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Association between different insulin resistance surrogates and erectile dysfunction in non-diabetic men: a large population-based study

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Abstract

Background Although it is widely recognized that insulin resistance (IR) plays a critical role in the development of erectile dysfunction (ED), the specific relationship between IR and ED among non-diabetics has been little studied, and no relevant large-scale studies have been conducted. The purpose of this study is to examine the association between different IR surrogates and the risk of ED in non-diabetic populations.

Methods National Health and Nutrition Examination Survey (NHANES) 2001–2004 data were used for this cross-sectional analysis. Weighted multivariable logistic regression and restricted cubic spline curves (RCS) were performed to evaluate the relationship between homeostasis model assessment (HOMA-IR), triglyceride glucose (TyG), TyG with body mass index (TyG-BMI), TyG with waist circumference (TyG-WC) and TyG with waist-to-height ratio (TyG-WHtR), and ED risk. When segmenting effects were detected, recursive algorithms were used to determine potential inflection points. Then log-likelihood ratio test and weighted segmented regression were carried out. In the sensitivity analysis, stratified and interaction analyses were performed.

Results A total of 1569 (weighted: 76450963) individuals eventually were enrolled in the study. After adjusting for all confounders, the TyG did not correlate with ED ($P > 0.05$), whereas the other IR surrogates, HOMA-IR, TyG-BMI, TyG-WC, and TyG-WHtR, remained positively correlated with ED [ORs (95% CIs) were 1.02 (0.95, 1.10), 1.01 (1.00, 1.02), 1.00 (1.00, 1.01), 1.17 (0.84, 1.63), respectively; all $P < 0.05$]. Furthermore, we found the risk of ED was significantly higher when TyG-BMI > 328.94 or TyG-WC > 1128.25 or TyG-WHtR > 6.42 [the ORs (95% CIs) were 1.05 (1.02, 1.08), 1.02 (1.01, 1.03) and 51.30 (4.46, 453.64), respectively]. No interactions were found between these IR surrogates and the stratification variables.

Conclusions In the non-diabetic population, ED risk was positively associated with elevated HOMA-IR, TyG-BMI, TyG-WC, and TyG-WHtR.

Keywords Erectile dysfunction, Insulin resistance, Insulin resistance surrogates, Male health, NHANES

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Background

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction [1]. ED is one of the most common sexual dysfunctions affecting men of all ages [2]. According to the consensus statement of the Fourth International Consultation on Sexual Medicine, more than 150 million men worldwide suffer from varying degrees of ED [3], and another study estimates that by 2025 there will be 322 million cases of ED worldwide [4]. While ED itself is not life-threatening, it can have a negative impact on partner relationships and quality of life, and it can be a precursor to other undiagnosed conditions [5].

The etiology of ED is complex and varied, and there is more research evidence available that suggests a strong association between insulin resistance (IR) and the development of ED. Trussell and Legro [6] demonstrated that IR disrupts phosphatidylinositol 3-kinase (PI3K)/Akt signaling, which reduces endothelial nitric oxide synthase (eNOS) activation-a key pathway for penile vasodilatation-thereby impairing nitric oxide (NO) bioavailability. At the same time, IR-induced hyperglycemia and oxidative stress exacerbate vascular injury, further impairing erectile function. Moon et al. [7] emphasized obesity-associated metabolic syndrome as a common etiology, in which chronic inflammation and leptin resistance amplify the inhibition of NO through TNF-α-mediated downregulation of eNOS. Schulster et al. [8] corroborated these findings, they linked metabolic dysregulation (e.g., IR, dyslipidemia) to hypogonadism and ED through androgen deficiency and vascular remodeling. Interventions targeting IR such as metformin have shown promise in restoring nitrogen oxide signaling and enhancing the efficacy of phosphodiesterase-5 (PDE5) inhibitors. Research into the association between IR and ED may refine personalized treatments for the ED population. Insulin resistance is a pathological condition in which the body's physiologic response to insulin is below normal. Clinically, it manifests itself as the inability of the body to promote glucose uptake and utilization as efficiently as in normal individuals under conditions of exogenous or endogenous insulin administration [9]. Conventional techniques used to evaluate IR, like the hyperinsulinemic-euglycemic clamp (HIEC) and homeostasis model assessment (HOMA-IR), require insulin measurements or invasive testing, which are complex and time-consuming to perform, and thus their application in research and clinical settings is somewhat limited [10]. To address this issue, researchers have proposed a series of non-insulin-based simple indicators based on calculations such as fasting triglycerides and blood glucose, known as surrogates, which are designed to effectively identify levels of IR, and these surrogates include the triglyceride glucose (TyG), TyG with body mass index (TyG-BMI), TyG with waist circumference (TyG-WC) and TyG with waist-to-height ratio (TyG-WHtR) [11, 12].

Although studies have initially examined the association on IR with ED, comparative research addressing the role of different IR surrogates in predicting risk of ED patients still rare [13, 14]. Additionally, while previous studies have focused on the population in general, including diabetic patients, insufficient attention has been paid to the potential impact of IR in non-diabetic ED patients [15, 16]. As far as we know, the association between different IR surrogates and ED in non-diabetic men has not been studied.

Hence, the objective of this study was to examine the potential association between different IR surrogates and ED in U.S. non-diabetic adult males from the National Health and Nutrition Examination Survey (NHANES) database, thus shedding new light on male reproductive health management strategies.

Methods

Study population

The data used in the present study were derived from the NHANES led by the National Center for Health Statistics (NCHS), a prominent national health survey aimed at evaluating the health and dietary status of the unstructured U.S. population and its patterns of health behaviors. The study utilizes a complex multi-stage probability sampling design that encompasses county, region, household, and individual levels, thereby ensuring that the participants included are highly representative of the U.S. population as a whole. Researchers can download and analyze the required dataset directly by visiting the official website (https://www.cdc.gov/nchs/nhanes/).

As the only two survey cycles with ED data available are 2001–2002 and 2003–2004, we chose these data sets for our cross-sectional analysis. Our study population included 10,301 males. We excluded 5347 participants < 20 years old, 838 participants with missing ED data, 2234 participants with missing triglyceride, insulin, glucose and BMl data, and 194 participants with diabetes and 119 participant with missing coronary heart disease, hypertension, education level, marital status, household income, and drinking status data. The final analysis included 1569 (representing 76450963) participants, including 378 (representing 12713541 participants) self-reported ED history. Figure 1 was a flowchart of participant enrollment.

Data collection and definition

All participants completed the questionnaire in their homes and underwent physical examination at the Mobile Examination Center (MEC) to ensure collecting accurate and reliable physical data such as height, weight,

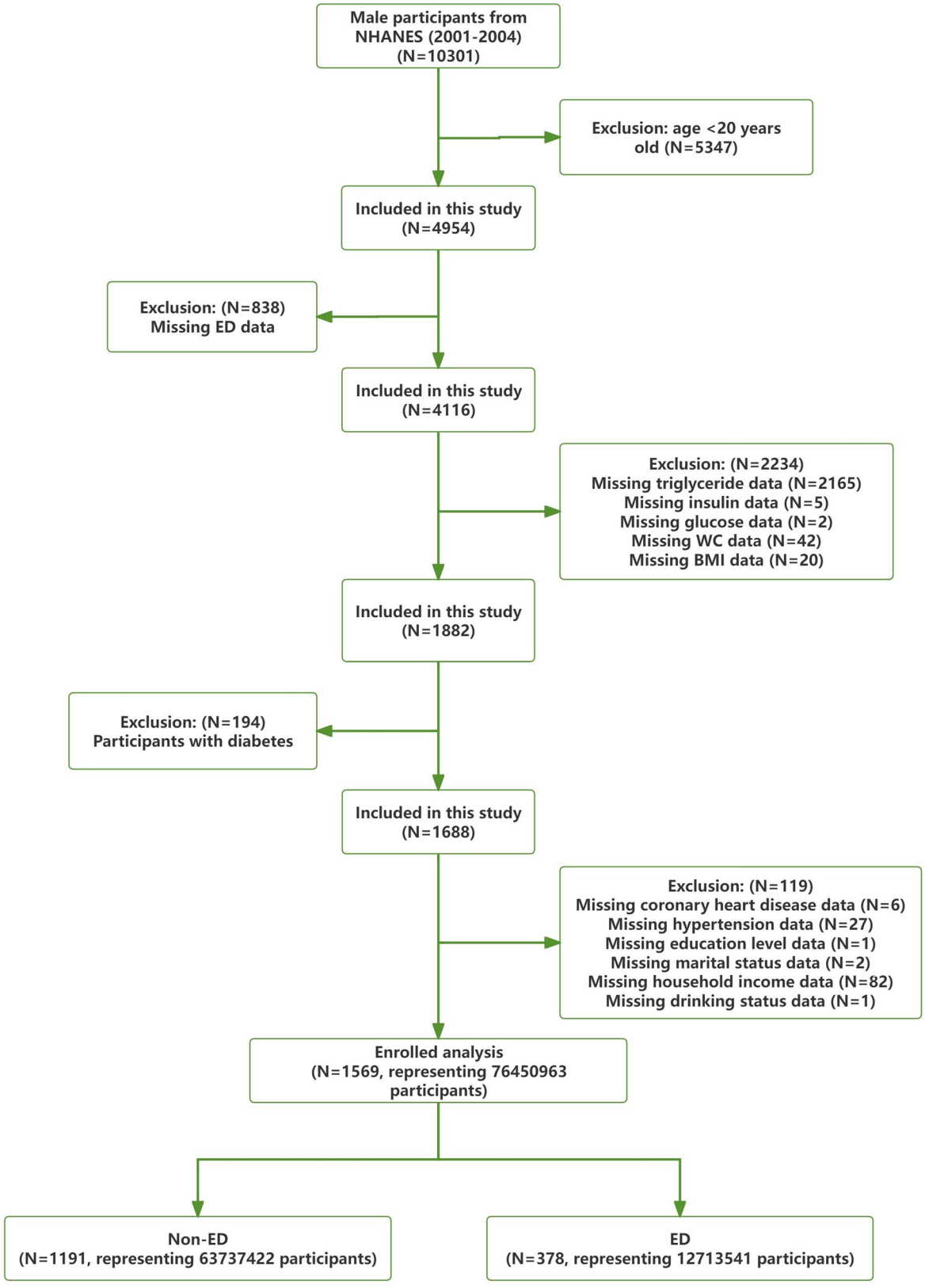

Fig. 1 Flow chart of eligible participants' selection (NHANES 2001–2004)

and waist circumference, and blood was collected after fasting for at least 9 h to collect data including insulin, glucose, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol. Evaluation indicators were calculated according to the following formula [17–19]:

HOMA-IR = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5;
TyG = Ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2];
BMI = weight (kg)/height^2 (m);
TyG-BMI = TyG × BMI;
WHtR = WC (cm)/height (cm);
TyG-WC = TyG x WC (cm);
TyG-WHtR = TyG x WHtR.

Erectile dysfunction was determined on the basis of a self-report questionnaire from each male (age ≥ 20 years), which was based on the following question: many men experience problems with sexual intercourse. How would you describe your ability to get and keep an erection adequate for satisfactory intercourse? We identified Non-ED case by answering "always or almost always able" or "usually able" and identified ED case by answering "sometimes able" or "never able". The above question have been validated by studies to provide the needed information related to ED incidence [20, 21]. In addition, diabetes mellitus was diagnosed when any of the following criteria were met: (1) self-reporting by the patient ("The doctor told you that you have diabetes mellitus"); (2) fasting blood glucose ≥ 7.0 mmol/L; and (3) glycosylated hemoglobin (HbA1c) > 6.5%.

Other variables included in this study encompassed: (1) demographic characteristics (age, race/ethnicity, marital status, education level, and household income; (2) lifestyle factors (smoking and alcohol consumption status); (3) anthropometric and metabolic parameters (BMI, WC, WHtR, fasting glucose, HbA1c, triglycerides, total cholesterol, LDL, HDL, insulin, testosterone, sex hormone-binding globulin (SHBG), and estradiol); and (4) medical history (hypertension and coronary heart disease); where income was assessed using the household poverty-to-income ratio (PIR), categorized as low (0-1.3 PIR), middle (> 1.3–3.5 PIR), and high (> 3.5 PIR). Drinking and smoking status were obtained from self-report questionnaires, with smoking categorized as yes/no (Do you now smoke cigarettes?) and drinking categorized as yes/no (Had at least 12 alcohol drinks/1 year?). Personal medical history (hypertension and coronary heart disease) were also obtained from subjects' self-reports on health questionnaires ("The doctor told you that you have hypertension or coronary heart disease").

Statistical analysis

In that cross-sectional study, the complexity of the sampling design was considered and the statistical analyses were weighted accordingly. For categorical variables, survey-weighted percentages (with 95% confidence intervals, CI) were used for presentation, while for continuous variables, survey-weighted means (with 95% CI) were presented. Weighted chi-square test and weighted Kruskal-Wallis H-test were performed to compare the differences between the two groups of ED and Non-ED. Weighted univariate and multivariate logistic regression analyses were used to estimate odds ratios (ORs, 95% CIs) for associations between different IR surrogates and ED. We constructed three multivariable logistic regression models, Model I was unadjusted; Model II was adjusted for the confounders of age, education level, marital status, household income; Model III was further adjusted for Model II + drinking status, smoking status, hypertension, coronary heart disease, testostosterone, SHBG, estradiol. Covariates were included as potential confounders in the models if they changed the estimates of IR surrogates on ED by more than 10% or were significantly associated with ED.

In addition, we utilized multivariate restricted cubic spline curves (RCS) based on regression Model III to investigate the nonlinear relationship between different IR surrogates and ED. Our objective was to find indicators with potential predictive value for ED by analyzing the shape of the RCS curve. We then employed recursive algorithms to accurately calculate the potential inflection points. On the basis of these inflection points, we applied Log-likelihood ratio test and segmented regression.

In sensitivity analyses, interaction and stratified analysis were performed based on subgroup age (≤ 40/>40), race (non-hispanic white/other), hypertension (yes/no) and coronary heart disease (yes/no). Data analysis was performed by R software (version 4.2.0). The "Survey" package in R was used to cope with the complex survey design involved in this study and to ensure the accuracy and reliability of the results. The results would be considered to be statistically significant if a two-sided p-value of < 0.05.

Results

Characteristics of participants

A total of 1569 (weighted: 76450963) men ultimately participated in this study and were divided into two groups, "Non-ED group" and "ED group". Demographic and clinical characteristics of participants are presented in Table 1. The ED group was significantly older than the Non-ED group (59.94 vs. 40.69 years, $p < 0.0001$). While there was no significant difference in BMI between the two groups (28.77 vs. 27.88 kg/m^2, $p = 0.1062$), WC and WHtR were markedly higher in the ED group ($p = 0.0002$

Table 1 Demographic and clinical characteristics of participants, weighted

	Non-ED	ED	*P*-value
N-observe (N-represent)	1191 (63737422)	378 (12713541)	
Age (years)	40.69 (39.82, 41.55)	59.94 (58.10, 61.78)	< 0.0001
BMI	27.88 (27.50, 28.26)	28.77 (27.87, 29.67)	0.1062
WC (cm)	98.87 (97.81, 99.93)	104.43 (102.25, 106.61)	0.0002
WHtR	0.56 (0.55, 0.56)	0.60 (0.59, 0.61)	< 0.0001
Race			0.0768
Non-Hispanic White	8.14 (5.91, 11.11)	6.19 (3.81, 9.88)	
Other	91.86 (88.89, 94.09)	93.81 (90.12, 96.19)	
Marital status			< 0.0001
Married	60.57 (56.29, 64.69)	73.07 (67.57, 77.95)	
Other	39.43 (35.31, 43.71)	26.93 (22.05, 32.43)	
Education level			< 0.0001
Less than high school	14.04 (11.93, 16.46)	26.70 (21.39, 32.78)	
High school or above	85.96 (83.54, 88.07)	73.30 (67.22, 78.61)	
Household income			0.0806
low	14.69 (12.24, 17.54)	15.23 (11.12, 20.51)	
Middle	35.88 (32.23, 39.70)	43.07 (35.63, 50.84)	
High	49.43 (45.55, 53.32)	41.70 (33.69, 50.18)	
Drinking status			0.0147
Yes	85.18 (80.34, 89.00)	78.34 (72.10, 83.51)	
No	14.82 (11.00, 19.66)	21.66 (16.49, 27.90)	
Smoking status			< 0.0001
Yes	28.34 (25.47, 31.39)	24.82 (19.88, 30.52)	
No	25.23 (22.03, 28.72)	46.25 (40.90, 51.68)	
Missing data	46.43 (41.99, 50.94)	28.93 (23.48, 35.07)	
Total cholesterol (mg/dL)	199.41 (195.97, 202.85)	201.19 (192.93, 209.45)	0.6579
HDL cholesterol (mg/dL)	47.46 (46.16, 48.75)	46.43 (44.96, 47.89)	0.1645
LDL cholesterol (mg/dL)	122.06 (119.34, 124.77)	117.61 (113.71, 121.51)	0.0405
Triglyceride (mg/dL)	159.33 (145.06, 173.60)	191.12 (154.93, 227.32)	0.1086
Glucose (mg/dL)	99.05 (98.06, 100.04)	106.03 (104.18, 107.87)	< 0.0001
HbA1c (%)	5.33 (5.30, 5.36)	5.57 (5.51, 5.63)	< 0.0001
Insulin (uU/mL)	11.20 (10.15, 12.25)	12.48 (11.47, 13.50)	0.1252
Testostosterone (ng/mL)	5.29 (5.04, 5.54)	4.48 (3.79, 5.17)	0.0330
SHBG (nmol/L)	34.05 (31.80, 36.29)	46.87 (42.30, 51.44)	< 0.0001
Estradiol (pg/mL)	35.54 (32.24, 38.83)	29.80 (25.27, 34.33)	0.0546
HOMA-IR	2.81 (2.53, 3.09)	3.49 (3.18, 3.80)	0.0079
TyG	8.73 (8.68, 8.78)	8.94 (8.87, 9.02)	< 0.0001
TyG-BMI	244.34 (240.49, 248.20)	258.26 (250.19, 266.33)	0.0055
TyG-WC	866.19 (855.38, 877.00)	936.54 (916.40, 956.68)	< 0.0001
TyG-WHtR	4.88 (4.83, 4.94)	5.35 (5.25, 5.46)	< 0.0001
Hypertension			< 0.0001
Yes	20.90 (17.72, 24.49)	46.52 (40.54, 52.59)	
No	79.10 (75.51, 82.28)	53.48 (47.41, 59.46)	
Coronary heart disease			< 0.0001
Yes	2.62 (1.75, 3.90)	13.92 (9.46, 20.01)	
No	97.38 (96.10, 98.25)	86.08 (79.99, 90.54)	

Data in the table: For continuous variables: survey-weighted mean (95% CI); For categorical variables: survey-weighted percentage (95% CI)

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-height ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; TyG, triglyceride glucose index; SHBG, sex hormone-binding globulin

and $p < 0.0001$, respectively). Participants with ED were more likely to be married (73.07% vs. 60.57%, $p < 0.0001$), have lower educational attainment (26.70% vs. 14.04% with less than high school education, $p < 0.0001$), and have higher rates of hypertension (46.52% vs. 20.90%, $p < 0.0001$) and coronary heart disease (13.92% vs. 2.62%, $p < 0.0001$).

No statistically significant differences were observed in BMI ($p = 0.1062$), total cholesterol ($p = 0.6579$), HDL cholesterol ($p = 0.1645$), insulin levels ($p = 0.1252$), triglycerides ($p = 0.1086$), or household income ($p = 0.0806$). LDL cholesterol ($p = 0.0405$), estradiol ($p = 0.0546$), and testosterone levels ($p = 0.0330$) showed mixed or marginal associations. Metabolic parameters, including glucose, HbA1c, SHBG, HOMA-IR, TyG, TyG-BMI, TyG-WC, and TyG-WHtR, were significantly elevated in the ED group (all $p < 0.05$). In addition, Table S1 provide results from the weighted univariate analysis.

The correlation among different IR surrogates and ED

Table 2 shows the results of the weighted multivariate logistic regression analysis. HOMA-IR, TyG, TyG-BMI, TyG-WC, and TyG-WHtR were positively correlated with ED in Model I and Model II (all $P < 0.05$). However, we found no correlation between the TyG index and ED in the fully adjusted model III ($P > 0.05$), whereas the other IR surrogates, HOMA-IR, TyG-BMI, TyG-WC, and TyG-WHtR, remained robustly positively correlated with ED [ORs (95% CIs) were 1.02 (0.95, 1.10), 1.01 (1.00, 1.02), 1.00 (1.00, 1.01), 1.17 (0.84, 1.63), respectively; all $P < 0.05$].

Dose-response associations between TyG-BMI, TyG-WC, and TyG-WHtR with ED

After adjusting for age, level of education, marital status, income, drinking status, smoking status, hypertension, coronary heart disease, testosterone, SHBG and estradiol, the RCS curves showed the nonlinear relationship between IR surrogates and ED. The results suggested that there may be a linear positive correlation between HOMA-IR and ED, but the effects of TyG-BMI, TyG-WC, and TyG-WHtR on ED may be nonlinear with significant inflection points (Fig. 2). Further, through recursive partitioning analysis, we identified statistically significant inflection points in the relationships between TyG-BMI, TyG-WC, and TyG-WHtR with ED [inflection points (p-values) were 328.94 ($p < 0.001$), 1128.25 ($p = 0.001$), and 6.42 ($p = 0.003$), respectively] (Table S2). Based on the above inflection points, we further investigated the segmented relationship between these three IR surrogates and ED. Weighted segmented regression analyses showed that the risk of ED was significantly higher when TyG-BMI > 328.94 or TyG-WC > 1128.25 or TyG-WHtR > 6.42 [the ORs (95% CIs) were 1.05 (1.02, 1.08), 1.02 (1.01, 1.03) and 51.30 (4.46, 453.64), respectively] (Table 3).

Table 2 Multivariate logistic regression analysis of different insulin resistance surrogates with ED, weighted

Exposure	Model I OR(95%CI) *P*-value	Model II OR(95%CI) *P*-value	Model III OR(95%CI) *P*-value
HOMA-IR index	1.06 (1.00, 1.12) 0.0662	1.07 (1.01, 1.14) 0.0288	1.02 (0.95, 1.10) 0.0395
TyG index	1.57 (1.33, 1.86) < 0.0001	1.36 (1.10, 1.69) 0.0096	1.11 (0.73, 1.68) 0.0624
TyG-BMI index	1.00 (1.00, 1.01) 0.0023	1.01 (1.00, 1.01) 0.0108	1.01 (1.00, 1.02) 0.0127
TyG-WC index	1.00 (1.00, 1.00) < 0.0001	1.00 (1.00, 1.00) 0.0051	1.00 (1.00, 1.01) 0.0353
TyG-WHtR index	1.74 (1.49, 2.04) < 0.0001	1.50 (1.17, 1.92) 0.0036	1.17 (0.84, 1.63) 0.0365

Model I adjust for: None

Model II adjust for: Age, Education level, Marital status, Household income

Model III adjust for: Model II + Drinking status, Smoking status, Hypertension, Coronary heart disease, Testosterone, SHBG, Estradiol

Subgroup analysis

In sensitivity analyses, by weighted interaction and stratified analyses, the effects of HOMA-IR, TyG-BMI, TyG-WC, and TyG-WHtR on the risk of ED according to the age (≤ 40/>40), race (non-hispanic white/other), hypertension (yes/no) and coronary heart disease (yes/no) were also similar (P-interaction > 0.05) (Table 4).

Discussion

Major findings

In the nationally representative population, our study found that high levels of HOMA-IR, TyG-BMI, TyG-WC and TyG-WHtR were positively associated with ED in the non-diabetic adult men, and the association was also similar in all of the subgroup participants. We further revealed threshold effects of TyG-BMI, TyG-WC, and TyG-WHtR on ED risk, with a significantly higher risk of ED developing when TyG-BMI > 328.94 or TyG-WC > 1128.25 or TyG-WHtR > 6.42. To the best of our knowledge, this is the first work to examine the relationship between different IR surrogates and ED in non-diabetic men.

Comparison with existing literature

Differential roles of central vs. generalized obesity

In our study, the ED and non-ED groups did not differ significantly in BMI but did differ significantly in WC and WHtR, which is consistent with evidence regarding the different roles of central versus generalized obesity in the pathogenesis of ED. While BMI reflects overall obesity, WC and WHtR specifically reflect central obesity, which is strongly associated with visceral fat accumulation, systemic inflammation, and endothelial dysfunction-a key

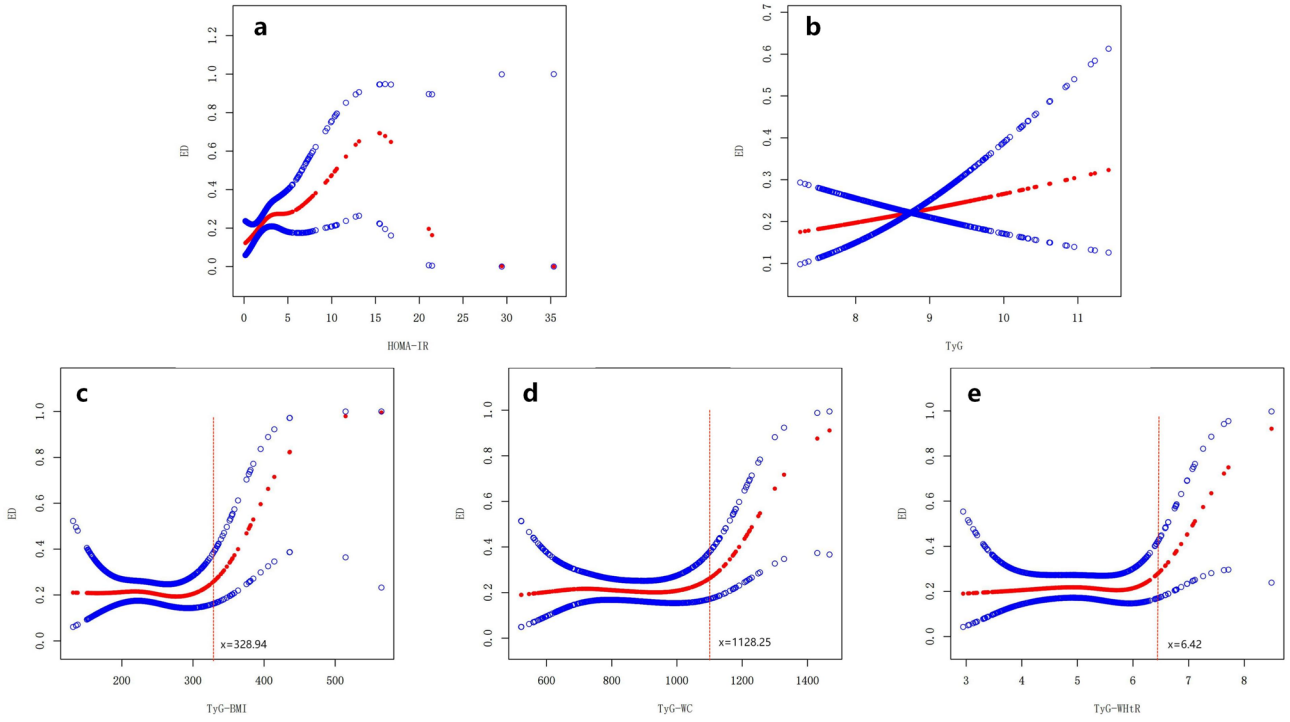

Fig. 2 Restricted cubic spline fitting for the association between HOMA-IR, TyG, TyG-BMI, TyG-WC, and TyG-WHtR with ED (adjusted for age, education level, marital status, household income, drinking status, smoking status, hypertension, coronary heart disease, testosterone, SHBG, estradiol)

Table 3 Threshold effect analysis of TyG-BMI, TyG-WC and TyG-WHtR on ED using segmented regression, weighted

	Adjusted OR(95%CI) *P*-value
TyG-BMI index	
≤ 328.94	1.00 (1.00, 1.01) 0.2291
> 328.94	1.05 (1.02, 1.08) 0.0036
TyG-WC index	
≤ 1128.25	1.00 (1.00, 1.00) 0.2530
> 1128.25	1.02 (1.01, 1.03) 0.0190
TyG-WHtR index	
≤ 6.42	1.25 (0.81, 1.93) 0.4145
> 6.42	51.30 (4.46, 453.64) 0.0024

Adjusted for age, education level, marital status, household income, drinking status, smoking status, hypertension, coronary heart disease, testosterone, SHBG, estradiol

mechanism in the pathogenesis of ED. Visceral adipose tissue secretes pro-inflammatory cytokines and adipokines that impair nitric oxide bioavailability, thereby disrupting cavernous smooth muscle relaxation, which is critical for erectile function [22]. A prospective study with 261 patients found that WC was the best predictor of the development of ED in men with hypogonadism compared to weight and BMI [23]. Similarly, another study explored the causal relationship between 42 modifiable risk factors and ED using Mendelian randomization analysis (MR), and the final results confirmed that an increase in WC was significantly associated with the risk of ED development ($P<0.05$), whereas BMI was suggestive of ED development ($P<0.05$ and adjusted $P>0.05$) [24]. These observations underscore the clinical importance of prioritizing WC/WHtR over BMI in ED risk stratification and prevention strategies targeting visceral adiposity.

Concordance of HOMA-IR with prior evidence

Previous studies have shown varying degrees of correlation between insulin resistance and erectile dysfunction. A cross-sectional observational study in an Indian population showed a statistically significant correlation between ED severity and metabolic syndrome and a statistically significant negative correlation between the HOMA-IR index and IIEF-5 score (the five-item International Index of Erectile Function questionnaire) in 304 ED patients [25]. Another cohort study from Korea analyzed 80 gout patients and 70 healthy controls and also found a significant negative correlation between HOMA-IR and ED, suggesting that IR is an independent predictor of ED in gout patients [26]. Similarly, another cohort study from China suggested that insulin resistance may be a potential pathogenetic mechanism for ED in young men under 40 years of age [27]. Moreover, Rey-Valzacchi et al. [28] conducted a randomized controlled trial (RCT) to evaluate the effect of treatment with insulin sensitizer metformin on the response to sildenafil in patients with ED combined with IR, and found that treatment with

Table 4 Association between different insulin resistance surrogates and ED according to baseline characteristics, weighted

	Age (years) group, OR(95%CI)		***P*-interaction**
	≤ 40	**> 40**	
HOMA-IR index	1.08 (0.87, 1.13)	1.13 (0.99, 1.17)	0.7471
TyG-BMI index	1.01 (0.98, 1.02)	1.01 (1.00, 1.02)	0.4454
TyG-WC index	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	0.5135
TyG-WHtR index	1.24 (0.54, 2.99)	1.81 (1.21, 3.15)	0.5567
	Race, OR(95%CI)		**P-interaction**
	Non-Hispanic White	Other	
HOMA-IR index	1.33 (0.89, 1.95)	1.24 (1.03, 1.31)	0.4762
TyG-BMI index	1.01 (0.99, 1.02)	1.01 (1.00, 1.02)	0.6571
TyG-WC index	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	0.2568
TyG-WHtR index	1.29 (0.35, 4.82)	1.78 (1.13, 2.75)	0.4108
	Hypertension, OR(95%CI)		**P-interaction**
	Yes	No	
HOMA-IR index	1.22 (1.03, 1.46)	1.15 (1.01, 1.38)	0.3518
TyG-BMI index	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	0.2267
TyG-WC index	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	0.4487
TyG-WHtR index	1.74 (0.89, 3.28)	1.75 (0.88, 3.13)	0.9864
	Coronary heart disease, OR(95%CI)		**P-interaction**
	Yes	No	
HOMA-IR index	1.01 (0.35, 2.89)	1.16 (1.04, 1.31)	0.4289
TyG-BMI index	1.01 (1.00, 1.03)	1.01 (1.00, 1.02)	0.8673
TyG-WC index	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	0.3561
TyG-WHtR index	2.78 (0.72, 10.43)	1.70 (1.08, 2.49)	0.3328

Each stratification adjusted for the factors (age, education level, marital status, household income, drinking status, smoking status, hypertension, coronary heart disease, testosterone, SHBG, estradiol) except the interaction factor itself

metformin resulted in a significant decrease in HOMA, an increase in IIEF-5 scores, and a significant improvement in erectile function in patients with ED. The level of IR in all four of these studies was measured by homeostasis model assessment (HOMA). Two other related studies used the Quantitative Insulin Sensitivity Check Index (QUICKI, similar to the HOMA-IR index) to determine levels of IR, and similarly found that IR had a negative impact on ED in men and was positively correlated with the severity of ED [29, 30]. Our results are consistent with these studies in that the negative association between HOMA-IR and ED remains stable even in non-diabetic populations.

Divergent TyG index findings: population-specific considerations

To date, there have been few reports on the impact of IR assessed by simple non-insulin surrogates on the occurrence of ED. Yilmaz et al. [13] performed a cross-sectional study to investigate the relationship between TyG index and ED, which included 142 participants, with 91 ED patients, and found that age and TyG index were independent predictors of ED after adjusting for confounders, respectively. Similarly, a cross-sectional observational study from Sambel et al. that included 199 ED patients and 51 control subjects without ED complaints revealed a significant negative correlation between the TyG index and the IIEF-5 score, suggesting that the TyG index is independently associated with the development of ED [31]. However, both studies had small sample sizes, and Sambel's study was missing important confounding variables sex hormone binding globulin and serum testosterone levels. The cross-sectional study by Lee et al. [14] also used data from public databases and recruited 3166 participants, including 606 self-reported histories of ED, and found that higher TyG indices were associated with higher prevalence of erectile dysfunction, and that this correlation was linear. Considering that existing relevant studies have focused on the general population, including people with diabetes, our study focused on the non-diabetic ED population. In our study, we found that TyG was not significantly associated with ED after fully adjusting for confounders, which is inconsistent with previous studies and may be due to the fact that our study population was primarily a non-diabetic ED population. And in comparison to the study of Li et al., our study added the consideration of sex hormone binding globulin as a confounding variable. Furthermore, the observed discrepancy between the TyG index and HOMA-IR in their association with ED after full adjustment may stem from their distinct pathophysiological implications. HOMA-IR directly reflects pancreatic β-cell function and hepatic insulin resistance through the incorporation of fasting insulin levels, which is essential for understanding the direct role of hyperinsulinemia in the pathogenesis of ED. Insulin resistance affects nitric oxide (NO) bioavailability through oxidative stress and inflammation, which promotes endothelial dysfunction and directly affects cavernous smooth muscle relaxation necessary for erection [6]. In contrast, the TyG index derived from triglycerides and glucose primarily reflects peripheral lipid metabolism and adipose tissue dysfunction, and may not fully reflect the direct effects of insulin on nitric oxide synthase activity or endothelial health [32]. Notably, hyperinsulinemia itself may exacerbate ED by enhancing sympathetic tone, promoting vascular fibrosis, and decreasing testosterone bioavailability through enhanced aromatase activity [33]. These insulin-specific pathways are intrinsically captured by HOMA-IR but not by TyG index, which lacks an insulin component.

Diagnostic advantage of composite indices (TyG-BMI/WC/WHtR)

It is worth noting that we added to our study the assessment of the correlation of TyG-related indices (TyG-BMI, TyG-WC and TyG-WHtR) with ED and found that TyG-BMI, TyG-WC and TyG-WHtR were positively correlated with ED in non-diabetic adult men. This is

probably explained because in contrast to the TyG index, the TyG-related index covers not only abnormal glucose metabolism and defective fatty acid metabolism, but also incorporates the obesity index (BMI, waist circumference, and waist-to-height ratio) as a comprehensive consideration, which improves its diagnostic power. Previous studies have shown varying degrees of relationship between erectile dysfunction and many indices of obesity, including BMI and waist circumference [34, 35].

Mechanistic interpretations

The negative effects of IR on male erectile function are thought to result from different mechanisms. In healthy men, nitric oxide (NO) activates guanylate cyclase in cavernous smooth muscle (CSM), which increases cyclic guanosine monophosphate production, activates protein kinase G, opens supracellular potassium channels, and closes calcium channels, leading to relaxation of the CSM to achieve induction of penile engorgement for normal erection [36]. In vitro and in vivo studies have demonstrated that insulin can effectively promote the expression and activity of endothelial nitric oxide synthase (ENOS), which enhances nitric oxide production [37, 38]. In contrast, the vascular nitric oxide synthesis capacity was significantly reduced in the insulin-resistant state, and the insulin-induced vasodilatation function was weakened, while the basal nitric oxide production was also significantly reduced [39, 40]. On the other hand, vascular endothelial dysfunction is one of the main pathogenic mechanisms leading to ED [41], and insulin resistance may exacerbate oxidative stress and promote the production of inflammatory cytokines in endothelial cells, which further leads to excessive nitric oxide depletion in tissues exposed to free radicals, which may ultimately cause vascular endothelial dysfunction [7, 42]. In addition, another potential trigger for ED in IR may be a decrease in testosterone levels. According to the study, the amount of testosterone released by Leydig cells decreases in the IR environment [43], and several other studies have also shown an association between high IR levels and lower testosterone levels and testosterone deficiency [44, 45].

In addition, the different dose-response relationships between the different IR surrogates and ED in our study may reflect their unique pathophysiologic mechanisms. HOMA-IR is a direct measure of hepatic insulin sensitivity and β-cell function that is linearly related to ED, as chronic hyperinsulinemia and hyperglycemia progressively impair endothelial NO synthesis by inducing oxidative stress, decreasing eNOS activity, and promoting microvascular dysfunction. This cumulative damage manifests itself as a sustained, graded increase in risk as HOMA-IR levels rise [6]. In contrast, the nonlinear relationships observed from other indices (TyG-BMI, TyG-WC, TyG-WHtR) suggest a threshold effect of integrated metabolic abnormalities. These composite metrics integrate dyslipidemia (via triglycerides), glucose metabolism (via fasting glucose), and adiposity measures. Excess visceral adiposity (reflected in WC and WHtR) exacerbates IR through pro-inflammatory adipokine secretion (e.g., TNF-α, IL-6) and free fatty acid flux, which directly impairs cavernous smooth muscle relaxation [22]. Once adiposity exceeds a critical threshold (e.g., TyG-WHtR > 6.42), the synergistic effects of adipotoxicity and chronic inflammation may overwhelm compensatory mechanisms, thereby non-linearly accelerating endothelial damage and ED risk. This is consistent with findings of exponential increases in cardiovascular risk above specific adiposity thresholds [46].

Limitations

Our study has some limitations. Because this was a cross-sectional observational study, we were unable to establish a causal relationship between different insulin resistance surrogates and ED prevalence, and a more comprehensive and prospective cohort study is needed in the future. Second, due to the limitations of the NHANES database, the diagnosis of ED in men is a self-reported diagnosis based on questionnaires, and the severity of ED has not been quantitatively assessed by accurate survey methods (e.g., using the IIEF-5 questionnaire or penile Doppler ultrasound). Third, given the limited sample size of participants in some subgroups, our findings need to be validated in a larger cohort. Fourth point, since our study data were derived from NHANES 2001–2004 and obesity rates have increased in the United States over the past two decades, the incidence of IR may also be increasing due to changes in dietary patterns, sedentary lifestyles, and the earlier onset of metabolic dysfunction. These trends may alter the strength or direction of the association between IR surrogates and ED due to greater metabolic stress and different comorbidities in modern populations. Although NHANES remains methodologically robust, temporal changes in risk profiles may limit the generalizability of our findings to contemporary cohorts. Last, detailed information on medications that may influence erectile function (e.g., β-blockers, diuretics, antidepressants, and α-blockers) was not systematically collected or available for analysis. While these medications could theoretically confound the observed associations, their absence in our models highlights the need for future studies to incorporate comprehensive medication data to refine risk assessments.

Strengths, clinical implications and future research directions

Our study, however, has several strengths despite its limitations. We adjusted for multiple covariates in our

study, including serum testostosterone, SHBG and estradiol, which have not been considered in other studies, to control for the effects of confounding factors as much as possible. Furthermore, this study had an adequate sample size, we included a total of 1,569 participants, and benefited from the complex sampling design of the NHANES database, the sample represented a national population of more than 70 million individuals after weighted statistical analyses, making our conclusions more credible. Our findings hold important clinical implications for improving early identification, risk stratification, and prevention of ED in non-diabetic men. The ease of access to these IR surrogates makes them both cost-effective and convenient tools for clinicians to screen for ED risk during standard health assessments. Further, we identified critical inflection points (TyG-BMI > 328.94, TyG-WC > 1128.25, and TyG-WHtR > 6.42) beyond which the risk of ED rises significantly. These thresholds provide feasible clinical benchmarks, i.e., clinicians can use these values to identify high-risk populations that may benefit from enhanced lifestyle modifications (e.g., weight loss, dietary modifications, physical activity) to mitigate IR and reduce ED risk. In summary, this study equips clinicians with simple, actionable tools to identify and manage ED risk in non-diabetic men, bridging the gap between metabolic and sexual health in clinical practice.

Conclusion

In the non-diabetic population, there is a positive correlation between the risk of developing ED and the elevation of HOMA-IR, TyG-BMI, TyG-WC, and TyG-WHtR, and in particular, the ED risk is significantly higher when TyG-BMI > 328.94 or TyG-WC > 1128.25 or TyG-WHtR > 6.42. In conclusion, these IR surrogates can serve as complementary indicators for assessing ED risk in non-diabetic men both in clinical and in future epidemiologic studies.

Abbreviations

IR	Insulin resistance
ED	Erectile dysfunction
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic spline curves
HOMA	Homeostasis model assessment
TyG	Triglyceride glucose
TyG-BMI	TyG with body mass index
TyG-WC	TyG with waist circumference
TyG-WHtR	TyG with waist-to-height ratio
HIEC	Hyperinsulinemic-euglycemic clamp
MEC	Mobile Examination Center
PIR	Poverty-to-income ratio
CSM	Cavernous smooth muscle
ENOS	Endothelial nitric oxide synthase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-23212-2.

Supplementary Material 1

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Author contributions

WX and SW wrote the main manuscript text. WX prepared tables. SW wrote the section on data analysis. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

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Data availability

Data set used in this study will be available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The NHANES study was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. All of the datasets were publicly accessible on the website (https://www.cdc.gov/nchs/nhanes/). All methods were carried out in accordance with relevant guidelines and regulations (declaration of Helsinki). All individuals provided written informed consent before participating in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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