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Negative association between 15 obesity- and lipid-related indices and testosterone in adult males: a population based cross-sectional study

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Abstract

Background An association exists between obesity and reduced testosterone levels in males. The propose of this research is to reveal the correlation between 15 indices linked to obesity and lipid levels with the concentration of serum testosterone, and incidence of testosterone deficiency (TD) among adult American men.

Methods The study utilized information gathered from the National Health and Nutrition Examination Survey (NHANES) carried out from 2011 to 2016. The condition known as TD is typically characterized by a total serum testosterone level that falls below 300 ng/dL. The analysis used weighted linear and logistic regression methods to announce the association between 15 obesity- and lipid-related factors and serum testosterone levels as well as TD. Subgroup analyses were further carried out to confirm and validate the findings. Additionally, restricted cubic spline plots were utilized to examine non-linear relationships. Receiver operating characteristic (ROC) curves were created for the 15 factors, and the area under the curves (AUC) was calculated to assess the efficacy of each factor in detecting TD.

Results Among a group of 3,540 adult males, it was observed that all 15 obesity- and lipid-related indices showed a negative relationship with testosterone concentration and a direct correlation with the presence of TD. After accounting for all covariates, the analysis revealed that individuals within the highest quartile (Q4) for metabolic score for visceral fat (METS-VF) had the excellent probability of developing TD (OR = 13.412, 95%CIs: 4.222, 42.262, $P < 0.001$). Additionally, a non-linear relationship was detected between the METS-VF with TD. Within the model that incorporated all adjustments, the triglyceride glucose-waist to height ratio (TyG-WHtR) has the best performance for predicting TD (Overall: AUC = 0.762, 95%CIs: 0.743, 0.782, cut-off = 5.186).

Conclusion Elevated levels of these 15 markers were inversely related to testosterone levels and were indicative of an elevated risk of TD. Among all indices analyzed, TyG-WHtR demonstrated the highest predictive value.

Trial registration Not available.

Keywords Obesity, Testosterone, Cross-sectional study, NHANES

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Background

Primarily synthesized by Leydig cells in the testes, testosterone makes great contribution to male health, whose production is largely controlled by mechanism of the hypothalamic-pituitary-gonadal axis (HPGA) [36]. Adequate levels of testosterone affect various physiological processes in men, including reproduction, cardiovascular health, sexual function, metabolism, cognitive function, neurological processes, and bone strength [7, 18, 23, 61, 74]. Insufficient levels of testosterone can result in organ dysfunction. Apart from decreased sexual desire and erectile dysfunction, low testosterone levels can contribute to or exacerbate metabolic conditions such as depression and osteoporosis, a condition known as testosterone deficiency syndrome [46, 59]. Testosterone deficiency (TD) is prevalent among men, affecting approximately 7% of those aged 50 and above, with an increasing incidence in correlation with age. The expectation is that the prevalence of TD will grow as life expectancy extends further in the forthcoming years [36]. TD has become a growing global concern.

Obesity and accumulation of fat are intimately linked to several metabolic disorders that can result in heightened glucose synthesis by the liver and reduced insulin responsiveness. These processes are pivotal in the onset and progression of type 2 diabetes mellitus (T2DM) [43]. In men, the presence of functional hypogonadism and low testosterone levels in serum (< 16 nmol/L) were more likely to develop T2DM. Conversely, higher testosterone levels appear to protect against disease onset [81]. Several factors can have detrimental effects on the health of the HPGA. These include increased transformation of testosterone to estradiol, elevated production of reactive oxygen species, and secretion of various endocrine molecules that can directly or indirectly affect the HPGA [29]. Kim demonstrated that individuals with obesity and irregular lipid metabolism tended to exhibit decreased testosterone levels. However, upon receiving treatment of obesity or dyslipidemia, testosterone levels are often markedly increased [48]. A study indicated that there is a link between swift weight gain in early life and reduced testosterone levels [53]. A study by Du et al. found that excess weight in animals can result in higher fat level in the testes. This can lead to a decline in the production of enzymes responsible for synthesizing testosterone, consequently affecting the synthesis and release of this hormone [20]. The intricate effects of testosterone also have potential advantages in regulating glycemia, reducing excess body fat, and enhancing muscle strength in men with diabetes [58]. Recent studies have brought to light the efficacy of testosterone therapy (TTh) in addressing T2DM in men with suboptimal testosterone levels who are more likely to develop obesity, as opposed to the outcomes attainable through lifestyle modifications exclusively [34]. A prospective clinical trial revealed that supplemental testosterone improved the function of blood vessels and the body's response to insulin in obese individuals with T2DM [33]. A study was conducted over an 11-year period and found that long-term TTh in overweight males with deficient testosterone levels led to ongoing and significant weight loss, potentially contributing to lower mortality rates and fewer major cardiovascular incidents [70]. Furthermore, an observational study carried out in the Chinese demographic revealed a potential association between obesity and thyroid dysfunction [85]. Consequently, assessing the distribution and amount of body fat in obese individuals is vital for determining their testosterone levels. These results underscore the significance of considering these elements in clinical settings.

The most precise method for directly assessing obesity and fat distribution in the human body is by using CT or MRI scans. Nevertheless, these approaches are expensive and demand specialized expertise, which can render them out of reach for the typical individual [6]. In recent years, many research results have revealed the effectiveness and applicability of these indirect measurement parameters for predicting the distribution of human fat. The abbreviations and full names of 15 indices were listed in the Table 1 [3, 4, 24, 43, 49, 56, 66, 69, 75, 78, 87].

The BMI has traditionally been employed as a widespread tool for assessing obesity and determining overweight status [64]. According to Ku et al., in American males diagnosed with prostate cancer within the past four years, elevated ABSI levels have been shown to be associated with an increased risk of prostate cancer-related

Table 1 15 indices investgated in the study

Abbreviation	Full name
ABSI	a body shape index
BMI	body mass index
BRI	body roundness index
CI	conicity index
LAP	lipid accumulation product
METS-IR	metabolic score for insulin resistance
METS-VF	metabolic score for visceral fat
WHtR	waist to height ratio
WC	waist circumstance
TyG	triglyceride-glucose index
TyG-WC	triglyceride glucose-waist circumference
TyG-BMI	triglyceride glucose- body mass index
TyG-WHtR	triglyceride glucose-waist to height ratio
VAI	visceral adiposity index
WWI	weight-adjusted-waist index

death, regardless of an individual's BMI [50]. Zhang's research findings offer support for suggesting the BRI as a noninvasive method to assess mortality. This novel idea has the potential to be integrated into public health strategies; however, further validation in diverse cohorts is necessary to confirm its effectiveness [86]. A significant amount of research has been dedicated to investigating the TyG index in conjunction with markers of obesity [11, 13, 82]. Initially proposed by Sun et al., the METS-IR serves as a user-friendly evaluation tool for identifying insulin resistance, enabling the timely identification of individuals at a heightened likelihood of experiencing erectile dysfunction [76]. Ebrahimi et al. proposed that the LAP index is a superior predictor, offering a cost-effective, sensitive, and specific approach for assessing nonalcoholic fatty liver disease (NAFLD), and potentially serving as a valuable screening tool for NAFLD [22]. Amato's research demonstrated that the VAI serves as a substantial indicator of the functionality of visceral adipose tissue and insulin responsiveness, with a robust correlation to the heightened risk of cardiometabolic diseases [2].

The goal of this research was to explore the relationship between 15 different obesity- and lipid-related indicators that are frequently employed to evaluate a range of metabolic issues, and the levels of testosterone. This study also assessed the efficacy of these 15 indicators in distinguishing TD by evaluating them separately across the general population and specific age cohorts. Moreover, we conducted a comparative analysis to appraise the discriminatory capacity of these indices with the goal of shedding new light on male reproductive health and providing valuable clinical insights.

Methods and materials

Survey description and study population

The study used data from the NHANES dataset, which is specifically designed to gather comprehensive and diverse information about the health, disease, family and nutritional status of the U.S. population. In order to ensure a varied and comprehensive sample, NHANES uses a stratified, multi-stage sampling method to select participants from various locations across the nation [88]. Given that this research entailed a secondary analysis of pre-existing data from the NHANES database, without infringing upon patient privacy or safety, there was no requirement for additional informed consent or ethical clearance.

Inclusion and exclusion criteria

NHANES survey data from 2011 to 2016, totaling 29,902 people, were obtained and the following exclusion criteria were employed: (1) individuals < 18 years of age, (2) female participants, and (3) individuals with insufficient data for calculating indices mentioned above. In the end, a total of 3,540 individuals were identified and chosen as the primary subjects for the study, as illustrated in Fig. 1. The participant data for the study is outlined in Supplementary Table 1.

Data collection and definition

The research collected demographic data including age, gender, ethnicity, poverty ratio, level of education, and marital status based on self-reported information provided by the participants. Body measurement data and laboratory examination data are obtained through the official NHANES database and matched based on IDs. The smoking status of participants was established by confirming whether they had smoked a minimum of 100 cigarettes throughout their lifetime. Similarly, the history of alcohol consumption was determined by examining whether individuals had consumed a 12-oz beer within the previous year, or other principles provided by guideline. Reports of hypertension and diabetes were obtained from the respondents' answers to the health questionnaire, which included questions such as "Has a doctor ever diagnosed you with diabetes?" or "Has a doctor ever informed you about high blood pressure?". A response of "yes" was recorded one case of diabetes or hypertension. Reports of family history were obtained from the question, "Close relative had diabetes?".

Indices calculation

The individuals involved in this research were segregated into four categories according to their obesity- and lipid-related measurements, and organized into quartiles. Except for WC, which could be easily measured, the remaining 14 obesity- and lipid-related indices required calculations. These calculations involved combining physical measurements with laboratory test data using the following Fig. 2.

Statistical analyses

All statistical analysis processes follow NHANES' data weighting requirements. Medians and interquartile ranges of continuous were provided, with group differences evaluated through the Wilcoxon rank-sum test, which is tailored for complex survey samples. Categorical variables, on the other hand, were analyzed using the chi-square test with a Rao-Scott second-order correction.

The study utilized three different models for analysis: Model 1, which did not include any adjustments; Model 2, which was adjusted for age, ethnicity, education, poverty ratio, and marital status; and Model 3, which was adjusted for hypertension, diabetes, drinking, smoking, and family history, in addition to the variables in Model 2. Subsequent to converting 15 continuous indices into

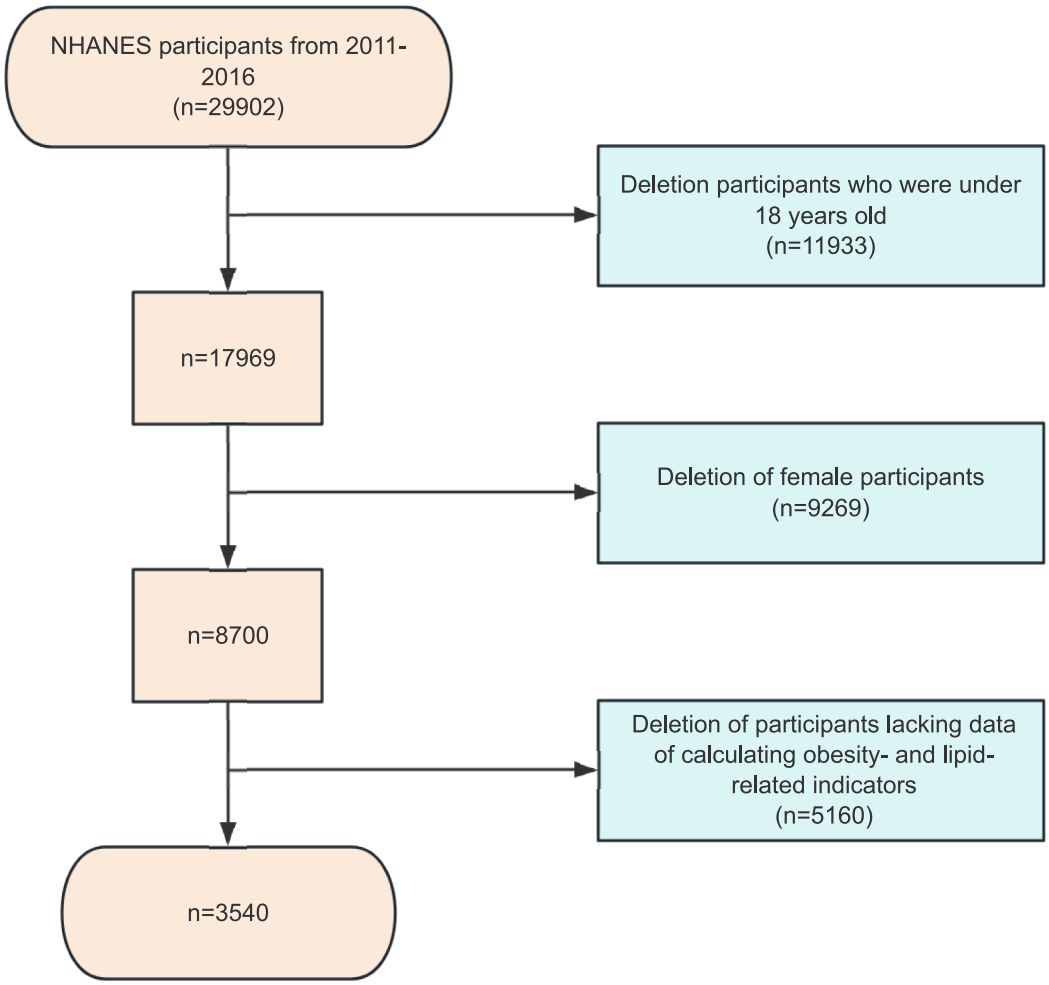

Fig. 1 Flow chart of the participants selection process

categorical variables (Quarter 1–4), stratified analyses were performed. The relationships between these categorical indices and testosterone levels were examined using weighted binary logistic regression and linear regression with both unadjusted and adjusted results. The research conducted a comprehensive analysis by calculating odds ratios (ORs) with 95% confidence intervals (CIs) through binary logistic regression. The study also computed beta coefficients and paired 95%CIs for the linear regression models utilized in the investigation. Additionally, the researchers generated restricted cubic spline curves to explore potential non-linear associations between 15 indices and testosterone levels. Furthermore, a subgroup analysis was conducted to examine the relationship between METS-VF and TD.

This study evaluates the predictive ability of the index by plotting the ROC curve and calculating its AUC [37]. The Youden index, determined by the formula [maximum (sensitivity + specificity - 1)], was used to identify the optimal cutoff values [26]. In addition, the index with the highest AUC was compared with the other indices.

R language version 4.4.1 and the MSTATA software (https://www.mstata.com/) were utilized for the analysis of all data. The significance level of 0.05 was utilized as the threshold for all analyses.

Results

Baseline characteristics

Table 2 presents the demographic data of the study participants, categorized into normal and deficient groups based on the weighted population data. The study included a total of 3540 individuals aged 18–80 years, with a recorded TD prevalence of 20.3%. Significant discrepancies were observed between the various groups in regards to the following: age, Glu, TG, HDL-c, weight, ABSI, BMI, BRI, CI, LAP, METS-IR, METS-VF, TyG, TyG-BMI, TyG-WC, TyG-WHtR, VAI, WC, WHtR,

$$\mathrm{ABSI} = \frac{\mathrm{WC(m)}}{\mathrm{Height(m)}^{\frac{1}{2}} \times \mathrm{BMI}^{\frac{2}{3}}}$$

$$\mathrm{BMI} = \frac{\mathrm{Weight(kg)}}{\mathrm{Height(m)}^2}$$

$$\mathrm{BRI} = 364.2 - 365.5 \times \sqrt{1 - \left(\frac{\mathrm{WC(cm)}}{\pi \times \mathrm{Height(cm)}}\right)^2}$$

$$\mathrm{CI} = \frac{\mathrm{WC(m)}}{0.019\sqrt{\frac{\mathrm{Weight(kg)}}{\mathrm{Height(m)}}}}$$

$$\mathrm{LAP} = [\mathrm{WC(cm)} - 65] \times \mathrm{TG(mmol/L)}$$

$$\mathrm{METS-IR} = \frac{\ln\left[\left(2 \times \mathrm{Glu(mg/dL)} + \mathrm{TG(mg/dL)}\right) \times \mathrm{BMI}\right]}{\ln\left[\mathrm{HDL-c(mg/dl)}\right]}$$

$$\mathrm{METS-VF} = 4.466 + 0.011 \times [\ln(\mathrm{METS-IR})]^3 + 3.239 \times [\ln(\mathrm{WHtR})]^3 + 0.594 \times [\ln(\mathrm{Age})]$$

$$\mathrm{TyG} = \ln\left[\frac{\mathrm{TG(mg/dL)} \times \mathrm{Glu(mg/dl)}}{2}\right]$$

$$\mathrm{TyG-BMI} = \mathrm{TyG} \times \mathrm{BMI}$$

$$\mathrm{TyG-WC} = \mathrm{TyG} \times \mathrm{WC}$$

$$\mathrm{WHtR} = \frac{\mathrm{WC(m)}}{\mathrm{Height(m)}}$$

$$\mathrm{TyG-WHtR} = \mathrm{TyG} \times \mathrm{WHtR}$$

$$\mathrm{VAI} = \frac{\mathrm{WC(cm)}}{39.68 + 1.88 \times \mathrm{BMI}} \times \frac{\mathrm{TG(mmol/l)}}{1.03} \times \frac{1.31}{\mathrm{HDL-c(mg/dl)}}$$

$$\mathrm{WWI} = \frac{\mathrm{WC(cm)}}{\sqrt{\mathrm{Weight(kg)}}}$$

Fig. 2 Formulas of 15 indices

WWI, hypertension, diabetes, family history, and marital status.

Association between 15 indices and TD

Table 3 shows the ORs and their corresponding 95%CIs for the 15 indices in the different models. In the absence of other variables, all these indicators displayed a favorable association with the occurrence of TD. Based on the analysis of Model 3, BRI, TyG, and WHtR showed significant differences in each quartile. By utilizing the BRI as an illustration, it was determined that the probability of individuals with TD in Q2 was 2.9 times greater than that in Q1 (OR = 2.900, 95%CIs: 1.364, 6.169, $P = 0.008$). Similarly, the odds of TD in Q3 were 3.633

Table 2 Weighted paticipants demographics and baseline characteristics

Variables	Total ($n=3540$)	Normal ($n=2821$)	Deficiency ($n=719$)	Statistic	*P*
Age	45 (31, 59)	43 (30, 58)	49 (36, 63)	4.08	<0.001[2]
Glu(mg/dl)	95 (89, 104)	94 (88, 102)	101 (92, 118)	7.68	<0.001[2]
TC(mg/dl)	183 (158, 210)	183 (158, 210)	185 (157, 210)	0.41	0.683[2]
LDL-c(mg/dl)	110 (87, 134)	110 (88, 134)	108 (83, 132)	−1.00	0.321[2]
TG(mg/dl)	102 (70, 154)	96 (67, 145)	136 (93, 203)	11.10	<0.001[2]
HDL-c(mg/dl)	46 (40, 55)	48 (41, 57)	41 (36, 50)	−9.58	<0.001[2]
Weight(kg)	86 (75, 100)	84 (73, 96)	101 (85, 117)	13.23	<0.001[2]
Height(cm)	176 (171, 181)	176 (171, 181)	176 (171, 182)	0.38	0.708[2]
Poverty Ratio	2.98 (1.45, 5.00)	2.98 (1.44, 5.00)	2.99 (1.49, 4.86)	−0.06	0.949[2]
ABSI	0.082 (0.079, 0.085)	0.081 (0.078, 0.085)	0.083 (0.081, 0.086)	6.15	<0.001[2]
BMI	27.9 (24.6, 31.8)	27.2 (24.0, 30.7)	32.1 (28.3, 37.6)	14.31	<0.001[2]
BRI	4.79 (3.68, 6.07)	4.55 (3.46, 5.71)	6.19 (4.88, 8.36)	13.75	<0.001[2]
CI	7.53 (7.16, 7.88)	7.45 (7.10, 7.80)	7.85 (7.52, 8.19)	10.80	<0.001[2]
LAP	41 (22, 75)	36 (20, 62)	76 (46, 124)	18.47	<0.001[2]
METS-IR	2.36 (2.21, 2.52)	2.33 (2.19, 2.48)	2.52 (2.37, 2.70)	14.52	<0.001[2]
METS-VF	6.47 (6.02, 6.78)	6.38 (5.87, 6.71)	6.75 (6.50, 6.98)	10.58	<0.001[2]
TyG	8.51 (8.11, 8.98)	8.45 (8.05, 8.87)	8.91 (8.44, 9.41)	13.96	<0.001[2]
TyG-BMI	239 (204, 281)	230 (197, 268)	289 (246, 340)	17.37	<0.001[2]
TyG-WC	8.60 (7.48, 9.76)	8.35 (7.23, 9.36)	9.99 (8.97, 11.47)	17.64	<0.001[2]
TyG-WHtR	4.91 (4.26, 5.57)	4.75 (4.13, 5.35)	5.68 (5.08, 6.53)	17.95	<0.001[2]
VAI	1.31 (0.77, 2.36)	1.18 (0.73, 2.03)	2.11 (1.22, 3.34)	12.94	<0.001[2]
WC(cm)	100 (90, 110)	98 (88, 108)	112 (103, 126)	13.48	<0.001[2]
WHtR	0.57 (0.52, 0.63)	0.56 (0.51, 0.61)	0.63 (0.57, 0.72)	13.77	<0.001[2]
WWI	10.77 (10.24, 11.33)	10.66 (10.15, 11.20)	11.24 (10.77, 11.77)	10.41	<0.001[2]
Hypertension				28.77	<0.001[3]
No	68.7%	71.4%	57.0%		
Yes	31.3%	28.6%	43.0%		
Diabetes				9.32	<0.001[3]
Borderline	1.3%	0.9%	3.0%		
No	80.2%	82.7%	69.2%		
Yes	18.6%	16.4%	27.8%		
Ethnicity				0.88	0.475[3]
Mexican American	9.2%	9.4%	8.0%		
Non-Hispanic Asian	5.2%	5.4%	4.1%		
Non-Hispanic Black	10.2%	10.3%	9.6%		
Non-Hispanic White	66.2%	65.6%	68.7%		
Other Hispanic	6.4%	6.5%	6.2%		
Others	2.9%	2.8%	3.4%		
Family history				7.95	0.007[3]
No	63.7%	65.8%	55.0%		
Yes	36.3%	34.2%	45.0%		
Drinking				3.36	0.073[3]
No	14.7%	14.0%	17.8%		
Yes	85.3%	86.0%	82.2%		
Smoking				0.59	0.446[3]
No	49.3%	49.8%	47.0%		
Yes	50.7%	50.2%	53.0%		
Marital status				2.70	0.026[3]
Divorced	8.1%	7.7%	9.7%		

Table 2 (continued)

Variables	Total ($n=3540$)	Normal ($n=2821$)	Deficiency ($n=719$)	Statistic	*P*
Living with partner	9.1%	9.6%	7.1%		
Married	58.3%	57.1%	63.2%		
Never married	20.7%	21.9%	15.7%		
Separated	1.7%	1.8%	1.6%		
Widowed	2.1%	2.0%	2.7%		
Education, n(%)				0.35	0.765[3]
9-11th grade	11.6%	11.6%	11.4%		
College	60.8%	60.8%	60.8%		
High school graduate	22.0%	21.7%	23.0%		
Less than 9th grade	5.6%	5.8%	4.8%		

Abbreviation: *IQR* Interquartile range, *Glu* Glucose, *TC* Total Cholesterol, *LDL-c* Low-Density Lipoprotein Cholesterol, *TG* Triglycerides, *HDL-c* High-Density Lipoprotein Cholesterol, *ABSI* A body shape index, *BMI* Body mass index, *BRI* Body roundness index, *CI* Conicity index, *LAP* Lipid accumulation product, *METS-IR* Metabolic score for insulin resistance, *METS-VF* Metabolical score for visceral fat, *TyG* Triglyceride-glucose index, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride glucose-waist circumference, *TyG-WHtR* Triglyceride glucose-waist to height ratio, *VAI* Visceral adiposity index, *WC* Waist circumference, *WHtR* Waist to height ratio, *WWI* Weight-adjusted-waist index

[1] Median (IQR); %

[2] Wilcoxon rank-sum test for complex survey samples

[3] chi-squared test with Rao & Scott's second-order correction

times higher than those in Q1 (OR = 3.633, 95% CIs: 1.254, 10.526, $P=0.020$), and in Q4, the odds increased significantly to 10.075 times (OR = 10.075, 95% CIs: 4.207, 24.124, $P<0.001$). Furthermore, the participants in Q4 displayed a greater likelihood of encountering TD than those in Q1 across all 15 indicators.

Association between 15 indices and testosterone level

Table 4 illustrates the beta values and their corresponding 95%CIs for 15 indices. Consistent with the findings of the weighted logistic regression, there was a noticeable downward trend in testosterone levels among participants as the 15 indicators increased. Furthermore, aside from the five indicators, including BMI, LAP, METS-IR, TyG, and VAI, an additional 10 indicators displayed statistically significant variances within each quartile group in Model 3. In the context of the BRI, in Models 1 and 2, significant differences were noted in the beta coefficients among the Q2-4 group in Models 1 and 2. (all $P<0.001$). Upon further analysis in Model 3, following the adjustment for potential confounding variables, it was observed that the testosterone levels in the Q2, Q3, and Q4 groups showed a significant decrease compared to the levels in the Q1 group.

Non-linear analysis between 15 indices and testosterone

Restricted cubic spline analysis was performed to conduct a more in-depth examination of the correlation between 15 indices and testosterone levels. To provide a clearer visualization, the OR values were logarithmically transformed; however, this transformation was not implemented for the beta values. Figures 3 and 4 show that the a clear inverse correlation between levels of testosterone and parameters related to both obesity and lipids. Specifically, a distinctive non-linear correlation was identified between METS-VF and TD (P for non-linearity = 0.01) but not between METS-VF and testosterone levels (P for non-linearity = 0.051). Regarding the results of linear regression, only BMI showed a non-linear relationship with testosterone levels (P for non-linearity = 0.025).

Subgroup analysis

Based on the results above, this study conducts further subgroup analysis on METS-VF, as shown in Table 5. Overall, a significant correlation was discovered between METS-VF and TD (OR = 5.43, 95%CIs: 3.64, 8.11, $P<0.001$), which was confirmed even after accounting for other confounding factors. Interestingly, there may be a potential interactive effect between participants' educational backgrounds and METS-VF, warranting further investigation for validation.

Diagnostic value of 15 indices

Since testosterone levels in males generally decrease as they age, further analyses were carried out by dividing the participants into different age groups. Two pivotal points, 39 and 59, were selected to divide the overall population into distinct groups. Group 1 (aged 18–39, excluding 39) consisted of 1263 participants, whereas Group 2 (aged 39–59, excluding 59) included 1180 participants. Group 3 (n = 59) included 1097 participants.

Table 3 The logistic regression model between obesity- and lipid-related indices with TD

	Model 1			Model 2			Model 3		
Indices	**OR[1]**	**95% CIs[1]**	***P***	**OR[1]**	**95% CIs[1]**	***P***	**OR[1]**	**95% CIs[1]**	***P***
ABSI									
Q1 [0.067,0.079)	—	—		—	—		—	—	
Q2 [0.079,0.082)	1.931	1.287, 2.896	0.002	1.802	1.200, 2.707	0.005	1.403	0.726, 2.711	0.298
Q3 [0.082,0.085)	2.287	1.511, 3.462	< 0.001	2.132	1.405, 3.233	< 0.001	1.432	0.863, 2.375	0.155
Q4 [0.085,0.106]	3.516	2.248, 5.498	< 0.001	3.334	2.078, 5.351	< 0.001	2.744	1.404, 5.363	0.005
BMI									
Q1 [15.7,24.2)	—	—		—	—		—	—	
Q2 [24.2,27.5)	1.855	1.255, 2.744	0.003	1.673	1.100, 2.544	0.017	0.817	0.440, 1.515	0.503
Q3 [27.5,31.2)	3.488	2.131, 5.710	< 0.001	3.023	1.785, 5.119	< 0.001	2.385	0.888, 6.411	0.082
Q4 [31.2,58.8]	8.683	5.810, 12.976	< 0.001	8.009	5.262, 12.188	< 0.001	4.513	2.272, 8.964	< 0.001
BRI									
Q1 [1.21,3.63)	—	—		—	—		—	—	
Q2 [3.63,4.78)	3.827	2.205, 6.641	< 0.001	3.350	1.900, 5.906	< 0.001	2.900	1.364, 6.169	0.008
Q3 [4.78,6.05)	5.587	3.010, 10.367	< 0.001	4.920	2.578, 9.389	< 0.001	3.633	1.254, 10.526	0.020
Q4 [6.05,16.9]	16.167	9.084, 28.772	< 0.001	14.581	8.045, 26.426	< 0.001	10.075	4.207, 24.124	< 0.001
CI									
Q1 [5.96,7.14)	—	—		—	—		—	—	
Q2 [7.14,7.52)	2.604	1.627, 4.167	< 0.001	2.531	1.528, 4.192	< 0.001	2.263	0.855, 5.988	0.096
Q3 [7.52,7.88)	4.574	2.796, 7.480	< 0.001	5.055	2.933, 8.712	< 0.001	3.337	1.123, 9.914	0.032
Q4 [7.88,9.47]	9.563	5.436, 16.820	< 0.001	11.182	5.931, 21.081	< 0.001	8.262	2.812, 24.278	< 0.001
LAP									
Q1 [0.343,21.1)	—	—		—	—		—	—	
Q2 [21.1,39.3)	1.705	0.953, 3.050	0.071	1.392	0.757, 2.557	0.280	0.733	0.314, 1.714	0.455
Q3 [39.3,70.2)	4.084	2.390, 6.976	< 0.001	3.460	1.974, 6.064	< 0.001	2.712	1.015, 7.246	0.047
Q4 [70.2,1.07e + 03]	9.657	5.877, 15.869	< 0.001	8.385	5.048, 13.929	< 0.001	5.195	2.321, 11.625	< 0.001
METS-IR									
Q1 [1.67,2.21)	—	—		—	—		—	—	
Q2 [2.21,2.36)	1.705	0.973, 2.987	0.062	1.881	1.022, 3.462	0.043	1.401	0.411, 4.782	0.574
Q3 [2.36,2.52)	3.333	2.168, 5.123	< 0.001	3.453	2.128, 5.603	< 0.001	2.698	0.995, 7.317	0.051
Q4 [2.52,5.44]	8.127	5.344, 12.361	< 0.001	8.313	5.255, 13.149	< 0.001	6.633	2.617, 16.812	< 0.001
METS-VF									
Q1 [3.25,6.01)	—	—		—	—		—	—	
Q2 [6.01,6.49)	2.934	1.615, 5.332	< 0.001	3.122	1.646, 5.923	< 0.001	2.026	0.816, 5.028	0.121
Q3 [6.49,6.82)	6.285	3.258, 12.124	< 0.001	8.929	4.321, 18.453	< 0.001	6.908	1.907, 25.031	0.005
Q4 [6.82,7.39]	11.696	6.464, 21.161	< 0.001	23.725	11.838, 47.546	< 0.001	13.412	4.222, 42.602	< 0.001
TyG									
Q1 [5.55,8.12)	—	—		—	—		—	—	
Q2 [8.12,8.53)	1.789	1.195, 2.679	0.006	1.879	1.192, 2.960	0.008	2.223	1.074, 4.602	0.033
Q3 [8.53,9)	3.062	2.058, 4.557	< 0.001	3.050	1.983, 4.692	< 0.001	3.277	1.630, 6.585	0.002
Q4 [9,12.4]	5.892	4.320, 8.037	< 0.001	5.972	4.273, 8.348	< 0.001	6.737	3.877, 11.707	< 0.001
TyG-BMI									
Q1 [118,202)	—	—		—	—		—	—	
Q2 [202,236)	2.387	1.432, 3.977	0.001	2.003	1.174, 3.418	0.012	1.701	0.838, 3.453	0.134
Q3 [236,278)	4.318	2.708, 6.886	< 0.001	3.838	2.405, 6.124	< 0.001	3.277	1.561, 6.880	0.003
Q4 [278,570]	13.505	8.581, 21.257	< 0.001	12.063	7.674, 18.961	< 0.001	9.093	4.362, 18.953	< 0.001
TyG-WC									
Q1 [4.47,7.4)	—	—		—	—		—	—	
Q2 [7.4,8.5)	3.116	1.779, 5.461	< 0.001	2.576	1.427, 4.651	0.002	1.493	0.666, 3.349	0.314

Table 3 (continued)

	Model 1			Model 2			Model 3		
Indices	**OR[1]**	**95% CIs[1]**	***P***	**OR[1]**	**95% CIs[1]**	***P***	**OR[1]**	**95% CIs[1]**	***P***
Q3 [8.5,9.68)	4.982	2.629, 9.439	< 0.001	4.202	2.183, 8.089	< 0.001	3.612	1.478, 8.823	0.007
Q4 [9.68,16.4]	17.868	10.210, 31.270	< 0.001	15.858	8.916, 28.206	< 0.001	11.577	5.394, 24.845	< 0.001
TyG-WHtR									
Q1 [2.53,4.25)	—	—		—	—		—	—	
Q2 [4.25,4.91)	2.402	1.364, 4.233	0.003	1.998	1.122, 3.559	0.020	2.169	0.945, 4.978	0.066
Q3 [4.91,5.57)	5.530	3.257, 9.390	< 0.001	4.969	2.879, 8.576	< 0.001	5.098	2.074, 12.530	0.001
Q4 [5.57,9.63]	14.705	8.688, 24.890	< 0.001	12.799	7.725, 21.205	< 0.001	13.802	5.876, 32.421	< 0.001
VAI									
Q1 [0.103,0.769)	—	—		—	—		—	—	
Q2 [0.769,1.3)	1.885	1.211, 2.936	0.006	2.050	1.236, 3.401	0.006	2.129	0.993, 4.566	0.052
Q3 [1.3,2.25)	3.125	2.049, 4.764	< 0.001	3.258	1.990, 5.334	< 0.001	2.986	1.242, 7.177	0.017
Q4 [2.25,53.1]	6.133	4.277, 8.795	< 0.001	6.308	4.198, 9.480	< 0.001	6.975	3.344, 14.549	< 0.001
WC									
Q1 [65.8,89)	—	—		—	—		—	—	
Q2 [89,98.7)	2.959	1.602, 5.465	< 0.001	2.518	1.325, 4.783	0.006	1.933	0.833, 4.488	0.118
Q3 [98.7,109)	5.187	2.692, 9.995	< 0.001	4.319	2.137, 8.729	< 0.001	2.827	0.952, 8.394	0.060
Q4 [109,176]	12.379	6.854, 22.359	< 0.001	10.754	5.836, 19.817	< 0.001	7.005	2.673, 18.363	< 0.001
WHtR									
Q1 [0.367,0.514)	—	—		—	—		—	—	
Q2 [0.514,0.57)	3.704	2.146, 6.395	< 0.001	3.239	1.837, 5.710	< 0.001	2.760	1.300, 5.858	0.011
Q3 [0.57,0.627)	5.517	2.967, 10.258	< 0.001	4.855	2.532, 9.309	< 0.001	3.864	1.338, 11.157	0.015
Q4 [0.627,0.978]	15.839	8.905, 28.174	< 0.001	14.235	7.850, 25.813	< 0.001	9.983	4.171, 23.895	< 0.001
WWI									
Q1 [8.29,10.3)	—	—		—	—		—	—	
Q2 [10.3,10.8)	2.455	1.556, 3.873	< 0.001	2.531	1.549, 4.135	< 0.001	2.695	0.886, 8.198	0.078
Q3 [10.8,11.4)	3.887	2.409, 6.273	< 0.001	4.451	2.681, 7.391	< 0.001	4.694	1.464, 15.053	0.012
Q4 [11.4,13.5]	8.678	5.519, 13.648	< 0.001	11.188	6.793, 18.426	< 0.001	10.821	4.603, 25.439	< 0.001

Abbreviation: *OR* odds ratio, *ABSI* A body shape index, *BMI* Body mass index, *BRI* Body roundness index, *CI* Conicity index, *LAP* Lipid accumulation product, *METS-IR* Metabolic score for insulin resistance, *METS-VF* Metabolical score for visceral fat, *TyG* Triglyceride-glucose index, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride glucose-waist circumference, *TyG-WHtR* Triglyceride glucose- waist to height ratio, *VAI* Visceral adiposity index, *WC* Waist circumference, *WHtR* Waist to height ratio, *WWI* Weight-adjusted-waist index

[1] *CIs* Confidence Intervals

Model 1: Unadjusted

Model 2: Adjusted with age, ethnicity, education, poverty ratio and marital status

Model 3: Adjusted with age, ethnicity, education, poverty ratio, marital status, hypertension, diabetes, drinking, smoking and family history

Table 6 illustrates the distinct threshold values that differentiate the AUC, sensitivity, and specificity of the parameters related to obesity and lipids. Figure 5 illustrates the ROC curves for each indicator in forecasting the venture. The data presented in the table and figure clearly indicate that the TyG-WHtR was the most reliable classifier of TD within the entire study population (AUC = 0.762, 95%CIs: 0.743, 0.782, cut-off = 5.186). Among the three age groups, TyG-WHtR continued to demonstrate the most robust diagnostic capability for detecting TD compared to the other 14 indices (Group 1: AUC = 0.788, 95%CIs: 0.751, 0.824, cut-off = 4.903; Group 2: AUC = 0.748, 95%CIs: 0.714, 0.781, cut-off = 5.816; Group 3: AUC = 0.719, 95%CIs: 0.684, 0.753, cut-off = 5.704). However, ABSI showed the lowest diagnostic capability for TD among all analyses conducted (Overall: AUC = 0.642, 95%CIs: 0.621, 0.664, cut-off = 0.081; Group 1: AUC = 0.673, 95%CIs: 0.633, 0.714, cut-off = 0.078; Group 2: AUC = 0.586, 95%CIs: 0.546, 0.625, cut-off = 0.082; Group 3: AUC = 0.575, 95%CIs: 0.538, 0.612, cut-off = 0.086).

To further illustrate the superior diagnostic accuracy of TyG-WHtR for TD, the AUC values of various indicators in both the general population and age-stratified

Table 4 The linear regression model between obesity- and lipid-related indices with testosterone level

	Model 1			Model 2			Model 3		
Indices	**Beta**	**95% CIs[1]**	***P***	**Beta**	**95% CIs[1]**	***P***	**Beta**	**95% CIs[1]**	***P***
ABSI									
Q1 [0.067,0.079)	—	—		—	—		—	—	
Q2 [0.079,0.082)	−73.299	−95.432, −51.166	< 0.001	−65.255	−90.324, −40.187	< 0.001	−39.921	−77.813, −2.029	0.040
Q3 [0.082,0.085)	−81.078	−105.135, −57.022	< 0.001	−78.284	−106.286, −50.281	< 0.001	−57.615	−91.819, −23.412	0.002
Q4 [0.085,0.106]	−112.378	−132.039, −92.717	< 0.001	−115.797	−144.586, −87.007	< 0.001	−88.276	−133.004, −43.548	< 0.001
BMI									
Q1 [15.7,24.2)	—	—		—	—		—	—	
Q2 [24.2,27.5)	−82.893	−108.484, −57.303	< 0.001	−71.084	−97.898, −44.271	< 0.001	−4.486	−57.892, 48.920	0.863
Q3 [27.5,31.2)	−134.255	−159.326, −109.183	< 0.001	−121.449	−147.624, −95.274	< 0.001	−62.652	−127.425, 2.121	0.057
Q4 [31.2,58.8]	−216.800	−237.972, −195.627	< 0.001	−207.932	−232.035, −183.828	< 0.001	−161.859	−206.860, −116.857	< 0.001
BRI									
Q1 [1.21,3.63)	—	—		—	—		—	—	
Q2 [3.63,4.78)	−102.162	−126.076, −78.249	< 0.001	−96.182	−123.878, −68.486	< 0.001	−77.313	−111.146, −43.480	< 0.001
Q3 [4.78,6.05)	−146.312	−165.840, −126.783	< 0.001	−144.600	−166.725, −122.474	< 0.001	−104.274	−149.518, −59.030	< 0.001
Q4 [6.05,16.9]	−226.201	−248.945, −203.457	< 0.001	−226.729	−252.426, −201.032	< 0.001	−195.000	−240.719, −149.281	< 0.001
CI									
Q1 [5.96,7.14)	—	—		—	—		—	—	
Q2 [7.14,7.52)	−90.082	−114.244, −65.919	< 0.001	−91.340	−118.361, −64.318	< 0.001	−68.047	−108.363, −27.730	0.002
Q3 [7.52,7.88)	−131.916	−152.866, −110.966	< 0.001	−144.798	−170.171, −119.424	< 0.001	−104.049	−155.079, −53.019	< 0.001
Q4 [7.88,9.47]	−186.894	−207.639, −166.149	< 0.001	−210.757	−236.040, −185.473	< 0.001	−179.067	−221.521, −136.613	< 0.001
LAP									
Q1 [0.343,21.1)	—	—		—	—		—	—	
Q2 [21.1,39.3)	−77.461	−101.550, −53.371	< 0.001	−67.668	−94.784, −40.553	< 0.001	−0.038	−38.902, 38.827	0.998
Q3 [39.3,70.2)	−147.764	−171.358, −124.170	< 0.001	−139.395	−166.731, −112.058	< 0.001	−84.968	−135.432, −34.504	0.002
Q4 [70.2,1.07e + 03]	−212.781	−236.140, −189.422	< 0.001	−204.778	−229.677, −179.879	< 0.001	−151.993	−197.480, −106.507	< 0.001
METS-IR									
Q1 [1.67,2.21)	—	—		—	—		—	—	
Q2 [2.21,2.36)	−72.253	−94.335, −50.170	< 0.001	−67.086	−88.958, −45.214	< 0.001	−37.114	−74.987, 0.758	0.054
Q3 [2.36,2.52)	−126.200	−146.675, −105.726	< 0.001	−116.886	−136.447, −97.325	< 0.001	−82.804	−126.947, −38.660	< 0.001
Q4 [2.52,5.44]	−188.606	−213.829, −163.382	< 0.001	−179.471	−204.786, −154.156	< 0.001	−141.220	−199.451, −82.990	< 0.001
METS-VF									
Q1 [3.25,6.01)	—	—		—	—		—	—	
Q2 [6.01,6.49)	−98.304	−120.645, −75.962	< 0.001	−111.707	−137.589, −85.826	< 0.001	−63.947	−105.289, −22.606	0.004
Q3 [6.49,6.82)	−150.792	−168.559, −133.025	< 0.001	−187.591	−210.543, −164.639	< 0.001	−154.819	−197.957, −111.682	< 0.001
Q4 [6.82,7.39]	−195.579	−216.349, −174.809	< 0.001	−267.627	−299.605, −235.649	< 0.001	−210.170	−262.783, −157.557	< 0.001
TyG									
Q1 [5.55,8.12)	—	—		—	—		—	—	
Q2 [8.12,8.53)	−43.137	−69.726, −16.548	0.002	−39.689	−68.271, −11.106	0.008	−25.056	−73.768, 23.656	0.297
Q3 [8.53,9)	−104.226	−124.273, −84.178	< 0.001	−97.642	−118.197, −77.088	< 0.001	−81.669	−121.379, −41.960	< 0.001
Q4 [9,12.4]	−157.290	−181.441, −133.138	< 0.001	−150.295	−173.654, −126.936	< 0.001	−139.979	−189.533, −90.424	< 0.001
TyG-BMI									
Q1 [118,202)	—	—		—	—		—	—	
Q2 [202,236)	−90.227	−111.261, −69.193	< 0.001	−81.130	−103.859, −58.401	< 0.001	−53.317	−86.991, −19.643	0.003
Q3 [236,278)	−148.739	−169.820, −127.658	< 0.001	−140.406	−162.639, −118.172	< 0.001	−87.005	−126.173, −47.837	< 0.001
Q4 [278,570]	−234.435	−257.245, −211.626	< 0.001	−227.205	−251.067, −203.344	< 0.001	−207.685	−251.775, −163.595	< 0.001
TyG-WC									
Q1 [4.47,7.4)	—	—		—	—		—	—	
Q2 [7.4,8.5)	−96.197	−118.754, −73.639	< 0.001	−89.614	−113.762, −65.465	< 0.001	−65.969	−104.827, −27.111	0.002

Table 4 (continued)

	Model 1			Model 2			Model 3		
Indices	**Beta**	**95% CIs[1]**	***P***	**Beta**	**95% CIs[1]**	***P***	**Beta**	**95% CIs[1]**	***P***
Q3 [8.5,9.68)	−147.961	−167.444, −128.478	< 0.001	−144.663	−168.600, −120.726	< 0.001	−110.114	−149.907, −70.322	< 0.001
Q4 [9.68,16.4]	−239.331	−261.796, −216.866	< 0.001	−238.441	−264.026, −212.856	< 0.001	−224.782	−277.588, −171.977	< 0.001
TyG-WHtR									
Q1 [2.53,4.25)	—	—		—	—		—	—	
Q2 [4.25,4.91)	−89.336	−109.467, −69.205	< 0.001	−84.578	−108.321, −60.835	< 0.001	−72.136	−105.409, −38.864	< 0.001
Q3 [4.91,5.57)	−158.844	−178.897, −138.790	< 0.001	−157.557	−180.518, −134.596	< 0.001	−137.784	−177.833, −97.735	< 0.001
Q4 [5.57,9.63]	−228.668	−253.479, −203.858	< 0.001	−229.145	−257.583, −200.707	< 0.001	−229.548	−283.023, −176.073	< 0.001
VAI									
Q1 [0.103,0.769)	—	—		—	—		—	—	
Q2 [0.769,1.3)	−46.319	−74.720, −17.918	0.002	−40.744	−71.418, −10.070	0.010	−19.261	−68.458, 29.935	0.425
Q3 [1.3,2.25)	−113.916	−136.846, −90.987	< 0.001	−106.453	−129.927, −82.978	< 0.001	−73.768	−121.212, −26.323	0.004
Q4 [2.25,53.1]	−158.181	−181.177, −135.184	< 0.001	−149.141	−171.947, −126.336	< 0.001	−126.813	−174.870, −78.755	< 0.001
WC									
Q1 [65.8,89)	—	—		—	—		—	—	
Q2 [89,98.7)	−89.265	−113.582, −64.948	< 0.001	−79.192	−107.617, −50.768	< 0.001	−48.424	−84.829, −12.018	0.012
Q3 [98.7,109)	−138.342	−162.690, −113.994	< 0.001	−130.225	−158.712, −101.738	< 0.001	−62.055	−118.795, −5.315	0.034
Q4 [109,176]	−221.601	−240.376, −202.826	< 0.001	−217.901	−240.808, −194.994	< 0.001	−183.681	−232.785, −134.576	< 0.001
WHtR									
Q1 [0.367,0.514)	—	—		—	—		—	—	
Q2 [0.514,0.57)	−101.685	−125.265, −78.104	< 0.001	−95.717	−122.760, −68.675	< 0.001	−74.913	−109.558, −40.267	< 0.001
Q3 [0.57,0.627)	−148.661	−168.303, −129.019	< 0.001	−147.565	−169.988, −125.143	< 0.001	−106.776	−152.129, −61.423	< 0.001
Q4 [0.627,0.978]	−226.496	−249.279, −203.713	< 0.001	−227.253	−252.976, −201.530	< 0.001	−194.399	−239.705, −149.092	< 0.001
WWI									
Q1 [8.29,10.3)	—	—		—	—		—	—	
Q2 [10.3,10.8)	−81.702	−104.075, −59.329	< 0.001	−85.475	−109.725, −61.224	< 0.001	−77.076	−118.566, −35.585	< 0.001
Q3 [10.8,11.4)	−121.556	−141.007, −102.104	< 0.001	−138.854	−161.965, −115.742	< 0.001	−115.184	−159.148, −71.220	< 0.001
Q4 [11.4,13.5]	−172.072	−189.258, −154.885	< 0.001	−201.552	−224.811, −178.294	< 0.001	−178.161	−210.380, −145.943	< 0.001

Abbreviation: *OR* odds ratio, *ABSI* A body shape index, *BMI* Body mass index, *BRI* Body roundness index, *CI* Conicity index, *LAP* Lipid accumulation product, *METS-IR* Metabolic score for insulin resistance, *METS-VF* Metabolical score for visceral fat, *TyG* Triglyceride-glucose index, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride glucose-waist circumference, *TyG-WHtR* Triglyceride glucose-waist to height ratio, *VAI* Visceral adiposity index, *WC* Waist circumference, *WHtR* Waist to height ratio, *WWI* Weight-adjusted-waist index

[1] *CIs* Confidence Intervals

Model 1: Unadjusted

Model 2: Adjusted with age, ethnicity, education, poverty ratio and marital status

Model 3: Adjusted with age, ethnicity, education, poverty ratio, marital status, hypertension, diabetes, drinking, smoking and family history

subgroups were analyzed, as outlined in Table 7. These results indicated statistically significant differences existed between TyG-WHtR and other indicators within the general population (all $P<0.001$), with the exception of TyG-WC (ΔAUC = 0.004, 95%CIs: -0.001, 0.009, $P=0.157$). When examining age-stratified data, TyG-WHtR showed superior discriminatory capability for detecting TD compared to most other indicators.

Discussion

The study included 3540 adult males in the U.S, with an overall TD proportion of 20.3%, based on the diagnostic criteria outlined in the AUA guidelines. Across different metrics, specifically the 15 indices associated with obesity and lipids, it was noted that individuals with TD displayed reduced levels of these markers. This finding further emphasized the association between obesity, metabolic abnormalities, and TD. With the help of these indices, more effective preventive methods could be implemented.

A strong relationship exists between obesity and TD, as shown in several studies [1, 28, 40, 77]. In this cross-sectional analysis, the risk of TD was observed to be increased significantly in nearly all quartile groups for various indicators compared with that in Q1, with the exception of Q2 for LAP and METS-IR. After

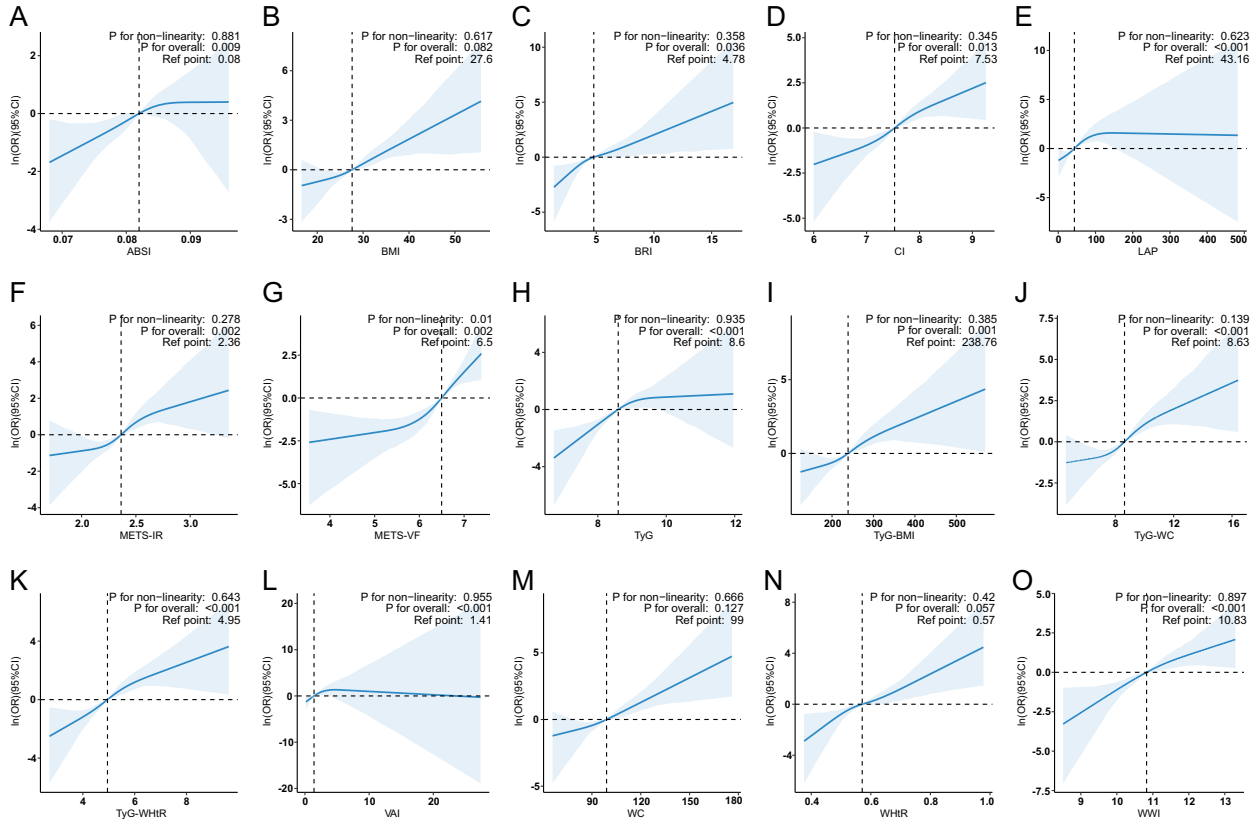

Fig. 3 Non-linear ananlysis of 15 indices and TD with ORs natural logarithmic transformation. **A** ABSI, **B** BMI, **C** BRI, **D** CI, **E** LAP, **F** METS-IR, **G** METS-VF, **H** TyG, **I** TyG-BMI, **J** TyG-WC, **K** TyG-WHtR, **L** VAI, **M** WC, **N** WHtR, **O** WWI

controlling for potential variables that could impact testosterone levels, it was noted that certain factors, like the second and third quartiles of ABSI, displayed a reduced level of heightened risk. However, these changes were not statistically significant. These results indicate that, despite adjusting for potential influencing factors, a significant inverse relationship between the 15 indices and testosterone levels was still apparent in the weighted linear regression analysis. Moreover, this study revealed that the prevalence of hypertension and diabetes differed significantly between individuals with and without TD (hypertension: 43.0% vs. 28.6%, $P<0.001$; diabetes: 27.8% vs. 16.4%, $P<0.001$). The results of other studies support this conclusion. As an example, Wei et al. found that increased testosterone levels were a protective factor for hypertension (OR = 0.69, 95%CIs: 0.53, 0.89) [80]. Additionally, results from a trial indicated that testosterone treatment over a 2-year period reduced the prevalence of T2DM among participants, surpassing the effects of lifestyle interventions [81]. Results mentioned above highlight the association between metabolic abnormalities and lower testosterone levels, indicating promising directions for further study within these specific groups.

Numerous studies have utilized restricted cubic bar plots to investigate the non-linear correlation between two variables [16]. In this study, the associations between 15 parameters, TD, and testosterone levels were investigated. With the exception of METS-VF, there was no statistically significant correlation identified between the other 14 parameters and TD (all P for non-linear > 0.05). METS-VF has been validated as a reliable discriminator of erectile dysfunction (AUC = 0.735) [15]. Accordingly, the subgroup analysis of METS-VF uncovered a potential interaction solely with education level (P for interaction = 0.004). However, the mechanism of this interaction remains unclear. One possible reason is the changes in family environment and lifestyle habits, which are manifested to some extent through different levels of education and are related to metabolic abnormalities such as obesity [19, 54].

Obesity, an unhealthy condition characterized with metabolic issues and long-term, low-level inflammation, is marked by elevated levels of leptin, secreted by adipose tissue and enterocytes in the small intestine. This

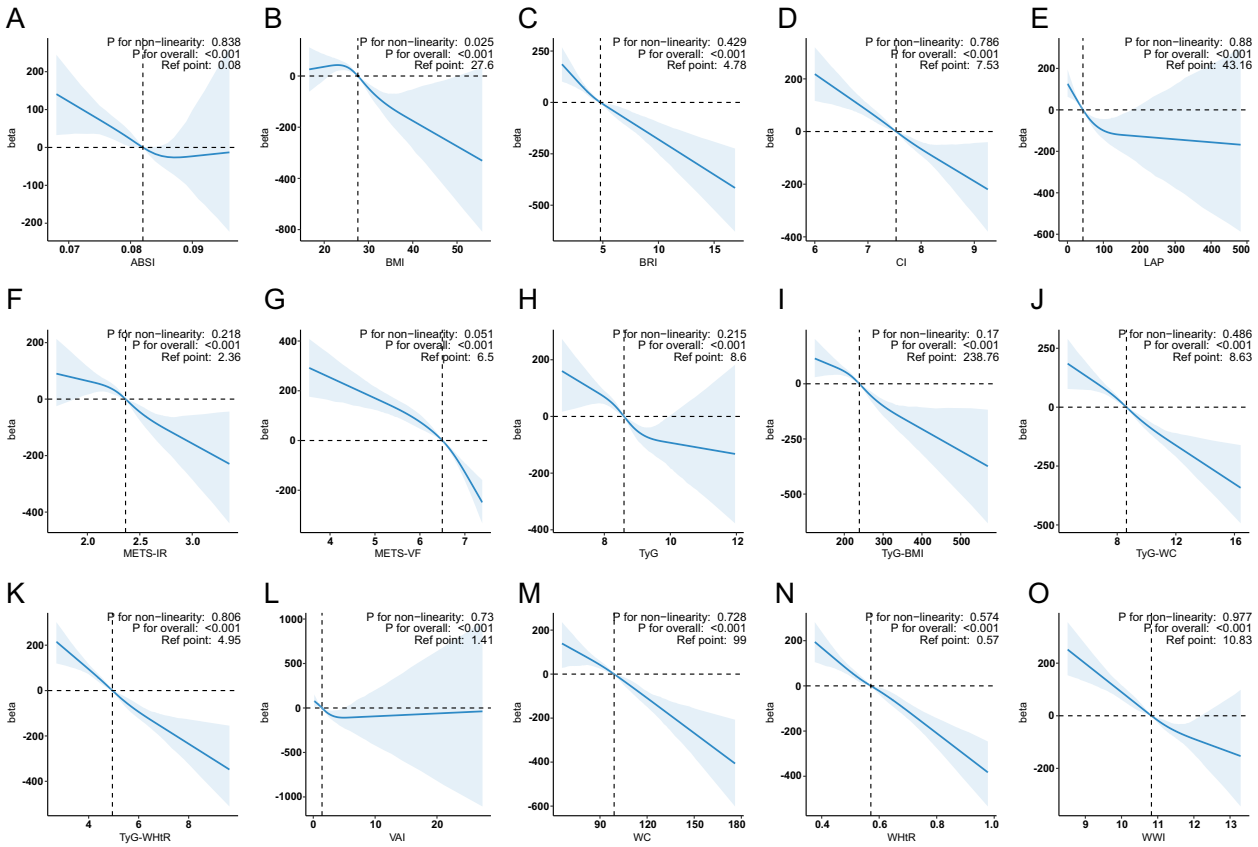

Fig. 4 Non-linear ananlysis of 15 indices and testosterone level. **A** ABSI, **B** BMI, **C** BRI, **D** CI, **E** LAP, **F** METS-IR, **G** METS-VF, **H** TyG, **I** TyG-BMI, **J** TyG-WC, **K** TyG-WHtR, **L** VAI, **M** WC, **N** WHtR, **O** WWI

condition is commonly referred to as hyperleptinemia [63]. The relationship between leptin and reduced testosterone levels may be attributed to the imbalance in leptin levels leading to elevated estrogen levels, subsequently increasing aromatase activity [47]. What's more, testosterone participate in the regulation of blood pressure by influencing the contractility of vascular smooth muscle, and in cases of prolonged hypertension, this regulatory mechanism may be disrupted [67]. A significant association has been observed between obesity and testosterone levels, suggesting that testosterone can reduce insulin resistance. Insulin is indispensable in the regulation of testosterone levels as it promotes the production of gonadotropin-releasing hormone (GnRH) in the hypothalamus, triggering the release of the hormone [10]. In males diagnosed with TD, there is a significant reduction in the expression of insulin signaling genes in adipose tissue. However, following testosterone treatment, there is a significant upregulation of these genes, further reinforcing this perspective [17]. Hyperglycemia have been found to reduce the production of mitochondrial acetylase 3 in hypothalamic neurons. This can negatively impact the functioning of mitochondria as well as insulin receptors in these neurons. The decrease in activity of the GnRH gene and protein caused by this inhibition ultimately leads to a suppression of GnRH neurons, which in turn results in lower levels of testosterone in the body [60]. At the cellular level, testosterone has been found to enhance the expression and activity of adenosine 5'-monophosphate-activated protein kinase α (AMPK α) in skeletal muscle, ultimately resulting in increased glucose transport [14]. A 22-week study involving 32 men showed a significant upregulation in the expression and phosphorylation of AMPK α following TTh. This suggests a potential mechanism by which TTh improves insulin signal transduction [12, 32]. Several other research studies have indicated a potential link between abnormal gliosis in the mediobasal hypothalamus, increased visceral fat, and reduced endogenous testosterone levels in healthy men across various BMI categories [5].

Inflammation is another critical mechanism by which obesity hinders testosterone production. According to recent in vitro investigations, it seems that testosterone may have the ability to hinder the synthesis of tumor necrosis factor-α (TNF-α), interleukin-1β and interleukin-6, and at the same time, encourage the production

Table 5 Association between METS-VF and testosterone deficiency by different subgroups

Subgroup	Crude OR (95% CIs)	*P*	*P* for interaction
Overall	5.43 (3.64–8.11)	< 0.001	
Age			0.429
< 38.7	7.77 (3.84–15.72)	< 0.001	
≥ 59.3	16.26 (7.44–35.54)	< 0.001	
38.7—59.3	12.70 (5.03–32.10)	< 0.001	
BMI			0.484
< 18.5	4.30 (1.56–11.87)	0.018	
≥ 40	0.90 (0.14–5.74)	0.909	
18.5—25	3.39 (1.77–6.49)	0.001	
25—30	2.89 (1.51–5.52)	0.003	
30—35	2.07 (0.99–4.31)	0.06	
35—40	8.10 (1.88–34.82)	0.008	
Hypertension			0.373
No	5.02 (3.34–7.56)	< 0.001	
Yes	7.24 (3.12–16.80)	< 0.001	
Diabetes			0.727
Borderline	20.13 (0.13–3083.58)	0.327	
No	3.62 (2.24–5.83)	< 0.001	
Yes	8.01 (2.11–30.38)	0.005	
Family history			0.226
No	6.32 (3.85–10.38)	< 0.001	
Yes	4.12 (2.17–7.82)	< 0.001	
Ethnicity			0.406
Mexican American	9.25 (4.62–18.52)	< 0.001	
Non-Hispanic Asian	4.65 (2.66–8.14)	< 0.001	
Non-Hispanic Black	7.28 (4.60–11.52)	< 0.001	
Non-Hispanic White	5.01 (2.87–8.74)	< 0.001	
Other Hispanic	7.14 (2.58–19.77)	0.001	
Others	5.38 (1.42–20.42)	0.024	
Drinking			0.136
No	7.91 (4.51–13.90)	< 0.001	
Yes	4.86 (3.09–7.63)	< 0.001	
Smoking			0.102
No	7.39 (4.16–13.12)	< 0.001	
Yes	4.15 (2.42–7.11)	< 0.001	
Marital status			0.914
Divorced	11.26 (2.35–54.06)	0.004	
Living with partner	2.55 (0.63–10.33)	0.197	
Married	7.14 (4.03–12.67)	< 0.001	
Never married	4.12 (2.18–7.79)	< 0.001	
Separated	40.21 (0.94–1729.33)	0.073	
Widowed	13.57 (0.60–308.70)	0.119	
Education			0.004
9-11th grade	2.94 (1.04–8.28)	0.047	
College	6.30 (3.92–10.14)	< 0.001	
High school graduate	4.44 (1.86–10.62)	0.002	
Less than 9th grade	55.00 (12.65–239.11)	< 0.001	

OR odds ratio

of the interleukin-10 [79]. Elevated levels of TNF-α had been demonstrated to reduce the activity of the hypothalamic-pituitary axis, leading to a decline in the secretion of testosterone [42]. An observational study revealed that inflammatory markers, like C-reactive protein, are independently linked with testosterone levels (both total and bioavailable) [65]. Ghanim et al. concluded that individuals with obesity demonstrate reduced levels of phosphorylated insulin receptor beta subunit in monocytes, as well as elevated levels of inflammatory mediators like B cell kinase beta, suppressor of cytokine signaling-3, and protein kinase C-beta 2 [31]. The discovery of low testosterone levels in overweight men can be attributed to a variety of factors, such as the natural aging process and other underlying health issues, such as heightened oxidative stress resulting from insulin resistance in obesity. Ultimately, the specific biological processes that link abnormal testosterone levels to obesity remain incompletely elucidated. This indicates a need for additional exploration and analysis in upcoming studies to gain a better understanding of this association.

Both obesity and hypogonadism are ienterconnected, as obesity can contribute to the development of hypogonadism, and vise versa [46, 62, 68]. A recent study using bidirectional Mendelian analysis revealed that an elevation in genetically controlled factors was linked with a reduction in testosterone levels. Conversely, no significant association has been observed between testosterone levels and BMI [25]. In a study examining older men with early-stage prostate cancer, who initially had healthy testosterone levels of 14 nmol/L, researchers found that after 12 months of androgen deprivation therapy (ADT) leading to a significant drop in total testosterone levels to 0.4 nmol/L, there was only a slight uptick in BMI by 0.65 kg/m2 (95%CIs: 0.14, 1.15) compared to similar prostate cancer patients who did not undergo ADT [8]. Earlier studies have elucidated that the inhibition of testosterone results in heightened retention levels of fatty acids within the adipose tissue of the femur. Additionally, it leads to elevated levels of lipoprotein lipase activity in both fasting and fed states, an increase in acyl coenzyme A synthetase activity, and a decrease in fat oxidation among male individuals [38, 71]. Multiple longitudinal studies have provided evidence suggesting that decreased testosterone may be a significant factor to the onset of obesity and the development of T2DM [35, 52, 73]. Testosterone plays a crucial role in the process of lipolysis and maintenance of lipid homeostasis, as evidenced by the fact that a lack of testosterone can disrupt lipid homeostasis, leading to an increase in adipogenesis [46, 72]. In a separate study, animals subjected to orchiectomy demonstrated decreased insulin responsiveness and sensitivity, resulting in weight loss various health

Table 6 Cut-off between AUC, sensitivity and specificity for indices to detect TD

Indices	AUC	95%CIs	Cut-off value	Sensitivity	Specificity	Youden's index
ABSI						
Overall	0.642	0.621—0.664	0.081	77.7%	42.8%	0.205
Group 1[18,39)	0.673	0.633—0.714	0.078	81.5%	44.8%	0.263
Group 2[39–59)	0.586	0.546—0.625	0.082	66.4%	47.8%	0.141
Group 3[59-	0.575	0.538—0.612	0.086	60.9%	52.8%	0.138
BMI						
Overall	0.719	0.697—0.740	28.9	65.0%	66.7%	0.317
Group 1[18,39)	0.757	0.717—0.797	32	55.5%	85.0%	0.404
Group 2[39–59)	0.713	0.677—0.749	29	68.0%	64.6%	0.327
Group 3[59-	0.688	0.652—0.724	29	61.3%	67.9%	0.292
BRI						
Overall	0.747	0.727—0.767	5.024	72.0%	63.4%	0.354
Group 1[18,39)	0.778	0.741—0.815	4.105	83.2%	60.1%	0.433
Group 2[39–59)	0.724	0.688—0.759	4.919	73.4%	58.3%	0.317
Group 3[59-	0.700	0.666—0.735	6.891	42.7%	86.0%	0.288
CI						
Overall	0.725	0.705—0.745	7.598	69.5%	63.0%	0.325
Group 1[18,39)	0.767	0.729—0.804	7.276	74.0%	66.1%	0.401
Group 2[39–59)	0.687	0.650—0.725	7.66	60.2%	68.7%	0.289
Group 3[59-	0.668	0.632—0.704	7.945	61.9%	65.3%	0.272
LAP						
Overall	0.729	0.709—0.749	50.844	66.3%	69.0%	0.353
Group 1[18,39)	0.772	0.735—0.809	52.081	64.7%	78.4%	0.432
Group 2[39–59)	0.714	0.679—0.749	46.461	77.9%	57.9%	0.358
Group 3[59-	0.686	0.651—0.721	50.844	61.3%	67.5%	0.288
METS-IR						
Overall	0.698	0.676—0.719	2.404	66.1%	63.1%	0.291
Group 1[18,39)	0.730	0.687—0.773	2.49	59.5%	80.2%	0.397
Group 2[39–59)	0.690	0.654—0.726	2.524	52.0%	76.9%	0.290
Group 3[59-	0.676	0.640—0.711	2.302	79.1%	45.8%	0.249
METS-VF						
Overall	0.735	0.715—0.755	6.504	76.6%	58.2%	0.348
Group 1[18,39)	0.776	0.740—0.812	6.073	78.6%	64.3%	0.429
Group 2[39–59)	0.722	0.686—0.758	6.719	56.6%	76.4%	0.329
Group 3[59-	0.709	0.675—0.743	7.068	45.4%	83.5%	0.289
TyG						
Overall	0.669	0.646—0.691	8.675	62.4%	64.1%	0.265
Group 1[18,39)	0.690	0.647—0.733	8.676	57.2%	72.9%	0.302
Group 2[39–59)	0.654	0.616—0.692	8.706	69.3%	57.4%	0.266
Group 3[59-	0.641	0.603—0.678	9.054	41.1%	80.8%	0.218
TyG-BMI						
Overall	0.742	0.721—0.762	261.606	62.3%	73.7%	0.360
Group 1[18,39)	0.776	0.737—0.814	255.036	67.1%	74.9%	0.419
Group 2[39–59)	0.740	0.705—0.774	257.408	70.5%	66.1%	0.366
Group 3[59-	0.708	0.673—0.743	261.606	58.3%	74.3%	0.326
TyG-WC						
Overall	0.759	0.739—0.778	8.96	69.7%	69.1%	0.387
Group 1[18,39)	0.787	0.750—0.824	8.34	76.3%	68.5%	0.448
Group 2[39–59)	0.742	0.707—0.776	9.003	73.8%	64.0%	0.378

Table 6 (continued)

Indices	AUC	95%CIs	Cut-off value	Sensitivity	Specificity	Youden's index
Group 3[59-	0.718	0.683—0.752	9.111	67.9%	65.3%	0.332
TyG-WHtR						
Overall	0.762	0.743—0.782	5.186	68.4%	69.8%	0.382
Group 1[18,39)	0.788	0.751—0.824	4.903	70.5%	72.6%	0.431
Group 2[39–59)	0.748	0.714—0.781	5.186	73.4%	66.1%	0.395
Group 3[59-	0.719	0.684—0.753	5.704	52.0%	81.0%	0.330
VAI						
Overall	0.666	0.644—0.688	1.389	66.2%	59.1%	0.253
Group 1[18,39)	0.706	0.664—0.748	1.335	70.5%	62.8%	0.333
Group 2[39–59)	0.650	0.613—0.688	1.626	63.1%	60.1%	0.233
Group 3[59-	0.646	0.609—0.682	1.367	63.9%	59.2%	0.232
WC						
Overall	0.742	0.722—0.762	102.5	69.3%	67.6%	0.369
Group 1[18,39)	0.775	0.737—0.813	94.5	80.9%	60.9%	0.418
Group 2[39–59)	0.715	0.679—0.752	102.4	69.3%	63.9%	0.332
Group 3[59-	0.700	0.665—0.735	104	68.5%	61.5%	0.301
WHtR						
Overall	0.747	0.727—0.767	0.582	72.0%	63.2%	0.352
Group 1[18,39)	0.778	0.741—0.815	0.538	83.2%	59.7%	0.430
Group 2[39–59)	0.724	0.688—0.759	0.622	52.0%	79.6%	0.316
Group 3[59-	0.700	0.665—0.735	0.661	42.7%	85.9%	0.286
WWI						
Overall	0.715	0.695—0.735	10.726	78.9%	51.5%	0.304
Group 1[18,39)	0.759	0.722—0.797	10.532	70.5%	69.0%	0.395
Group 2[39–59)	0.679	0.641—0.716	10.745	75.4%	49.5%	0.249
Group 3[59-	0.651	0.615—0.687	11.513	59.6%	63.6%	0.233

Abbreviations: *AUC* Area under curve, *CIs* Confidence Intervals, *ABSI* A body shape index, *BMI* Body mass index, *BRI* Body roundness index, *CI* Conicity index, *LAP* Lipid accumulation product, *METS-IR* Metabolic score for insulin resistance, *METS-VF* Metabolical score for visceral fat, *TyG* Triglyceride-glucose index, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride glucose-waist circumference, *TyG-WHtR* Triglyceride glucose-waist to height ratio, *VAI* Visceral adiposity index, *WC* Waist circumference, *WHtR* Waist to height ratio, *WWI* Weight-adjusted-waist index

conditions including cardiovascular disease, psoriasis, frailty, and gallstones[30]. Based on these findings, it can be inferred that a lack of testosterone may result in obesity by increasing fat storage and disrupting lipid and glucose processing.

This study focused on the efficacy of 15 indices for detecting TD using ROC curves. The standout performer in terms of predictive power was TyG-WHtR. When analyzing the overall population or stratifying by age, the diagnostic capacity of TyG-WHtR for TD was consistently rated as moderate, showing the strongest diagnostic capability among all the studied indices. In recent years, TyG and its derivatives have garnered significant attention. Numerous studies have linked TyG to various health conditions including cardiovascular disease, psoriasis, frailty, and gallstones [13, 27, 39, 84]. However, TyG demonstrated a weaker diagnostic potential for TD than its derived indicators, with ROC values consistently below 0.7 across all analyses. Among all the parameters assessed, ABSI exhibited the lowest ability to detect TD. While the ABSI showed a slightly better performance in diagnosing TD among younger individuals (aged 18–39 years), its effectiveness was diminished in other age groups. Some studies have associated ABSI with certain cancers, such as prostate cancer, esophageal cancer, and breast cancer [9, 21, 41]. Significantly, of the 15 indicators analyzed for TD, individuals between the ages of 18–39 years demonstrated the strongest diagnostic ability compared to other age brackets and the general population. Importantly, men in this age range ideally have elevated levels of sex hormones; however, this may be hindered by obesity. Liu and his colleagues conducted a comprehensive research study that investigated the potential correlation between WWI and testosterone levels. The findings showed that individuals between the ages of 20 and 40 experienced a more pronounced reduction in testosterone levels (72.84 ng/dL) for every one-unit increase in WWI, compared to those in the 40–60

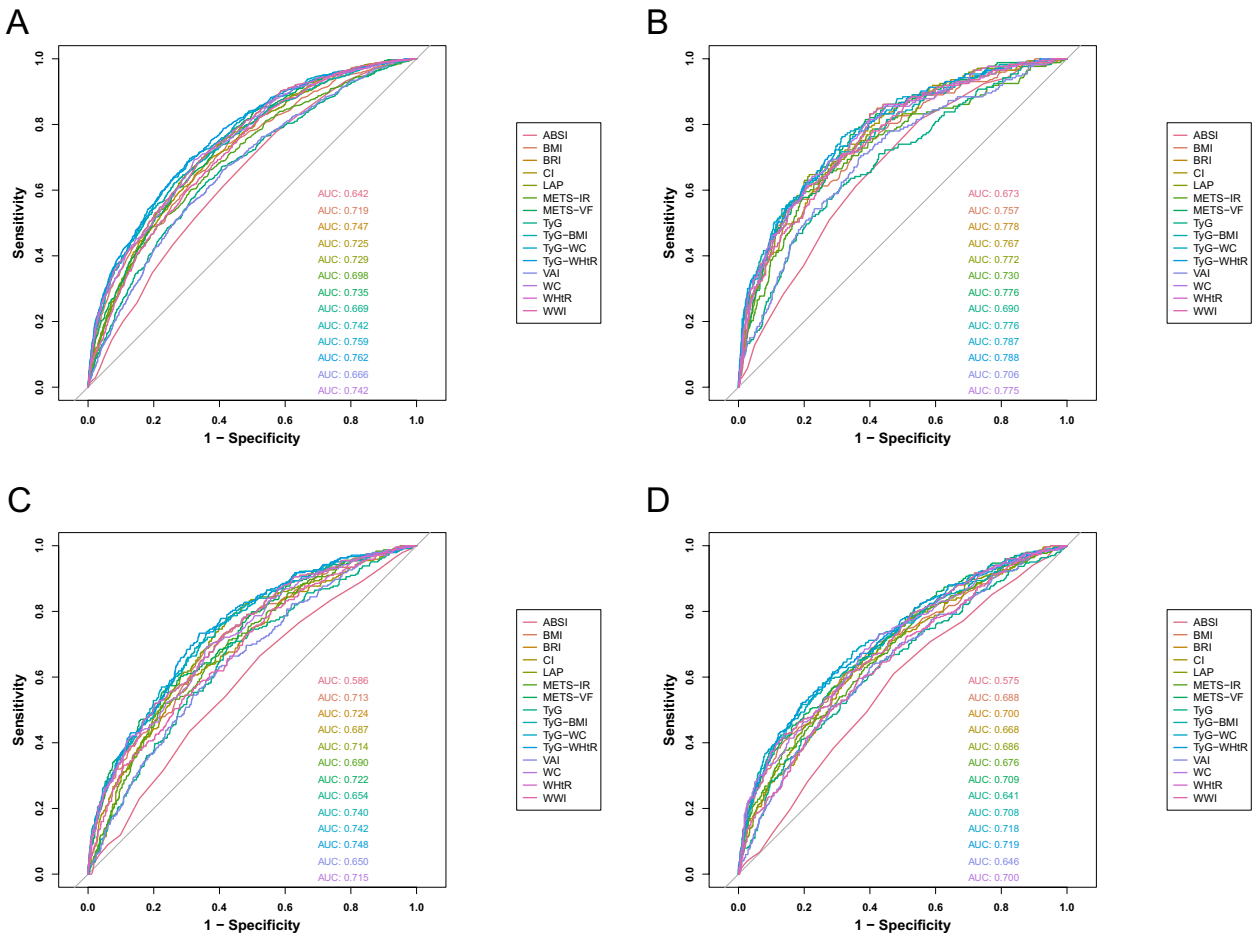

Fig. 5 ROC curves of 15 obesity- and lipid-related indices to detect TD in different population group. **A** overall population, **B** 18–39 years, **C** 39–59 years, **D** above 59 years

age bracket (55.64 ng/dL) and individuals over the age of 60 (55.11 ng/dL) [57]. In their study, Kaplan and colleagues brought to light the significant influence of obesity on testosterone levels in aging men. They found that older men with obesity experience a marked decline in testosterone levels when compared with their healthier aging counterparts [45]. A randomized controlled trial has highlighted the association between severe childhood-onset obesity and compromised Leydig cell function in young males. This particular hyperlink has the potential to cause a reduction of testosterone in the body, which in turn, can lead to the development of skeletal issues over time [51]. Li et al. discovered that young males diagnosed with male obesity-associated secondary hypogonadism exhibited noticeably decreased levels of follicle-stimulating hormone compared to those in their middle-aged counterparts. Hence, the reduction in testosterone levels among young males could potentially be attributed to the suppression of HPGA [55]. A clear inverse relationship was observed between testosterone levels and indicators such as HbA1c, diabetes, and metabolic syndrome, which intensified over time [44]. For individuals aged 18–39 years, incorporating regular physical activity into daily routines is crucial. Exercise has a significant impact on testosterone levels, particularly in individuals with obesity. The reduced intensity and frequency of physical activity in obese individuals can exacerbate obesity and hinder potential increases in testosterone levels. The relationship between exercise and testosterone may have implications on outcomes in this specific age group. Engaging in regular-, moderate-, and high-volume exercise over an extended period can play a significant role in decreasing body fat and enhancing the abnormalities in testicular leptin signal transduction caused by obesity. Research has demonstrated that moderate exercise can counteract the negative impact of obesity on reproductive health [83]. The results suggest that a decrease in testosterone levels can be attributed to metabolic disorders like obesity, as well as the natural aging process. This underscores the urgency for further

Table 7 Differences of TyG-WHtR compared to other indices in the different age groups

Indices	Z-statistic	*P*	ΔAUC	95%CIs L	95%CIs H
Overall					
ABSI	9.887	< 0.001	0.12	0.096	0.144
BMI	6.682	< 0.001	0.044	0.031	0.057
BRI	3.242	0.001	0.015	0.006	0.025
CI	4.867	< 0.001	0.038	0.023	0.053
LAP	6.573	< 0.001	0.033	0.023	0.043
METS-IR	7.545	< 0.001	0.065	0.048	0.082
METS-VF	3.871	< 0.001	0.028	0.014	0.042
TyG	10.155	< 0.001	0.094	0.076	0.112
TyG-BMI	5.129	< 0.001	0.021	0.013	0.029
TyG-WC	1.414	0.157	0.004	−0.001	0.009
VAI	10.022	< 0.001	0.096	0.078	0.115
WC	3.527	< 0.001	0.02	0.009	0.032
WHtR	3.241	0.001	0.015	0.006	0.025
WWI	5.953	< 0.001	0.047	0.032	0.063
Group 1[18,39)					
ABSI	5.474	< 0.001	0.115	0.074	0.156
BMI	2.959	0.003	0.031	0.01	0.052
BRI	1.348	0.178	0.01	−0.005	0.025
CI	1.849	0.064	0.021	−0.001	0.044
LAP	2.06	0.039	0.016	0.001	0.031
METS-IR	3.672	< 0.001	0.058	0.027	0.089
METS-VF	1.44	0.15	0.012	−0.004	0.028
TyG	5.49	< 0.001	0.098	0.063	0.133
TyG-BMI	2.073	0.038	0.012	0.001	0.024
TyG-WC	0.129	0.897	0.001	−0.007	0.008
VAI	4.577	< 0.001	0.082	0.047	0.117
WC	1.337	0.181	0.013	−0.006	0.031
WHtR	1.356	0.175	0.01	−0.005	0.025
WWI	2.396	0.017	0.028	0.005	0.052
Group 2[39–59)					
ABSI	7.268	< 0.001	0.162	0.118	0.206
BMI	3.009	0.003	0.035	0.012	0.057
BRI	2.472	0.013	0.024	0.005	0.043
CI	4.18	< 0.001	0.06	0..032	0.088
LAP	3.521	< 0.001	0.033	0.015	0.052
METS-IR	4.146	< 0.001	0.057	0.03	0.085
METS-VF	2.418	0.016	0.026	0.005	0.047
TyG	5.704	< 0.001	0.094	0.061	0.126
TyG-BMI	1.322	0.186	0.008	−0.004	0.02
TyG-WC	1.256	0.209	0.006	−0.003	0.015
VAI	5.727	< 0.001	0.097	0.064	0.131
WC	2.851	0.004	0.032	0.01	0.054
WHtR	2.467	0.014	0.024	0.005	0.043
WWI	4.778	< 0.001	0.069	0.041	0.097
Group 3[59-					
ABSI	7.268	< 0.001	0.162	0.118	0.206
BMI	3.009	0.003	0.035	0.012	0.057
BRI	2.472	0.013	0.024	0.005	0.043
CI	4.18	< 0.001	0.06	0..032	0.088
LAP	3.521	< 0.001	0.033	0.015	0.052
METS-IR	4.146	< 0.001	0.057	0.03	0.085
METS-VF	2.418	0.016	0.026	0.005	0.047
TyG	5.704	< 0.001	0.094	0.061	0.126
TyG-BMI	1.322	0.186	0.008	−0.004	0.02
TyG-WC	1.256	0.209	0.006	−0.003	0.015
VAI	5.727	< 0.001	0.097	0.064	0.131
WC	2.851	0.004	0.032	0.01	0.054
WHtR	2.467	0.014	0.024	0.005	0.043
WWI	4.778	< 0.001	0.069	0.041	0.097

Abbreviations: *AUC* Area under curve, *CIs* Confidence Intervals, *ABSI* A body shape index, *BMI* Body mass index, *BRI* Body roundness index, *CI* Conicity index, *LAP* Lipid accumulation product, *METS-IR* Metabolic score for insulin resistance, *METS-VF* Metabolical score for visceral fat, *TyG* Triglyceride-glucose index, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride glucose-waist circumference, *TyG-WHtR* Triglyceride glucose-waist to height ratio, *VAI* Visceral adiposity index, *WC* Waist circumference, *WHtR* Waist to height ratio, *WWI* Weight-adjusted-waist index

exploration and investigation in this particular field of study.

Strengths and limitations

This research boasts numerous impressive strengths that deserve acknowledgment. Initially, this study is notable for its scale, marking it as the most comprehensive investigation to date in exploring the potential correlation between 15 obesity- and lipid-related parameters with testosterone. The large sample size enabled in-depth analyses across various demographic subgroups, thereby reinforcing the robustness of the outcomes. Furthermore, the incorporation of high-quality data from the NHANES allowed the consideration of potential confounding variables that could influence the relationship between the 15 metrics and testosterone levels. Ultimately, the research took the weight into account during the process of data analysis, thereby improving the accuracy and dependability of the results. In addition, this study further grouped the age when exploring the discrimination ability of these 15 indexes, making the results more specific.

However, there are numerous limitations to be aware of in this study that require further attention. A key limitation is the use of the stusy design, which makes it difficult to definitively establish causation. In addition, some confounding factors that have not been excluded may affect the interpretability of the results. Moreover, due to limitations within the NHANES database, the identification of testosterone deficiency was based solely on total testosterone levels below 300 ng/dL, without considering associated symptoms or clinical signs. It is important

to recognize that the NHANES database only reflects the US population, underscoring the need for deeper research to validate the relationship between testosterone levels and factors linked to obesity and lipids in different national and regional populations.

Conclusion

This research emphasizes the significance of utilizing these 15 indicators as essential resources in both public health and clinical environments. These indicators make it easier to detect and address individuals in vulnerable population groups at an early stage. Notably, the TyG-WHtR index demonstrated the most potent discriminatory capacity for predicting TD across a broader population and specific age groups. For individuals presenting with metabolic disorders, medical practitioners are poised to gauge the risk of TD by scrutinizing these indices, which in turn can guide the development and deployment of tailored prevention strategies or interventions.

Abbreviations

TD	Testosterone deficiency
NHANES	The National Health and Nutrition Examination Survey
ROC	Receiver operating characteristic
HPGA	Hypothalamic-pituitary–gonadal axis
ABSI	A body shape index
BMI	Body mass index
BRI	Body roundness index
CI	Conicity index
LAP	Lipid accumulation product
METS-IR	Metabolic score for insulin resistance
METS-VF	Metabolic score for visceral fat
TyG	Triglyceride-glucose index
TyG-BMI	Triglyceride-glucose index–body mass index
TyG-WC	Triglyceride-glucose index-waist circumstance
TyG-WHtR	Triglyceride-glucose index-waist to height ratio
WHtR	Waist to height ratio
VAI	Visceral adiposity index
WC	Waist circumstance
WWI	Weight-adjusted-waist index
NAFLD	Nonalcoholic fatty liver disease
AUC	Area under the curve
OR	Odds ratio
GnRH	Gonadotropin-releasing hormone
TNF-α	Tumor necrosis factor-α
AMPK α	Adenosine 5′-monophosphate-activated protein kinase α

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02436-6.

Additional file 1.

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Authors' contributions

GW and ZS designed the study. GW, CQZ, and SJJ collected and analyzed the data and drafted the manuscript. FYD and LJK revised the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the NCHS Ethics Review Board. All patients and participants provided written informed consent to participate in the study.

Consent for publication

All participants provided informed permission for publication.

Competing interests

The authors declare no competing interests.

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