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Association between cardiometabolic index and risk of testosterone deficiency in adult men: a cross-sectional study

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Abstract

Background Metabolic health is closely related to testosterone levels, and the cardiometabolic index (CMI) is a novel metabolic evaluation metric that encompasses obesity and lipid metabolism. However, there is currently a lack of research on the relationship between CMI and testosterone, which is the objective of this study.

Methods This study utilized data from the National Health and Nutrition Examination Survey (NHANES) cycles from 2011 to 2016. Only adult males who completed physical measurements, lipid metabolism assessments, and testosterone measurements were included in the final analysis. The exposure variable CMI was analyzed both as a continuous variable and a categorical variable divided into quartiles. Testosterone was measured using the isotope dilution liquid chromatography-tandem mass spectrometry technique. Linear and logistic regression analyses were used to explore the relationship between CMI and total testosterone (TT) levels, as well as the risk of testosterone deficiency (TD). Smooth curve fittings were employed to visualize their linear relationships. Subgroup analyses were conducted to evaluate the stability of our results across different participant characteristics. Finally, ROC analysis was used to assess the performance of CMI in predicting TD.

Results A total of 2,747 participants were included in the analysis, including 552 with TD (20.10%). The average CMI of the sample was 1.59 ± 0.03, with TD participants having a higher CMI of 2.18 ± 0.08 compared to non-TD participants at 1.46 ± 0.03. Corresponding testosterone levels were 223.79 ± 3.69 ng/dL and 508.36 ± 5.73 ng/dL, respectively. After adjusting for all covariates, participants with higher CMI showed lower TT (β = -23.84, 95% CI: -33.94, -13.74, $p < 0.0001$) and a higher risk of TD (OR = 1.26, 95% CI: 1.08, 1.48, $p = 0.01$). When CMI was categorized into quartiles with Q1 as the reference, participants in Q4 exhibited significantly lower TT (β = -74.04, 95% CI: -106.01, -42.08, $p < 0.0001$) and a higher risk of TD (OR = 2.34, 95% CI: 1.18, 4.64, $p = 0.02$). Smooth curve fittings indicated a linear relationship between these variables. Subgroup analyses confirmed the stability of these associations across different population characteristics. ROC curve analysis demonstrated that CMI had good predictive performance for TD with a cut-off value of 1.126 and an AUC (95% CI) of 0.673 (0.649, 0.700).

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Conclusion CMI is associated with lower TT and a higher risk of TD, and it can predict the risk of TD. Using CMI for early detection and timely intervention could reduce the disease burden and promote reproductive health. Further prospective studies with large sample sizes are needed to validate these findings.

Keywords Cardiometabolic index, Testosterone, NHANES, Cross-sectional study, Predictive performance

Introduction

Testosterone is the primary androgen in males, predominantly secreted by Leydig cells in the testes under the regulation of the hypothalamic-pituitary-gonadal axis (HPGA), with a small amount also secreted by the adrenal glands [1]. Throughout a man's life, testosterone plays crucial roles at different stages of development. During the fetal period, it promotes the differentiation of the male reproductive tract and the masculinization of external genitalia [2]. In puberty, it stimulates growth, development, and the emergence of secondary sexual characteristics [3]. As men reach adulthood, testosterone plays more extensive and critical roles in both sexual functions (libido, erectile function, and spermatogenesis) and non-sexual functions (strength, cognition, cardiovascular health, and mental well-being) [4–6]. Unfortunately, the beneficial and critical functions of testosterone are often unsustainable. Studies indicate that testosterone levels begin to decline at an approximate rate of 1% per year after the age of 30 years old [7]. This decline is associated with various symptoms, including reduced libido, erectile dysfunction, cognitive decline, and metabolic disturbances, collectively referred to as testosterone deficiency (TD) syndrome or hypogonadism [8–10]. It is estimated that about 30% of men aged 40–70 years are affected by this condition, and the prevalence is expected to increase in the coming decades as life expectancy rises [11]. In the United States alone, projections suggest that nearly 6.5 million men will be affected by varying degrees of testosterone decline by 2025 [12]. This has emerged as an increasingly alarming global health concern.

Currently, it has been observed that TD is more prevalent in individuals with metabolic complications, including obesity, diabetes, and lipid metabolism disorders, which strongly supports the relationship between metabolic health and testosterone [13]. Guided by this perspective, numerous studies have explored the relationship between them using a variety of assessment indicators [14, 15]. Recently, the cardiometabolic index (CMI), calculated using waist-to-height ratio (WHtR), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c), has emerged as a new metric in the research community to reflect metabolic health by assessing both obesity and lipid profile [16]. Furthermore, the influx of recent studies has shown that CMI is closely related to diabetes, hypertension, atherosclerosis, non-alcoholic fatty liver disease, and chronic kidney diseases, and performs well in predicting the occurrence and progression of these conditions [17–20]. However, no studies have yet investigated the relationship between CMI and testosterone levels, which remains an open question.

Given the critical role of testosterone in male health and the rising prevalence of TD, it is essential to understand the relationship between CMI and testosterone levels. Therefore, based on the National Health and Nutrition Examination Survey (NHANES) database, we aim to explore the association between them in adult men in the United States. Our findings are expected to provide robust evidence regarding the role of cardiometabolic health in testosterone regulation and offer valuable insights for clinicians and healthcare professionals in their daily practice. Additionally, this research may pave the way for future studies to further investigate the complex interplay between metabolic health and reproductive health.

Materials and methods

Study design and participants

The NHANES is a publicly accessible program designed to assess the health and nutritional status of individuals across all age groups in the United States. It is overseen and conducted by the National Center for Health Statistics (NCHS) at the US Centers for Disease Control and Prevention (CDC). The survey is carried out biennially, enrolling approximately 5,000 individuals from various counties nationwide. The collected data are made available to researchers globally and include demographic, dietary, physical examination, laboratory, and questionnaire data. The sample collection employs a complex, multistage, probability sampling design to ensure unbiased estimates of the national population. More information about NHANES methods and protocols can be found on their official website. All study designs and protocols of NHANES were approved by the NCHS Research Ethics Review Board, and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

Initially, a total of 29,902 participants were included from three NHANES cycles: 2011–2012, 2013–2014, and 2015–2016. Figure 1 illustrates the detailed sample selection process. Specific exclusion criteria were applied as follows: (1) Female participants (n=15,151), (2) Participants under the age of 20 (n=6,506), (3) Participants without testosterone data or CMI-related information (n=4,158), (4) Participants without data on potential covariates (n=1,340). After excluding participants who

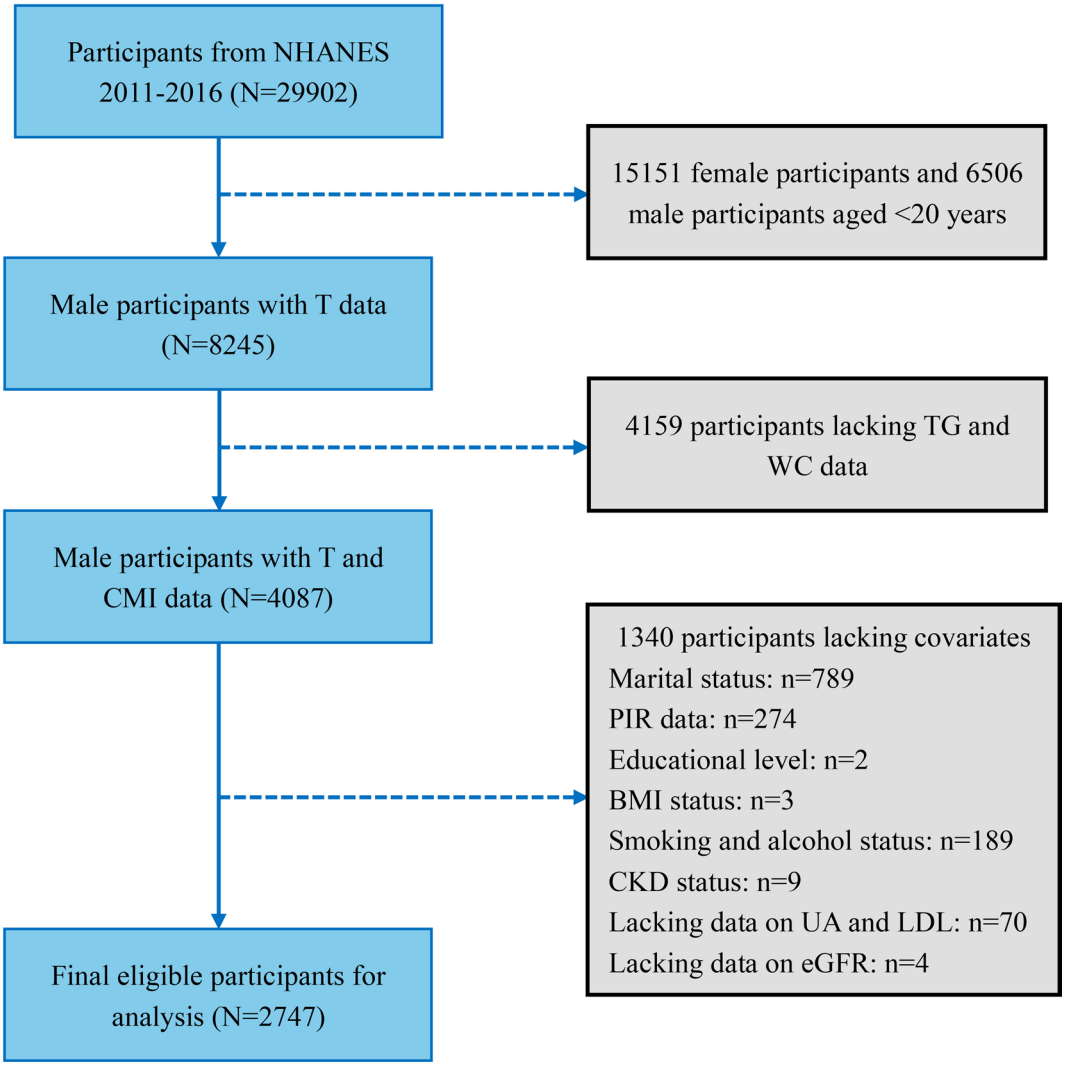

Fig. 1 Flowchart of participant selection and exclusion criteria. NHANES, National Health and Nutrition Examination Survey; T, Testosterone; TG, Triglycerides; WC, Waist Circumference; PIR, Poverty Income Ratio; BMI, Body Mass Index; CKD, Chronic Kidney Disease; UA, Uric Acid; LDL, Low-Density Lipoprotein; eGFR, Estimated Glomerular Filtration Rate

met the above criteria, a total of 2,747 participants were retained and included in the final statistical analysis.

Calculation of the CMI

According to the formula, the CMI is calculated by combining blood biochemical indices and body measurement indices, including triglycerides (TG), HDL-c, waist circumference (WC), and height [16]. The calculation formula is:

$$CMI=(TG/HDL\text{-}c)\times(WC/Height).$$

Blood sample collection and processing were conducted by trained technicians at the Mobile Examination Center (MEC) following standardized sample handling procedures. The biochemical measurements included total cholesterol (TC), TG, HDL-c, low-density lipoprotein cholesterol (LDL-C), uric acid (UA), and estimated glomerular filtration rate (eGFR). All participants were required to fast for more than 8 h before blood collection. Body measurements were also completed at the MEC, including height, weight, and WC.

Definition of the outcomes

Serum total testosterone (TT) and the clinically defined testosterone deficiency (TD) were our two primary outcomes. To account for the diurnal variation in hormone secretion, we selected only adult men who completed their laboratory examinations in the morning, ensuring a more representative measurement of TT levels. Testosterone measurements were performed using isotope dilution high-performance liquid chromatography tandem mass spectrometry (ID-LC-MS/MS), a method capable of high-throughput processing of large sample volumes with a detection limit of 0.75 ng/dL. According to the guidelines of the American Urological Association

(AUA), the diagnosis of TD is based on a combination of TT levels < 300 ng/dL and corresponding clinical symptoms [21]. Due to database limitations and the inability to access participants' clinical symptoms, we cautiously used TT < 300 ng/dL as the criterion for diagnosing TD, consistent with previous related studies [15, 22–24].

Assessments of covariates

Potential covariates were selected based on previous literature and included factors that might influence the relationship between testosterone and CMI. These covariates included demographics, biochemical indices, lifestyle habits, and medical comorbidities. Demographic characteristics included age (categorized into 20-40y, 40-60y, and > 60y), BMI (categorized into < 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2), family income (measured by the Poverty Income Ratio (PIR) and categorized into < 1.3, 1.3–3.5, and > 3.5), race (Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Race, and Other Hispanic), education level (less than high school, high school graduate, and more than high school), and marital status (categorized as Solitude and Cohabitation). Biochemical indices included LDL-c, TG, UA, and eGFR.

Lifestyle habits included alcohol consumption and smoking. Alcohol consumption was defined based on whether the average annual intake exceeded 12 drinks, classifying participants as drinkers or non-drinkers. Smoking status was determined based on whether participants had smoked more than 100 cigarettes in their lifetime and whether they currently smoked. Participants were classified as current smokers if both conditions were met, non-smokers if neither condition was met, and former smokers otherwise. Medical comorbidities included hypertension, diabetes, hyperlipidemia, cardiovascular disease (CVD), and chronic kidney disease (CKD). Hypertension was defined as having a previous diagnosis, taking antihypertensive medication, or having a measured blood pressure ≥ 140/90 mmHg. Diabetes was defined as having a previous diagnosis, taking antidiabetic medication, hemoglobin A1c level ≥ 6.5%, fasting plasma glucose level ≥ 126 mg/dL, or a plasma glucose level ≥ 200 mg/dL at 2 h after an oral glucose tolerance test (OGTT). Prediabetes was diagnosed according to the criteria set by the American Diabetes Association. Specifically, prediabetes was defined as having one of the following: (1) FPG levels between 100 and 125 mg/dL, (2) a 2-hour plasma glucose level between 140 and 199 mg/dL after OGTT, or (3) Hemoglobin A1c levels between 5.7% and 6.4%. Hyperlipidemia was defined as having TC ≥ 5.17 mmol/L, LDL-c ≥ 3.36 mmol/L, HDL-c < 1.03 mmol/L, or TG ≥ 1.69 mmol/L. CVD was defined based on a history of congestive heart failure, coronary heart disease, angina, or heart attack. CKD was defined as having an eGFR < 60 ml/min per 1.73 m^2 according to the CKD Epidemiology Collaboration creatinine equation, equivalent to CKD stages 3–4 [25].

Statistical analysis

Based on the complex sampling design of NHANES, all statistical analyses applied appropriate sample weights to each participant to ensure the representativeness of the statistical results. When describing the basic characteristics of the sample, continuous variables were presented as weighted means ± standard errors (SE), while categorical variables were expressed as weighted percentages. For group comparisons, weighted linear regression was used for continuous variables and weighted chi-square tests for categorical variables. Linear regression analysis and logistic regression analysis were employed for different outcomes. The results of the linear regression analysis were expressed as beta coefficients and 95% confidence intervals (CIs), while the results of the logistic regression analysis were expressed as odds ratios (ORs) and 95% CIs. To improve the stability and reliability of our results, we used different models to adjust for potential covariates in both types of regression analyses. Model 1 included only the exposure variable. Model 2 adjusted for age, race, marital status, education, PIR, and BMI. Model 3 further adjusted for all remaining potential covariates, including UA, TC, LDL, eGFR, lifestyle habits, and medical comorbidities. During the analysis, CMI was further converted into quartile variables for analysis, with Q1 as the reference. We also conducted trend tests for the quartile variables of CMI using linear regression analysis.

To test the stability of the statistical results across different population characteristics, we conducted subgroup analyses and interaction tests for key demographic and health-related factors, including age, BMI, smoking status, DM, hypertension, CVD, and CKD. To investigate whether CMI is linearly related to TT or the risk of TD, we used smooth curve fitting and generalized additive models. Finally, ROC curve analysis was employed to compare the predictive diagnostic value of CMI for TD, expressed as the area under the curve (AUC) and 95% CI. All statistical analyses were conducted using EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc.) and the statistical software packages R (http://www.R-project.org; The R Foundation). Statistical significance was defined as a two-sided p-value of less than 0.05.

Results

Baseline characteristics of research population

The final sample included a total of 2,747 participants with a mean age of 47.6 years. Among these, 552 participants were classified as having TD with a mean age of 51.6 years, while 2,195 participants were classified as

Table 1 Baseline characteristics of study participants stratified by TD status, weighted

Characteristics	Total participants	Participants without TD	Participants with TD	*P* value
Participants number	2747	2195	552	
Age, years	47.55 ± 0.42	46.64 ± 0.54	51.59 ± 0.75	< 0.0001
BMI, kg/m^2	28.72 ± 0.16	27.80 ± 0.15	32.82 ± 0.47	< 0.0001
WC, cm	101.88 ± 0.45	99.30 ± 0.46	113.34 ± 1.23	< 0.0001
Height, cm	175.91 ± 0.21	175.83 ± 0.19	176.27 ± 0.51	0.36
TC, mg/dl	186.53 ± 1.08	186.78 ± 1.12	185.45 ± 2.37	0.59
TG, mg/dl	117.72 ± 1.91	112.77 ± 1.92	139.71 ± 4.04	< 0.0001
HDL-c, mg/dl	49.69 ± 0.44	50.69 ± 0.48	45.27 ± 0.70	< 0.0001
LDL, mg/dl	113.29 ± 0.85	113.53 ± 0.92	112.24 ± 2.07	0.57
UA, mg/dl	6.10 ± 0.03	6.00 ± 0.03	6.53 ± 0.07	< 0.0001
eGFR	93.76 ± 0.53	94.40 ± 0.59	90.94 ± 0.84	< 0.001
CMI	1.59 ± 0.03	1.46 ± 0.03	2.18 ± 0.08	< 0.0001
Total testosterone, ng/dl	456.10 ± 5.18	508.36 ± 5.73	223.79 ± 3.69	< 0.0001
Age group, %				< 0.001
20-40y	35.37	37.75	24.75	
40-60y	37.42	36.50	41.47	
≥ 60y	27.22	25.74	33.78	
BMI, %				< 0.0001
Normal (< 25 kg/m^2)	26.97	30.54	11.13	
Overweight (25–30 kg/m^2)	38.82	40.53	31.22	
Obese (≥ 30 kg/m^2)	34.21	28.93	57.65	
PIR, %				0.67
< 1.3	20.60	20.52	20.97	
1.3–3.5	35.40	35.01	37.12	
>=3.5	44.00	44.47	41.91	
Race, %				0.83
Non-Hispanic White	8.49	8.64	7.81	
Non-Hispanic Black	69.73	69.35	71.44	
Mexican American	8.29	8.32	8.14	
Other Race	7.39	7.56	6.62	
Other Hispanic	6.10	6.12	5.99	
Education, %				0.72
Less than high school	15.90	15.59	17.30	
High school	22.47	22.44	22.63	
More than high school	61.63	61.98	60.08	
Marital status, %				0.40
Solitude	33.07	33.54	30.97	
Cohabitation	66.93	66.46	69.03	
Smoke, %				< 0.0001
Never	48.69	49.92	43.19	
Former	30.37	27.79	41.83	
Current	20.94	22.29	14.99	
Alcohol, %				0.01
No	20.50	18.90	27.59	
Yes	79.50	81.10	72.41	
Hypertension, %				< 0.001
No	60.81	63.25	49.95	
Yes	39.19	36.75	50.05	
Diabetes, %				< 0.0001
No	63.66	68.35	42.78	
Prediabetes	20.05	18.65	26.30	
Yes	16.29	13.00	30.93	
Hyperlipidemia, %				< 0.0001

Table 1 (continued)

Characteristics	Total participants	Participants without TD	Participants with TD	*P* value
No	32.00	35.21	17.75	
Yes	68.00	64.79	82.25	
CVD, %				< 0.001
No	90.26	91.42	85.07	
Yes	9.74	8.58	14.93	
CKD, %				< 0.0001
No	88.57	90.15	81.57	
Yes	11.43	9.85	18.43	

Abbreviations:

TD, Testosterone Deficiency; BMI, Body Mass Index; WC, Waist Circumference; TC, Total Cholesterol; TG, Triglycerides; HDL-c, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; CMI, Cardiometabolic Index; PIR, Poverty Income Ratio; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease

Statistical Analysis:

Continuous variables are presented as mean ± standard error. Categorical variables are presented as weighted percentages. Group comparisons were made using weighted linear regression analysis for continuous variables and weighted chi-square tests for categorical variables. A p-value of less than 0.05 was considered statistically significant

Table 2 Linear and logistic regression analyses for the association of continuous and quartile CMI with TT and risk of TD, weighted

	Model 1	Model 2	Model 3
Total testosterone (ng/dl)-β (95%CI) p-value			
Continuous CMI	-48.82(-56.52, -41.11), < 0.0001	-27.2(-36.42, -17.98), < 0.0001	-23.84(-33.94, -13.74), < 0.0001
Quartile 1	Reference	Reference	Reference
Quartile 2	-37.8(-66.16, -9.44), 0.01	-10.77(-35.76, 14.22), 0.39	-13.92(-41.94, 14.09), 0.31
Quartile 3	-108.41(-132.32, -84.50), < 0.0001	-57.06(-82.14, -31.98), < 0.0001	-57.65(-87.36, -27.94), < 0.001
Quartile 4	-153.14(-176.56, -129.73), < 0.0001	-82.46(-110.97, -53.95), < 0.0001	-74.04(-106.01, -42.08), < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001
Testosterone deficiency-OR (95% CI) p-value			
Continuous CMI	1.60(1.45,1.76), < 0.0001	1.34(1.20,1.51), < 0.0001	1.26(1.08,1.48), 0.01
Quartile 1	Reference	Reference	Reference
Quartile 2	1.78(1.03,3.08), 0.04	1.31(0.73,2.37), 0.01	1.33(0.73,2.44), 0.34
Quartile 3	3.52(2.19,5.67), < 0.0001	2.03(1.16,3.57), < 0.001	1.83(1.00,3.34), 0.04
Quartile 4	5.88(3.69,9.36), < 0.0001	2.91(1.62,5.23), < 0.0001	2.34(1.18,4.64), 0.02
P for trend	< 0.0001	< 0.001	0.015

Abbreviations:

CMI, Cardiometabolic Index; TT, Total Testosterone; TD, Testosterone Deficiency; BMI, Body Mass Index; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; PIR, Poverty Income Ratio; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; β, Beta; OR, Odds Ratio; CI, Confidence Interval

Statistical Analysis:

Model 1: No variable adjustment

Model 2: Adjusted for age, race, marital status, education, PIR, and BMI

Model 3: Further adjusted for TC, LDL, UA, eGFR, smoking, alcohol consumption, history of hypertension, diabetes, hyperlipidemia, CVD, and CKD

non-TD with a mean age of 46.6 years. Table 1 presents the detailed population characteristics stratified by TD status. Compared to non-TD participants, those with TD had higher CMI values (2.18 ± 0.08 vs. 1.46 ± 0.03). Additionally, TD participants exhibited higher BMI, WC, TG, and UA levels, while having lower HDL-c and eGFR levels. Moreover, there were notable differences in lifestyle habits and the distribution of medical comorbidities between the two groups. TD participants had a higher prevalence of medical comorbidities, while the proportion of smokers and drinkers was lower compared to non-TD participants.

Association of CMI with TT and TD

When considering CMI as the exposure and TT as the outcome, multiple linear regression analysis showed that an increase in CMI was negatively associated with total testosterone levels (Model 3: -23.84 (-33.94, -13.74), $P < 0.0001$). When CMI was converted into quartile variables with Q1 as the reference, the negative association remained statistically significant (Model 3 Q4: -74.04 (-106.01, -42.08), $P < 0.0001$). Additionally, all trend tests had p-values less than 0.05, indicating a linear relationship. When considering CMI as the exposure and the risk of TD as the outcome, an increase in CMI increased the risk of TD (Model 3: 1.26 (1.08, 1.48), $P = 0.01$). Similarly, when CMI was converted into quartile variables with Q1 as the reference, participants in Q4 had an increased risk of TD (Model 3: 2.34 (1.18, 4.64), $P = 0.02$). Trend tests also showed significant differences, confirming a linear association. Detailed regression analysis results are presented in Table 2. To compare the correlation of CMI with other metabolic markers, including BMI, LDL, TG, and IR, with testosterone levels, we also incorporated these variables into regression models for analysis. The results showed that CMI exhibited the strongest

association with low testosterone levels and the risk of testosterone deficiency (Table S1). Finally, smooth curve fitting provides a more intuitive display of whether there is a linear trend between CMI, TT, and TD risk. The results indicate a linear trend for both CMI and TT, as well as the risk of TD, which are depicted in Fig. 2A and B, respectively.

Subgroup analysis and predictive performance

Subgroup analyses were conducted using logistic regression analysis, consistent with the primary analysis, with TT and TD as outcomes. When TT was the outcome, linear regression analysis indicated that the negative association between CMI and TT remained stable across different subgroups with no significant interactions. The results are shown in Table 3. As shown in Fig. 3, when TD was the outcome, the positive association between CMI and the risk of TD was primarily observed in participants aged over 60 years (OR (95%CI): 1.51 (1.17 to 1.95), $P=0.003$), those with obesity (OR (95%CI): 1.55 (1.25 to 1.93), $P<0.001$), non-smokers (OR (95%CI): 1.28 (1.03 to 1.61), $P=0.03$), former smokers (OR (95%CI): 1.47 (1.17 to 1.85), $P=0.02$), participants with diabetes (OR (95%CI): 1.40 (1.05 to 1.85), $P=0.02$), and those with hypertension (OR (95%CI): 1.38 (1.13 to 1.67), $P=0.002$). For participants with or without CVD and CKD, the association remained significant regardless of the presence of these comorbidities.

Similarly, when CMI was converted into quartile variables with Q1 as the reference for subgroup analysis, the linear regression analysis results remained significant across subgroups with no interactions. Trend tests consistently showed p-values < 0.05 (Table 4). As shown in Fig. 4, compared to Q1, participants in Q4 still showed positive associations in subgroups including those aged over 60 years (OR (95%CI): 3.36 (1.25 to 9.01)), those with obesity (OR (95%CI): 4.53 (1.76 to 11.69)), non-smokers (OR (95%CI): 2.56 (1.05 to 6.24)), former smokers (OR (95%CI): 3.95 (1.49 to 10.49)), participants with hypertension (OR (95%CI): 3.29 (1.52 to 7.12)), and those with CVD (OR (95%CI): 7.48 (2.13 to 26.31)).

Figure 5 details the predictive value of CMI for TD, including the best threshold, sensitivity, specificity, and AUC with 95% CI. The results indicate that CMI has a good predictive value for TD, with a cut-off value of 1.126. Overall, this demonstrates that CMI is stably associated with TT and TD and exhibits good predictive value with an AUC (95% CI) of 0.673 (0.649, 0.700).

Discussion

To our knowledge, this is the first study to investigate the relationship between the CMI and testosterone. Utilizing the nationally representative NHANES database, we meticulously adjusted for covariates that could influence the relationship between CMI and testosterone. Furthermore, we conducted subgroup analyses across different population characteristics and supplemented our findings with ROC analysis to assess the predictive performance of CMI for TD. Our results indicate that higher levels of CMI are associated with lower TT levels and a higher risk of TD. This linear relationship remained stable across various subgroups with no interactions. Additionally, CMI demonstrated good predictive performance for TD.

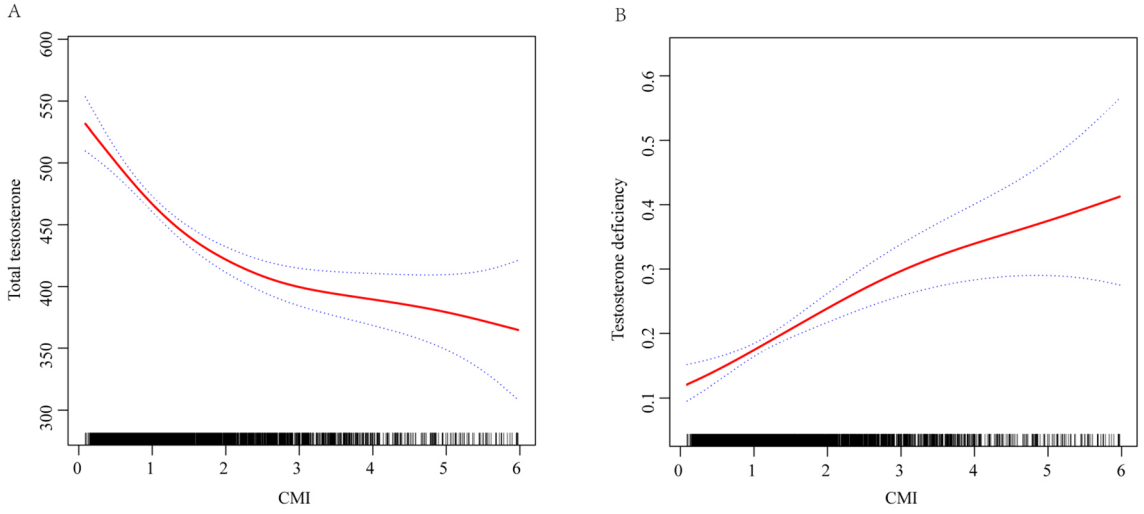

Fig. 2 Graphics of smooth curve fittings between the CMI and TT (**A**) and TD (**B**). All analyses were adjusted using Model 3, which includes adjustments for age, race, marital status, education, PIR, BMI, TC, LDL, UA, eGFR, smoking, alcohol consumption, history of hypertension, diabetes, hyperlipidemia, CVD, and CKD. The dashed lines represent the 95% CI from the fit. The solid red line represents the smooth curve fit between variables. CMI, Cardiometabolic Index; TT, Total Testosterone; TD, Testosterone Deficiency; PIR, Poverty Income Ratio; BMI, Body Mass Index; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease

Table 3 Subgroup analysis on the association of continuous CMI with TT, weighted

Subgroup	β (95%CI)	*P* value	*P* for interaction
Age group			0.52
20-40y	-30.67(-51.53, -9.82)	0.01	
40-60y	-19.08(-28.10, -10.07)	< 0.001	
>60y	-28.66(-46.79, -10.53)	0.003	
BMI			0.07
Normal	-37.04(-53.81, -20.28)	< 0.001	
Overweight	-35.29(-47.21, -23.37)	< 0.0001	
Obese	-15.99(-30.58, -1.40)	0.03	
Smoking status			0.91
Never	-28.78(-42.25, -15.32)	< 0.001	
Former	-21.56(-39.58, -3.55)	0.02	
Current	-27.19(-48.37, -6.01)	0.01	
Diabetes			0.54
No	-28.41(-41.20, -15.61)	< 0.001	
Borderline	-18.57(-39.51, -2.37)	0.04	
Yes	-22.18(-39.47, -4.90)	0.01	
Hypertension			0.37
No	-24.4(-34.13, -14.68)	< 0.0001	
Yes	-24.93(-40.10, -9.76)	0.002	
CVD			0.74
No	-22.66(-33.97, -11.35)	< 0.001	
Yes	-36.44(-59.78, -13.10)	0.004	
CKD			0.60
No	-22.64(-32.97, -12.32)	< 0.001	
Yes	-36.09(-56.29, -15.90)	0.001	

Abbreviations:

CMI, Cardiometabolic Index; TT, Total Testosterone; BMI, Body Mass Index; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; PIR, Poverty Income Ratio; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; β, Beta; 95%CI, 95% Confidence Interval

Statistical Analysis:

All analyses were adjusted for all variables included in Model 3, except for the stratifying variable. The variables adjusted for included age, race, marital status, education, PIR, BMI, TC, LDL, UA, eGFR, smoking, alcohol consumption, history of hypertension, diabetes, hyperlipidemia, CVD, and CKD

Obesity has long been considered a modifiable risk factor for the development of delayed testicular development [26, 27]. Several studies have shown a significant negative correlation between the degree of obesity and levels of total testosterone, free testosterone, and bioavailable testosterone (free and albumin-bound) [28–32]. This association is consistently observed across different age groups [33]. Furthermore, some studies have reported a negative correlation between the level of obesity and total testosterone [34–38], independent of metabolic syndrome (MetS) [39]. Specifically, multiple studies have demonstrated a relationship between the degree of obesity and testosterone levels. Plasma total testosterone, free testosterone, and SHBG levels are negatively correlated with WC [31, 32], and both BMI and WC are related to testosterone deficiency in male patients with diabetes [36, 37]. Common complications of male obesity include hypogonadism (low testosterone levels accompanied by signs and symptoms) [40, 41]. Additionally, a meta-analysis indicated that weight loss through exercise, diet, or bariatric surgery significantly increases testosterone levels in men [42]. Currently, MetS (including obesity, dyslipidemia, hypertension, and IR) is closely associated with TD [43],, and several clinical studies have shown that MetS is negatively correlated with total testosterone levels and is a risk factor for TD [35, 39, 44, 45]. IR, as a central component of MetS, is closely associated with TD [43]. It reduces the secretion of testosterone by Leydig cells in the testes [46] and is independently associated with low testosterone levels [47].

CMI, a new indicator first proposed by Wakabayashi et al., combines lipid and obesity markers (TG/HDL-c, WHtR) and can serve as a valuable marker for identifying diabetes [16]. CMI, which integrates indices of abdominal obesity and dyslipidemia, has been demonstrated to be a reliable and independent clinical indicator of adiposity. Compared to traditional anthropometric measurements, CMI shows a stronger correlation with metabolic abnormalities [48, 49]. Additionally, related studies have indicated that CMI is closely associated with obesity-related diseases and cardiovascular dysfunctions, including hyperuricemia, non-alcoholic fatty liver disease, and erectile dysfunction [50–52]. A recent NHANES study showed that CMI was positively associated with increased IR, IFG, and T2DM [17]. Given the close relationship between obesity, metabolic syndrome, and TD, there may also be a link between CMI and TD, and our study demonstrates that CMI has good predictive performance for TD.

The exact mechanisms associated with CMI and TD need to be further explored. CMI integrates dyslipidemia and abdominal obesity indices, which are key drivers of metabolic disorders. TG/HDL-c is closely associated with metabolic disorders, obesity, and IR [53]. High plasma TG levels can reduce the number of insulin receptors on adipocytes, preventing insulin from binding to its receptors, thereby leading to diabetes [54]. Additionally, obese individuals with a high WHtR impede glucose transport activity, limiting insulin's contribution to glucose metabolism, resulting in IR [55]. Excess adipose tissue can promote IR by altering the inflammatory microenvironment and enhancing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), leading to low-grade chronic inflammation and oxidative stress [56, 57].

In our study, TD was diagnosed based solely on total testosterone levels below 300 ng/dL, without considering associated clinical symptoms such as reduced libido, fatigue, and muscle loss [58]. This could lead to the inclusion of individuals with normal free testosterone levels in the TD group, which may exaggerate the impact of metabolic factors on the risk of TD. Additionally, when

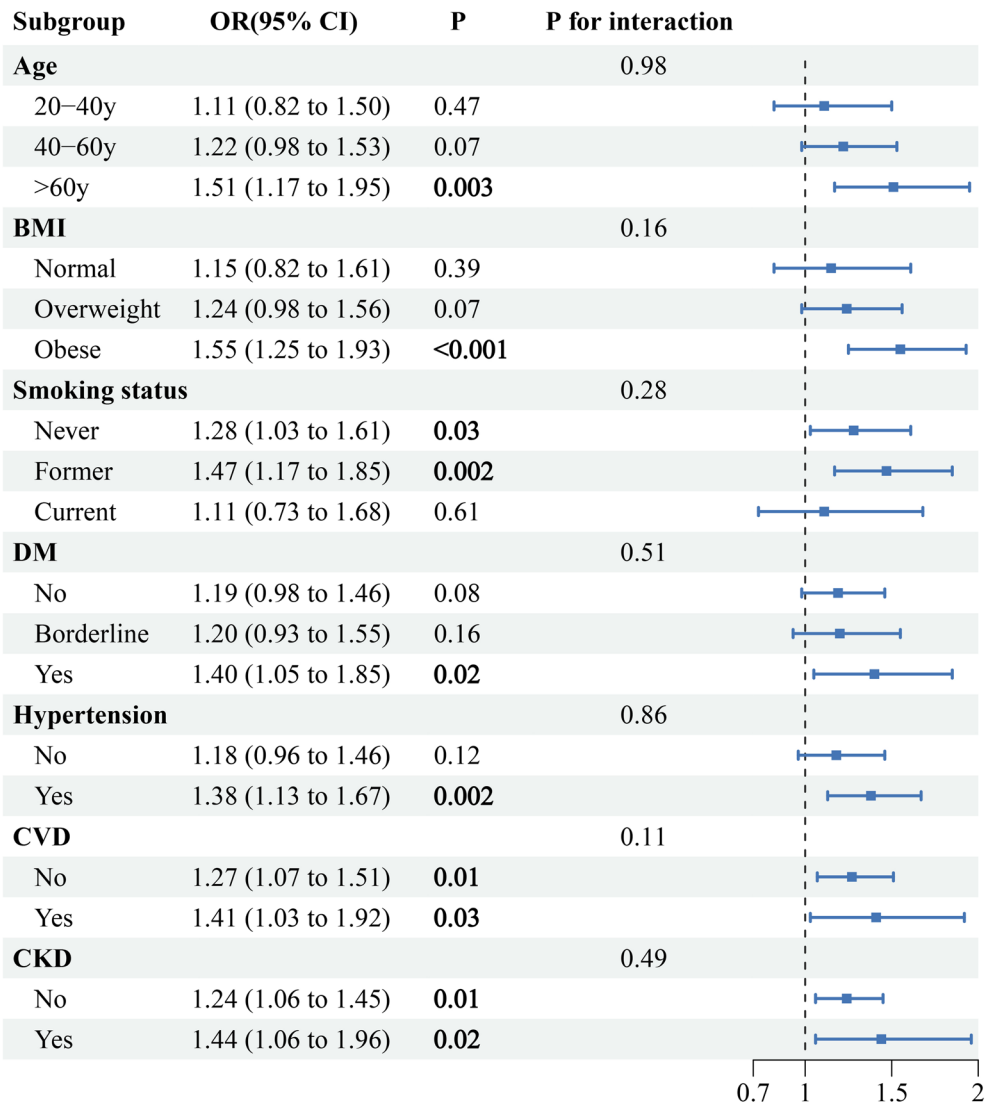

Fig. 3 Subgroup analysis on the association of continuous CMI with risk of TD, weighted. All analyses were adjusted for all variables included in Model 3, except for the stratifying variable. This includes adjustments for age, race, marital status, education, PIR, BMI, TC, LDL, UA, eGFR, smoking, alcohol consumption, history of hypertension, DM, hyperlipidemia, CVD, and CKD. CMI, Cardiometabolic Index; TD, Testosterone Deficiency; PIR, Poverty Income Ratio; BMI, Body Mass Index; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; DM, Diabetes Mellitus; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; OR, Odds Ratio; 95% CI, 95% Confidence Interval

exploring the influence of metabolic factors on testosterone levels, we did not account for changes in estrogen, SHBG, and LH [59]. Obesity, for instance, exacerbates the conversion of testosterone to estrogen through increased aromatase activity in adipose tissue, which can further reduce testosterone levels. However, in individuals with metabolic abnormalities, chronic inflammation may lower SHBG levels, leading to an increase in free testosterone despite lower total testosterone [60]. This phenomenon could mask the effects of TD in individuals with obesity and metabolic syndrome, as free testosterone is the active form that exerts biological effects on target tissues. Therefore, a more comprehensive evaluation, including SHBG and estrogen levels, would provide a clearer understanding of the hormonal balance in these populations.

Finally, while we focused on testosterone deficiency as a key factor in our study, it is important to consider the potential influence of prediabetes on TD. Individuals with prediabetes often experience insulin resistance, which can disrupt testosterone metabolism and increase the risk of TD [23]. Previous studies have shown that insulin resistance and other components of metabolic syndrome are frequently associated with lower testosterone levels [61]. The relationship between prediabetes and TD is a critical area for further research, as prediabetes may serve as an early indicator of metabolic disturbances that contribute to the development of TD in men

Table 4 Subgroup analysis on the association of quartile CMI with TT, weighted

Subgroup	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend	*P* for interaction
Age group						0.70
20-40y	Reference	-10.99(-48.51, 26.53)	-71.61(-107.96, -35.25)	-94.16(-146.37, -41.95)	< 0.001	
40-60y	Reference	-13.58(-64.27, 37.11)	-56.3(-97.01, -15.59)	-64.91(-110.23, -19.59)	0.001	
>60y	Reference	-16.01(-71.58, 39.55)	-36.71(-110.53, 37.11)	-74.9(-137.25, -12.54)	0.04	
BMI						0.14
Normal	Reference	-5.17(-50.70, 40.37)	-64.45(-113.25, -15.66)	-56.37(-102.48, -10.26)	0.01	
Overweight	Reference	-11.44(-51.72, 28.84)	-57.07(-102.74, -11.40)	-108.11(-152.22, -64.00)	< 0.0001	
Obese	Reference	-9.98(-66.93, 46.96)	-32.97(-85.42, 19.48)	-47.52(-93.23, -1.81)	0.02	
Smoking status						0.38
Never	Reference	3.88(-30.58, 38.33)	-43.4(-86.48, -0.32)	-81.45(-128.73, -34.17)	< 0.001	
Former	Reference	-24.84(-84.37, 34.69)	-74.01(-143.72, -4.30)	-75.02(-132.90, -17.13)	0.01	
Current	Reference	-52.03(-107.57, 3.51)	-76.16(-129.11, -23.21)	-82.9(-142.42, -23.37)	0.01	
Diabetes						0.19
No	Reference	-17.45(-92.94,58.04)	3.44(-82.02,88.90)	-55.65(-135.02,23.73)	0.13	
Borderline	Reference	-65.9(-119.03, -12.77)	-96.17(-148.38, -43.96)	-105.76(-159.01, -52.52)	0.001	
Yes	Reference	-2.34(-36.48, 31.79)	-63.94(-95.39, -32.48)	-68.44(-109.24, -27.64)	< 0.001	
Hypertension						0.02
No	Reference	12.66(-18.74, 44.06)	-49.79(-85.24, -14.35)	-61.59(-95.56, -27.62)	< 0.001	
Yes	Reference	-71.78(-118.77, -24.78)	-80.42(-124.98, -35.86)	-109.22(-156.83, -61.62)	< 0.001	
CVD						0.14
No	Reference	-8.34(-38.44, 21.76)	-48.6(-80.36, -16.84)	-67.78(-105.62, -29.94)	< 0.001	
Yes	Reference	-56.67(-129.74, 16.40)	-114.65(-189.56, -39.74)	-133.46(-214.42, -52.51)	0.001	
CKD						0.53
No	Reference	-16.31(-45.01, 12.40)	-55.84(-86.92, -24.76)	-71.45(-105.44, -37.45)	< 0.0001	
Yes	Reference	29.56(-41.57,100.68)	-31.1(-103.63, 41.42)	-100.04(-178.29, -21.80)	0.01	

Abbreviations:

CMI, Cardiometabolic Index; TT, Total Testosterone; BMI, Body Mass Index; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; PIR, Poverty Income Ratio; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; β, Beta; 95%CI, 95% Confidence Interval

Statistical Analysis:

All analyses were adjusted for all variables included in Model 3, except for the stratifying variable. The variables adjusted for included age, race, marital status, education, PIR, BMI, TC, LDL, UA, eGFR, smoking, alcohol consumption, history of hypertension, diabetes, hyperlipidemia, CVD, and CKD

[43]. Understanding how prediabetes affects testosterone levels and contributes to the onset of TD will help refine treatment strategies and improve patient care.

However, it is important to acknowledge the limitations inherent in our study, which necessitate cautious interpretation of our results. First, due to the inherent limitations of a cross-sectional study, the observed association between CMI and testosterone levels should be interpreted as a correlation rather than a causal relationship. Second, our diagnosis of TD was based solely on a single testosterone measurement without considering associated clinical symptoms, a limitation imposed by the NHANES database. Third, although we adjusted for many potential covariates that could influence the relationship between CMI and testosterone levels, there may be other unmeasured or unconsidered variables that could confound our results. Finally, given that our study utilized the AUA's definition of TD, which may differ from other regional guidelines, the applicability of our findings to populations with different TD cutoffs should be approached with caution. Further studies conducted in different regions or using alternative definitions for TD are warranted to validate our findings. However, these limitations do not undermine the validity of our findings but rather highlight the need for future research to confirm our results and to explore whether early intervention in CMI can reduce the burden of TD and further promote male reproductive health.

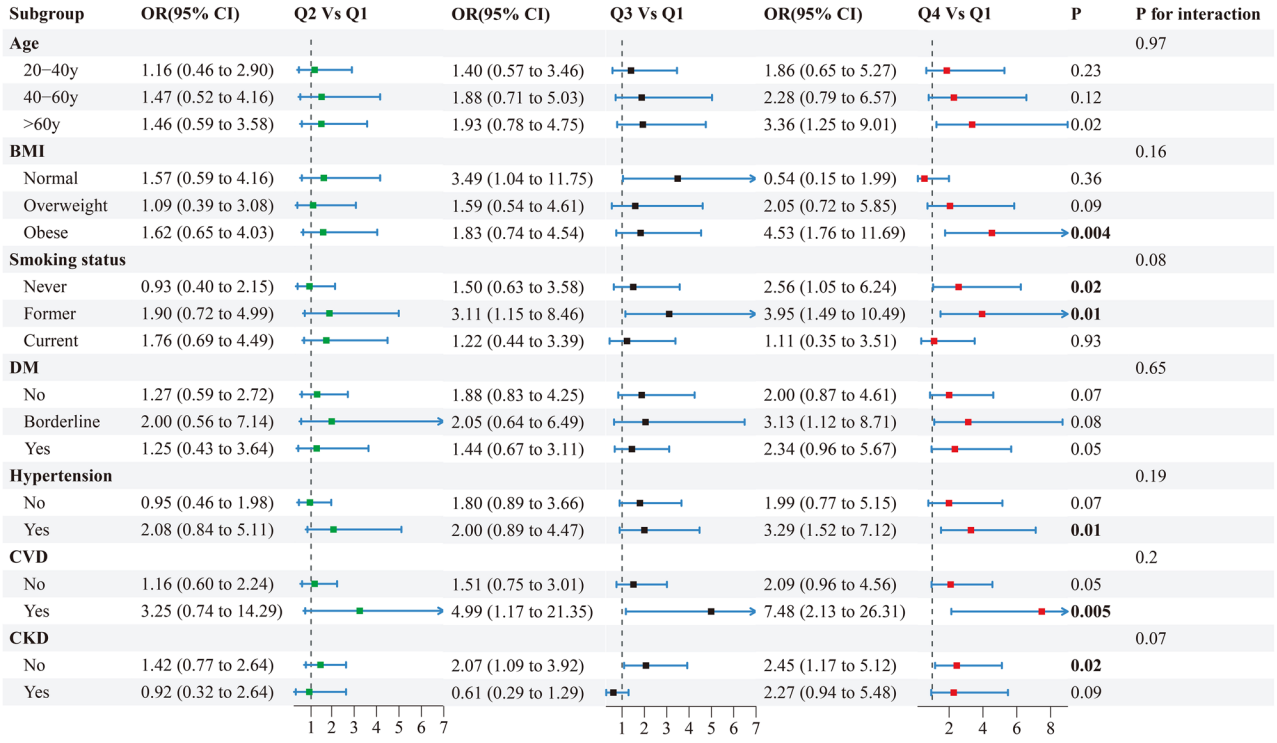

Fig. 4 Subgroup analysis on the association of quartile CMI with risk of TD, weighted. All analyses were adjusted for all variables included in Model 3, except for the stratifying variable. This includes adjustments for age, race, marital status, education, PIR, BMI, TC, LDL, UA, eGFR, smoking, alcohol consumption, history of hypertension, DM, hyperlipidemia, CVD, and CKD. CMI, Cardiometabolic Index; Q1-Q4: Quartile 1-quartile 4; TD, Testosterone Deficiency; PIR, Poverty Income Ratio; BMI, Body Mass Index; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; UA, Uric Acid; eGFR, Estimated Glomerular Filtration Rate; DM, Diabetes Mellitus; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; OR, Odds Ratio; 95% CI, 95% Confidence Interval

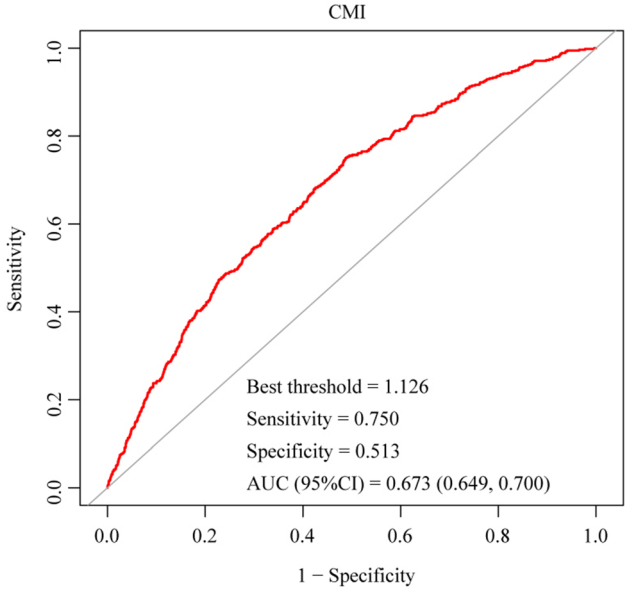

Fig. 5 ROC curve analysis for CMI in predicting testosterone deficiency. The analysis includes the area under the ROC curve (AUC) and the 95% confidence interval (95% CI). ROC, Receiver Operating Characteristic; CMI, Cardiometabolic Index; AUC, Area Under the Curve; 95% CI, 95% Confidence Interval

Conclusion

In summary, our results demonstrate that an increased CMI is negatively associated with total testosterone levels and positively associated with the risk of TD, with both associations showing a linear trend. Additionally, when using CMI to predict TD, it exhibited good predictive performance. We infer that our findings have important implications for the early screening and timely treatment of TD, which can effectively reduce the disease burden of TD and promote reproductive health. However, more prospective studies with large sample sizes are urgently needed to further validate our results.

Abbreviations

AUC	Area Under the Curve
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CKD	Chronic Kidney Disease
CMI	Cardiometabolic Index
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
HDL-c	High-Density Lipoprotein cholesterol
HPGA	Hypothalamic-Pituitary-Gonadal Axis
ID-LC-MS/MS	Isotope Dilution Liquid Chromatography-Tandem Mass Spectrometry
IFG	Impaired Fasting Glucose
IR	Insulin Resistance

LDL	Low-Density Lipoprotein
MEC	Mobile Examination Center
MetS	Metabolic Syndrome
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PIR	Poverty Income Ratio
ROC	Receiver Operating Characteristic
SE	Standard Error
SHBG	Sex Hormone-Binding Globulin
TD	Testosterone Deficiency
TG	Triglycerides
TT	Total Testosterone
UA	Uric Acid
WHtR	Waist-to-Height Ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-21230-0.

Supplementary Material 1

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Author contributions
Yangyang Mei contributed to the conception, design, methodology, software, analyses, and original draft writing; Bo Zhang and Xiaogang Wang contributed to the methodology, software, analyses; Renfang Xu was involved in software, analyses, and interpretation of data; Wei Xia contributed to the methodology and software; Yiming Chen and Xingliang Feng contributed to writing-reviewing, project management, and funding acquisition.

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Data availability
The datasets used and/or analyzed during the current study are available from the NHANES database(https://www.cdc.gov/nchs/nhanes/index.html). Data can be accessed in compliance with the data usage policies of NHANES. More detailed data can be requested from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (Protocol #2011-17 and continuation of Protocol #2011-17) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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