, 1.9]). Additionally, there was a significant association between ED and CRP-TyG in the 4th quartile vs. the 1st (OR [95%CI] = 2.69 [1.07, 6.74]). No substantial difference was observed in the 2nd (OR [95%CI] = 1.48 [0.6, 3.66]) and 3rd (OR [95%CI] = 1.64 [0.58, 4.65]) quartiles vs. the 1st.

Another study by Xu et al. [14] found a significant link between the 4th quartile of VAI and the likelihood of experiencing ED vs. the 1st quartile (OR [95%CI] = 1.404 [1.008, 1.954]). There was not a significant difference in the 2nd (OR [95%CI] = 1.197 [0.849, 1.689]) and 3rd (OR [95%CI] = 1.147 [0.820, 1.606]) quartiles vs. 1st.

Sun et al. [13] discovered that METS-IR, had a notable effect on ED in the 3rd tertile vs. the 1st (OR [95%CI] = 1.6 [1.15, 2.22]). No significant difference was seen in the 2nd tertile vs. the 1st (OR [95%CI] = 1.6 [1.15, 2.22]). Furthermore, a one-unit increase in METS-IR was found to increase the odds of having ED significantly (OR [95%CI] = 1.03 [1.01, 1.04]).

Lastly, Aleksandra et al. [27] found that there was no significant link between the LAP index and ED (OR [95%CI] = 1.02 [1.00, 1.034]).

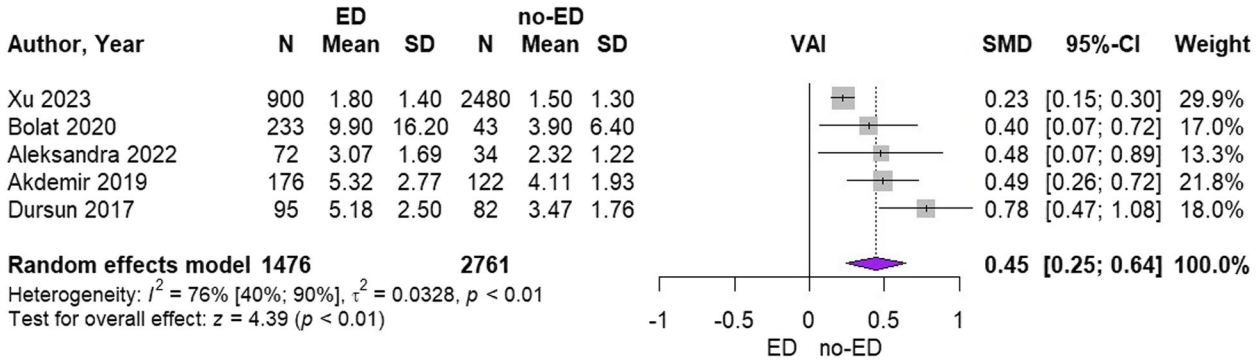

Fig. 6 Forest plot of the VAI index levels in ED vs. no ED patients

AUC for the prediction of ED

The AUC for discriminating ED from non-ED males using HOMA-IR was reported to be 0.81 (AUC [95%CI] = 0.81 [0.71, 0.91]) by Yang et al. [16] and hence a good predictor. However, Yao et al. [17] reported an AUC of 0.76 (AUC [95%CI] = 0.76 [0.68, 0.84]; HOMA-IR cut-off = 1.22) and found it to be a poor predictor of ED.

Additionally, the ability of TyG to distinguish between males with and without ED was found to be worthless (AUC [95%CI] = 0.67 [0.59, 0.74]; TyG cut-off = 8.91) [21] and poor (AUC = 0.739; TyG cut-off = 8.88) [22] in the prediction of ED.

Furthermore, Aleksandra et al. found that VAI has an AUC of 0.63 (AUC = 0.63; VAI cut-off = 3.23) and LAP has an AUC of 0.64 (AUC = 0.64; LAP cut-off = 63.74) in distinguishing between males with and without ED, indicating they are worthless predictors of ED.

Publication bias

Egger's regression intercept was employed to assess publication bias in the HOMA-IR level analyses comparing ED with no-ED (Supplemental file 1: Figure S9). No indication of bias in publication was observed ($P = 0.25$).

Discussion

This was the first comprehensive systematic review and meta-analysis that assessed the association of IR and ED. By inclusion of 17 studies assessing various markers of IR, this study showed that males with ED had significantly higher HOMA-IR, TyG, and VAI index levels compared to those without. Although there is a need for further studies on the topic to solidify these findings, our analyses could have clinical and research implications. A clinician can now take IR and its markers into consideration when evaluating patients with ED, correction of which might lead to control of ED. Similarly, these emphasize the evaluation of sexual dysfunction in those with IR with the aim of identifying patients in need of interventions. Our investigation provides insight into further research on the role of IR in ED since most of our findings were based on a limited number of studies, and in some cases, the precision of our findings could be affected by that.

It has been known for several years that there are various degrees of association between ED and components of MetS such as hypertension, high BMI, high blood cholesterol levels, and hyperglycemia [30, 31]. Moreover, it is obvious that the primary pathophysiology of MetS is IR since hyperglycemia plays a major role in MetS [32]. It has been shown that in up to 75% of men with diabetes, ED occurs in varying degrees, and in some, it is the first symptom of diabetes [33]. Mechanistically, insulin induces the enhancement of NO generation by promotion of activity and expression of endothelial-type nitric oxide synthase (ENOS) [34, 35]. Hence, IR causes impairment in vascular and basal NO production and defective insulin-induced vasodilation, all of which are predictors of ED [34, 36]. Additionally, increased free-fatty acid circulatory levels secondary to a high-fat diet lead to a decline in NO production through downregulation in the 5'-adenosine monophosphate-activated protein kinase (AMPK)-phosphatidylinositol 3-kinase (PI3K)-eNOS pathway in endothelial cells [37]. Finally, among the possible mechanisms, low testosterone levels might play an intermediary role since it has been shown that the release of testosterone is reduced under IR conditions [38].

One of our main findings in this meta-analysis was the association of higher HOMA-IR and ED. The predictive ability of HOMA-IR was also assessed in studies that showed variable levels of prediction ranging from an AUC of 0.76 to 0.81 [16, 17]. HOMA-IR is one of the classic markers of IR, calculated from fasting plasma glucose and fasting plasma levels of insulin. This is also highly correlated with the gold standard of IR measurement, which is glucose clamp [39, 40]. However, the main limitation of HOMA-IR might be the challenges in the measurement of insulin levels. This is of higher importance in settings with low resources or in low-income countries with limited availabilities in their healthcare systems [41]. Therefore, searching for alternative accessible IR indices with the same level of diagnostic ability for IR seems reasonable in these subjects.

Among other surrogate markers of IR, the TyG index has gained popularity in recent years, mainly due to its ease of measurement. It is calculated from fasting plasma glucose and TG levels, both of which are routinely measured in common laboratory tests. Compared to the HOMA-IR, the TyG index is a more cost-effective alternative and easy-to-measure marker of the IR [42–44]. Moreover, it has been measured and shown effectiveness as a diagnostic and prognostic index in several cardiovascular and non-cardiovascular diseases in systematic reviews and meta-analyses [7, 45–51]. Our meta-analysis of studies that assessed TyG levels in patients with ED compared to non-ED controls showed that ED cases had significantly higher TyG levels. However, it should be noted that moderate-to-high heterogeneities were observed in these analyses, resulting from the low number of studies, differences in methodologies, and varieties in populations. Similarly, Yilmaz et al. reported that the TyG index above 8.88 is an independent predictor of ED [22]. By performing studies to determine cut-off values for the TyG index in local settings, these higher levels of TyG could have clinical applications for primary care physicians as well.

In addition to the HOMA-IR and TyG index, markers of central obesity have been suggested to be suitable IR

indicators. Among these, visceral fat area (VFA) and VAI have been suggested, of which VFA is more complicated to measure and has a higher cost [52]. While no systematic review has previously compared VAI in patients with and without ED, the efficacy of VAI in other metabolic and non-metabolic diseases has been investigated in several systematic reviews and meta-analyses [53–55]. Using the NHANES database, Xu and colleagues revealed that VAI was increased in patients with ED [14]. This was in line with previous studies by Aleksandra et al. [27], Dursun et al. [20], and our pooled meta-analysis. One of the plausible mechanisms of this association is the fact that visceral obesity has a clear relation with endothelial dysfunction, a major contributor to ED [56]. In addition, the effect of central obesity and IR on the reduction of testosterone levels might finally lead to ED [57]. Among other composite lipid indices, LAP could be another potential candidate for assessment in ED, as in the investigation by Aleksandra et al. [27].

Strengths and limitations

Our investigation has several strengths that should be mentioned. First, the key strength of this study was the assessment of all IR markers in relation to ED, making this investigation the first and the most comprehensive systematic review to date. Second, we searched all the internationally recognized databases for included studies, lowering the risk of missing any possible studies. However, there were some limitations to this study. First, the low number of studies in each individual comparison, which prevented us from performing meta-analysis in some instances, such as LAP and METS-IR studies, could be a limiting factor in interpreting these results. Further studies with rigorous methodologies are warranted to confirm these findings. Second, the heterogeneity was high in some of the meta-analyses performed. This stems from differences in populations, clinical settings, and measurement methods and threatens the generalizability of these findings. Then, although we addressed publication bias by visual inspection of funnel plots and Egger's methods, due to the low number of studies in each analysis, the accuracy of these tests was reduced, increasing the chance of publication bias. Moreover, all of the studies were observational in nature, and hence, no causal effect could be deduced from them. Finally, we were not able to perform a meta-analysis for the diagnostic and predictive ability of these indices using AUC, sensitivity, and specificity.

Conclusion

In this study, we demonstrated that HOMA-IR is elevated in individuals with erectile dysfunction (ED), underscoring the metabolic aspect of ED. The TyG index, as a simpler and less invasive marker of insulin resistance, could offer greater clinical utility. Incorporating such markers into routine evaluations may help mitigate both the progression of ED and associated cardiovascular risks. Further studies are needed to validate these findings and explore the potential of these markers in guiding treatment strategies for ED.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-024-01317-4.

Supplementary Material 1.

Prospero
CRD42024571940

Authors' contributions
S.J. = Conceptualization, investigation, methodology, project administration, supervision, validation, writing-review & editing. N.Z. = Conceptualization, validation, writing-original draft, writing-review & editing. A.H.B. = data curation, writing-original draft, methodology. A.A. = Formal analysis, writing-original draft, writing-review & editing. S.Y.H. = data curation, writing-original draft. A.S. = writing-review & editing. A.J. = writing-review & editing. A.G.R. = project administration, supervision, validation, writing-review & editing

Funding
There is no funding source for authors to declare.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 19 August 2024 Accepted: 6 November 2024
Published online: 19 November 2024

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