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RESEARCH

Association between Low Serum Testosterone Levels and All-cause Mortality in Patients With Cardiovascular Disease: A Study Based on the NHANES Database

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Abstract
The association between low serum testosterone levels and all-cause mortality in male and female patients with cardiovascular disease (CVD) was investigated. This study extracted data on CVD patients from the National Health and Nutrition Examination Survey (NHANES) database (1999–2000, 2003–2004, 2011–2012, and 2013–2014). The association between low serum testosterone levels (≤ 300 ng/dL) and all-cause mortality in male and female CVD patients was evaluated using univariate and multivariate Cox regression analyses, with hazard ratios (HR) and 95% confidence intervals (CI). A total of 1,177 participants (689 males) with a mean age of 66.01 ± 12.52 years were included in the study. The median follow-up time was 55 (44, 71) months. Low serum testosterone levels occurred in 487 (70.68%) males and 394 (80.74%) females. Additionally, 202 (29.32%) male patients and 94 (19.26%) female patients with CVD were dead. After adjusting for covariates, low serum testosterone levels were associated with an increased risk of all-cause mortality in male CVD patients (HR = 1.48, 95% CI 1.08–2.02, P = 0.013), while the association was not significant in females. Low serum testosterone levels may be associated with an increased risk of all-cause mortality in male CVD patients, but not in female patients.

Keywords Testosterone · Cardiovascular diseases · Mortality · Estradiol · National health and nutrition examination survey

Introduction

The World Health Organization (WHO) reported that cardiovascular disease (CVD) accounted for 32% of worldwide deaths in 2019, and an estimated 605,000 individuals experience their first myocardial infarction each year [1, 2]. CVD is the leading cause of death in both the United States of America (USA) and China, responsible for over a quarter of all deaths in the USA and affecting approximately 290 million people in China [3, 4]. Mortality from ischemic heart disease is higher in males under the age of 65, but gender differences in mortality rates narrow after the age of 65, likely due to the loss of estrogen's protective effect in postmenopausal females [5]. Hence, CVD accounted for 35% of total deaths among females in 2019 [6]. These findings underscore the potential importance of considering gender-specific factors in the management and treatment of cardiovascular disease.

Testosterone, the main androgen, influences the cardiovascular system by shortening the heart-rate-corrected QT interval, improving glycemic control, inducing vasodilation, being prothrombotic, and having anti-obesity effects [7]. On the other hand, the associations between testosterone and atherosclerosis and inflammation are less clear [7]. Low testosterone levels are associated with a higher risk of all-cause mortality in males [8]. A Swiss prospective cohort study indicated that approximately 40% of males with acute coronary syndromes (ACS) had low testosterone levels, which were associated with higher 1-year mortality [9]. In a cohort of Greek males, low testosterone levels were associated with a higher 5-year risk of CVD-related death in patients with stable coronary heart disease [10]. Several studies suggested an association between testosterone levels and mortality in male patients [8–10]. Testosterone also has beneficial effects on endothelial function improvements, blood pressure lowering, and myocardial function in women [11]. Although some evidence suggests a detrimental effect of low testosterone

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levels on cardiovascular health in women [11], the effect of different testosterone levels on mortality in female patients with CVD has not been thoroughly studied.

Furthermore, the impact of testosterone replacement therapy on cardiovascular risk remains debated. Several previous retrospective studies [12–16] and small-scale trials [17–21] reached conflicting conclusions about testosterone supplementation on cardiovascular risk. A longitudinal study of 77 males with hypogonadism treated with testosterone for at least 8 years showed that testosterone improved the cardiovascular risk factors [22]. In a cohort study of 1470 males, Oni et al. [23] showed that testosterone replacement therapy was associated with decreased all-cause mortality compared with males with non-normalized testosterone levels. The largest randomized controlled study on the subject investigated testosterone replacement therapy in 5246 males with hypogonadism and showed that testosterone replacement therapy was non-inferior to placebo [24].

Although large studies have reported beneficial effects of testosterone replacement therapy in males with hypogonadism, data from the general population, including females, are lacking. Therefore, this study aimed to investigate the association between testosterone levels and all-cause mortality in male and female patients with CVD, respectively.

Methods

Study Design and Participants

This retrospective study analyzed data extracted from the National Health and Nutrition Examination Survey (NHANES) database, an ongoing study conducted by the Centers for Disease Control and Prevention (CDC) that evaluates the nutritional and health status of the non-institutionalized population in the United States. The study populations were extracted from NHANES surveys conducted in 1999–2000, 2003–2004, 2011–2012, and 2013–2014, which provided information on serum testosterone levels, CVD, and mortality. All data used in this manuscript are de-identified and freely available to the public through https://www.cdc.gov/nchs/nhanes/index.htm. The study included CVD patients aged 18 years and older with serum testosterone data. The inclusion criteria were 1) age $\geq$ 18 years old, 2) with serum testosterone data, and 3) diagnosed with cardiovascular disease (CVD). The exclusion criteria were 1) missing testosterone data, 2) diagnosis of primary (e.g., congenital cause) or secondary (e.g., chronic debilitating disease, drugs that cause sexual dysfunction, radiotherapy, or testicular trauma) hypogonadism, or 3) females pregnant at the time of the clinical examination. The NHANES database was approved by the NCHS Institutional Review Board (Protocol #2018–01 and Continuation of Protocol #2011–17) in accordance with the revised Helsinki Declaration. Informed consent forms were completed before data collection procedures and extensive health examinations. No ethical approval of our Institutional Review Board was required since these survey data were publicly available.

Diagnosis of CVD

CVD was determined based on a combination of self-reported physician diagnoses and standardized medical status questionnaires administered during individual interviews. A multiple-choice examination was used to identify CVD, with participants asked, "Have you ever been told you had (congestive) heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke?" If a participant answered "yes" to any of the above questions or self-reported a physician diagnosis of CVD, he or she was considered a CVD patient.

Measurement of Serum Testosterone Levels

Serum testosterone measurement was performed via the isotope dilution liquid chromatography-tandem mass spectrometry (ID-LC–MS/MS) method for routine quantitation of serum testosterone based on the National Institute for Standards and Technology's (NIST) reference method [25]. The lower limits of detection of the assays were 0.36 ng/dL for serum testosterone and 0.5 mg/dL for serum uric acid (SUA). Concentrations below the limit of detection were replaced with the limit of detection divided by the square root of 2 [26]. Normal testosterone levels for females are 15–70 ng/dL, while the normal range for males is 300–1000 ng/dL. Clinically, symptomatic males with total testosterone lower than 300 ng/dL should be treated with testosterone therapy [27, 28]. In females, testosterone $\leq$ 20 ng/dL indicates androgen deficiency [29]. Therefore, we classified the participants with testosterone levels of $\leq$ 300 ng/dL (males) or $\leq$ 20 ng/dL (females) as the low testosterone group, while the other participants were grouped as normal. Since the study focused on examining the impact of low testosterone levels, participants with high testosterone levels were included in the normal group, following previous classification methods [30, 31]. This study examined whether there is a threshold for testosterone concentrations that increases cardiovascular disease risk in females.

Outcome and Follow-up

The primary outcome was all-cause mortality. The mortality data were obtained from the NHANES public-use linked mortality file. In the NHANES database, deaths were obtained through the National Death Index up to December 31, 2013. The follow-up endpoint was either death or until December 2013.

Data Collection and Definitions

This study collected [1] sociodemographic data including age, ethnicity, education, the poverty income ratio (PIR), body mass index (BMI), smoking, drinking and CVD treatment; [2] comorbidities including hypertension, diabetes, and dyslipidemia; and [3] laboratory indicators including sex hormone-binding globulin (SHBG) and estradiol from the NHANES database.

BMI was calculated as the weight in kilograms divided by the square of the height in meters and categorized into normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity ($\geq$30 kg/m^2), and underweight ($<$18.5 kg/m^2). Hypertension was identified on the basis of reported high blood pressure, current use of medication for high blood pressure, or measured systolic blood pressure (SBP) $\geq$ 140 mm Hg or diastolic blood pressure (DBP) $\geq$ 90 mm Hg. Diagnosis of diabetes was determined by fasting blood glucose $\geq$ 7.0 mmol/L or hemoglobin A1c (HbA1c) $\geq$ 6.5%, self-reported diabetes, or hypoglycemic therapy. The presence of dyslipidemia was defined based on having been diagnosed with dyslipidemia by a physician. Serum SHBG detection in NHANES was described in detail on the website (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/TST_H.htm).

Statistical Analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R (version 4.1.2, 2021–11-01). Continuous data conforming to normal distribution were expressed as mean $\pm$ standard deviation (SD) and analyzed using Student's t-test. Continuous data that did not conform to normal distribution were expressed as median (p25, p75) and analyzed using the Mann–Whitney U-test. Categorical data were presented as n (%) and analyzed using the chi-square test.

A univariate Cox regression model was used for screening confounding factors, with factors demonstrating a significance level of $p < 0.05$ being incorporated into the multivariate Cox regression analysis. A multivariate Cox regression model was used to assess the association between low testosterone levels and all-cause mortality in both male and female CVD patients. For male patients with CVD, adjusted confounding factors included continuous variables such as age, SHBG, and PIR, as well as categorical variables such as ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, and Other), education (Less than High School, High School Graduate, Some College, College Graduate or higher), hypertension (Yes/No), and CVD (Yes/No).

Hypertension, a known risk factor for developing CVD, has been associated in adult males with the effects and differences of sex-related steroid hormones [32, 33]. Older age and hypertension are recognized as major risk factors for CVD [34, 35]. Given the established association between hypertension and CVD risk, subgroup analyses were stratified by age and hypertension history. In addition, the relationship between testosterone levels (low vs. Physiological) and survival in male CVD patients was analyzed by the Kaplan–Meier survival curve. For missing variables, the default predicted mean matching multiple imputation method within the mice package was used. Sensitivity analyses were performed for both male and female CVD patients before and after data imputation. A two-sided $P < 0.05$ was considered statistically significant.

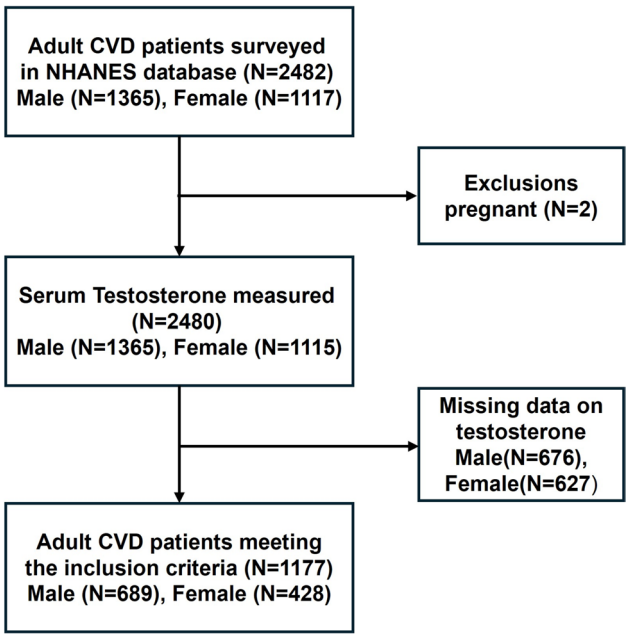

Fig. 1 Flowchart of the study

Table 1 Characteristic of male CVD patients

	Total ($n=689$)	Groups		P value
		Survival ($n=487$)	Mortality ($n=202$)	
Age, years	66.55 ± 12.03	64.25 ± 12.39	72.09 ± 8.94	< 0.001
Ethnicity, n (%)				0.001
Mexican American	78 (11.32)	56 (11.50)	22 (10.89)	
Other Hispanic	52 (7.55)	45 (9.24)	7 (3.47)	
Non-Hispanic White	369 (53.56)	239 (49.08)	130 (64.36)	
Non-Hispanic Black	135 (19.59)	101 (20.74)	34 (16.83)	
Other race, including multi-racial	55 (7.98)	46 (9.45)	9 (4.46)	
Education, n (%)				0.689
Less than 9th grade	91 (13.21)	59 (12.11)	32 (15.84)	
9-11th grade	98 (14.22)	69 (14.17)	29 (14.36)	
High school	171 (24.82)	126 (25.87)	45 (22.28)	
Some college or AA degree	182 (26.42)	129 (26.49)	53 (26.24)	
College graduate or above	147 (21.34)	104 (21.36)	43 (21.29)	
PIR	1.75 (1.02, 3.39)	1.66 (0.97, 3.43)	1.87 (1.18, 3.16)	0.274
Hypertension, n (%)	485 (70.39)	339 (69.61)	146 (72.28)	0.485
Diabetes, n (%)	239 (34.69)	166 (34.09)	73 (36.14)	0.606
Smoking, n (%)	465 (67.49)	322 (66.12)	143 (70.79)	0.233
Drinking, n (%)	574 (83.31)	410 (84.19)	164 (81.19)	0.336
Height, cm	172.70 ± 7.31	172.79 ± 7.35	172.47 ± 7.22	0.606
Weight, kg	89.76 ± 22.23	90.95 ± 22.70	86.91 ± 20.86	0.030
BMI, kg/m^2	29.99 ± 6.64	30.34 ± 6.71	29.12 ± 6.42	0.028
DBP, mmHg	67.28 ± 15.13	68.05 ± 15.14	65.41 ± 14.97	0.037
SBP, mmHg	131.19 ± 20.65	130.13 ± 19.15	133.76 ± 23.74	0.054
Testosterone, ng/dL	345.00 (246.00, 468.00)	346.00 (254.00, 471.42)	343.06 (224.15, 467.00)	0.208
SHBG, nmol/L	48.56 (34.86, 70.07)	46.61 (33.69, 66.73)	53.75 (38.52, 77.82)	0.002
Estradiol, pg/ml	24.50 (18.10, 30.60)	24.20 (18.32, 30.40)	24.78 (17.30, 31.59)	0.993
Dyslipidemia, n (%)	659 (95.65)	466 (95.69)	193 (95.54)	0.933
CVD treatment, n (%)	149 (21.63)	83 (17.04)	66 (32.67)	< 0.001
Survival months	56.00 (44.00, 75.00)	61.00 (49.00, 76.00)	40.50 (20.00, 64.00)	< 0.001

CVD Cardiovascular disease, *PIR* Poverty–income ratio, *BMI* Body mass index, *DBP* Diastolic blood pressure, *SBP* Systolic blood pressure, *SHBG* Sex hormone-binding globulin

Results

A total of 2,482 adult patients with CVD, including 1,365 males, were initially collected from the database. Patients with missing testosterone data (676 males, 627 females) and two pregnant females were subsequently excluded. Finally, a total of 1,177 patients, with a mean age of 66.01 ± 12.52 years, were included for analysis, comprising 689 males and 488 females (Fig. 1). Low serum testosterone levels occurred in 487 (70.68%) males and 394 (80.74%) females. Among male patients with CVD, 202 (29.32%) were dead (Table 1). Among female patients with CVD, 94 (19.26%) were dead (Table 2).

The Kaplan–Meier survival curve in males showed that low serum testosterone levels were associated with a reduced survival probability among CVD patients (Fig. 2). The median follow-up time was 55 months, with an interquartile range (IQR) of 44 to 71 months, and no follow-up data were missing or excluded. Multivariate Cox regression analysis showed that low serum testosterone levels (HR = 1.48, 95% CI 1.08–2.02, P = 0.013) were associated with an increased risk of all-cause mortality in male CVD patients (Table 3). In female CVD patients, no significant association was observed between low serum testosterone levels and all-cause mortality (Table 4).

Sensitivity analysis was performed on male CVD patients before and after data imputation, including education level, PIR, smoke status, drinking, height, weight, BMI, DBP, SBP, SHBG, estradiol, dyslipidemia, survival months, and all-cause mortality, revealing no significant differences (Table S1). Similarly, in female CVD patients, there was also no significant difference before and after sensitivity analysis

Table 2 Characteristic of female CVD patients

Total ($n=488$)		Groups		P value
		Survival ($n=394$)	Mortality ($n=94$)	
Age, year	65.24 ± 13.15	63.06 ± 13.07	74.40 ± 8.85	< 0.001
Ethnicity, n (%)				< 0.001
Mexican American	46 (9.43)	38 (9.64)	8 (8.51)	
Other Hispanic	59 (12.09)	55 (13.96)	4 (4.26)	
Non-Hispanic White	227 (46.52)	164 (41.62)	63 (67.02)	
Non-Hispanic Black	111 (22.75)	99 (25.13)	12 (12.77)	
Other race, including multi-racial	45 (9.22)	38 (9.64)	7 (7.45)	
Education, n (%)				0.952
Less than 9th grade	62 (12.70)	49 (12.44)	13 (13.83)	
9-11th grade	85 (17.42)	70 (17.77)	15 (15.96)	
High school	133 (27.25)	109 (27.66)	24 (25.53)	
Some college or AA degree	153 (31.35)	121 (30.71)	32 (34.04)	
College graduate or above	55 (11.27)	45 (11.42)	10 (10.64)	
PIR	1.42 (0.90, 2.55)	1.43 (0.89, 2.55)	1.39 (0.90, 2.55)	0.756
Hypertension, n (%)	363 (74.39)	285 (72.34)	78 (82.98)	0.034
Diabetes, n (%)	165 (33.81)	130 (32.99)	35 (37.23)	0.435
Smoking, n (%)	249 (51.02)	198 (50.25)	51 (54.26)	0.486
Drinking, n (%)	246 (50.41)	204 (51.78)	42 (44.68)	0.216
Height, cm	158.45 ± 7.35	159.04 ± 7.22	155.99 ± 7.46	< 0.001
Weight, kg	78.96 ± 22.56	80.16 ± 22.45	73.96 ± 22.46	0.016
BMI, kg/m^2	31.38 ± 8.49	31.61 ± 8.27	30.40 ± 9.33	0.213
DBP, mmHg	64.41 ± 15.85	65.11 ± 15.80	61.46 ± 15.81	0.045
SBP, mmHg	133.10 ± 23.70	131.34 ± 21.85	140.49 ± 29.25	0.005
Testosterone, ng/dL	15.55 (10.35, 24.95)	16.10 (11.00, 25.10)	13.42 (8.74, 21.80)	0.050
SHBG, nmol/L	64.99 (43.12, 99.38)	62.17 (41.24, 92.45)	76.81 (53.75, 116.40)	0.002
Estradiol, pg/ml	6.06 (2.12, 12.90)	6.49 (2.12, 15.20)	5.09 (2.12, 8.76)	0.014
Dyslipidemia, n (%)	460 (94.26)	369 (93.65)	91 (96.81)	0.237
Menopause, n (%)	465 (95.29)	375 (95.18)	90 (95.74)	1.000
CVD treatment, n (%)	97 (19.88)	61 (15.48)	36 (38.30)	< 0.001
Survival months	54.00 (43.00, 70.00)	59.00 (47.00, 73.00)	34.00 (20.00, 50.00)	< 0.001

CVD Cardiovascular disease, *PIR* Poverty–income ratio, *BMI* Body mass index, *DBP* Diastolic blood pressure, *SBP* Systolic blood pressure, *SHBG* Sex hormone-binding globulin

with missing variables such as PIR, hypertension, diabetes, alcohol use, height, weight, BMI, DBP, SBP, SHBG, estradiol, dyslipidemia, and menopause (**Table S2**).

Subgroup analysis indicated that low serum testosterone levels were associated with all-cause mortality in male CVD patients aged ≥ 65 (HR = 1.45, 95% CI 1.09–1.93, P = 0.010) or < 65 years (HR = 1.39, 95% CI 1.01–1.90, P = 0.041) (Table 5). Among male CVD patients, low testosterone levels were associated with an increased risk of all-cause mortality, both in those with hypertension (HR = 1.35, 95% CI 1.06–1.71, P = 0.015) and those without hypertension (HR = 1.93, 95% CI 1.25- 2.96, P = 0.003). However, there was no evidence of an association between testosterone levels and all-cause mortality in female CVD patients across different age and hypertension status (Table 5).

Discussion

The results showed that low levels of serum testosterone were associated with an increased risk of all-cause mortality in male CVD patients. Furthermore, low levels of serum testosterone were significantly associated with all-cause mortality in males of different ages and with or without a history of hypertension. However, no such association was observed between low serum testosterone levels and all-cause mortality in female CVD patients. This study highlights the potential clinical significance of low serum testosterone levels as a predictor of increased all-cause mortality risk in male cardiovascular disease patients, suggesting a potential role for testosterone replacement therapy in improving survival outcomes.

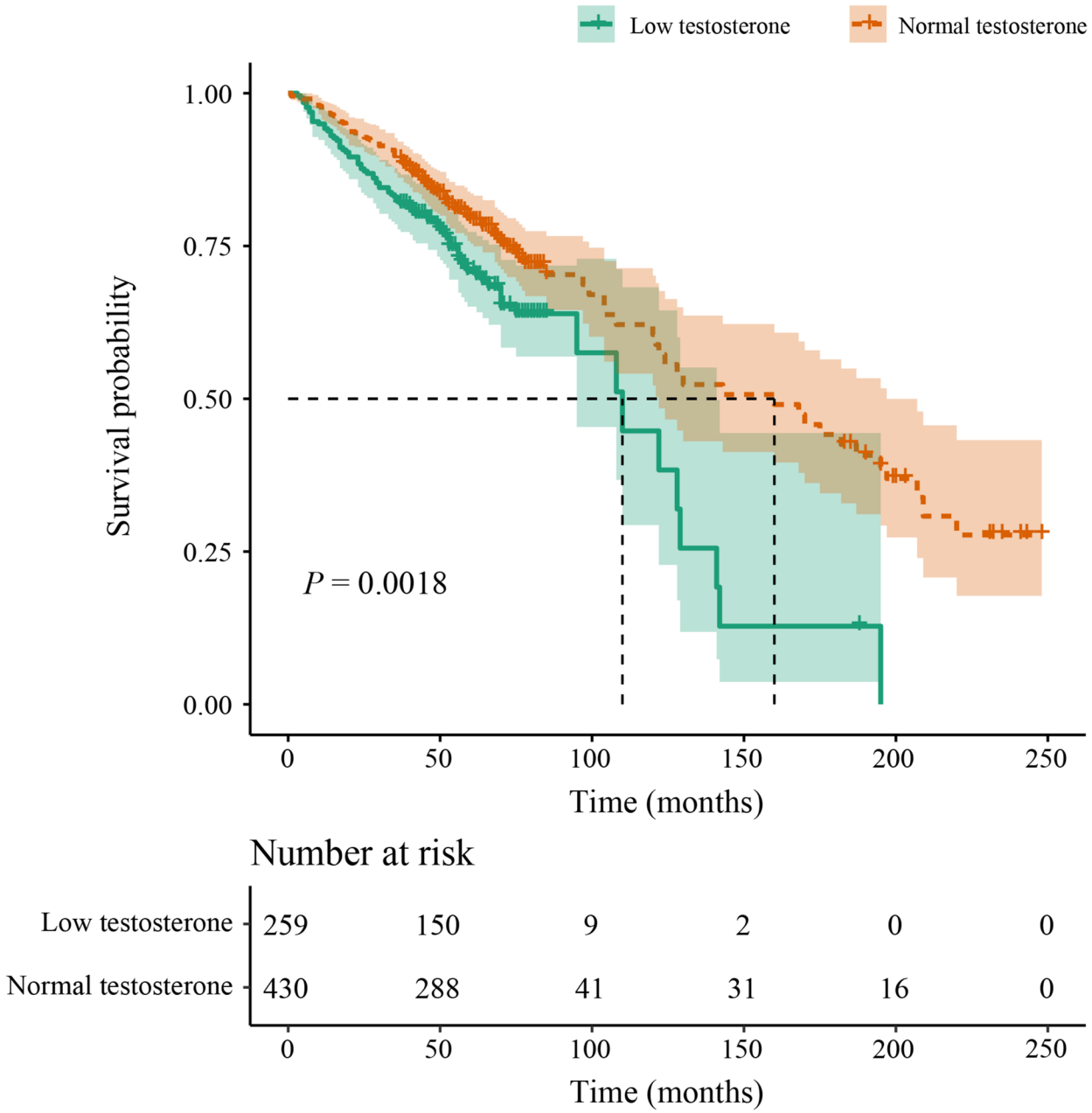

Fig. 2 Kaplan–Meier survival curve of the relationship between serum testosterone levels (low vs. Normal) and all-cause mortality in male CVD patients

Several studies have indicated that low serum testosterone levels were associated with increased all-cause mortality in males of the general population [36, 37], including a recent meta-analysis [38]. A longitudinal analysis of younger males aged ≥ 20 years concluded that lower testosterone levels were associated with all-cause mortality between baseline and 9 years of follow-up [39]. Our findings were consistent with these results, suggesting that testosterone was associated with an increased risk of all-cause mortality in male CVD patients across age groups (Table 5). Studies have shown that testosterone has complex mechanisms of action, including cardio- protective, vasodilatory, and anti-inflammatory properties [40, 41]. Previous research has indicated that testosterone may play an important role in the regulation of ventricular repolarization and heart-rate-corrected QT (QTc) interval [42]. It is reasonable to infer that low testosterone levels affect the prognosis of patients with cardiovascular disease, resulting in shorter life expectancy and increased overall mortality. Previous studies in patients with hypogonadism suggest that testosterone supplementation

Table 3 Association between serum testosterone levels and all-cause mortality in male CVD patients

	Unadjusted Model		Adjusted Model	
	HR (95% CI)	P value	HR (95% CI)	P value
Testosterone levels				
Normal	Ref	–	Ref	–
Low	1.41 (1.17–1.70)	< 0.001	1.48 (1.08–2.02)	0.013

CVD Cardiovascular disease, *HR* Hazard ratio, *CI* Confidence interval, *Ref* reference

Unadjusted model: Univariate COX regression model. Continuous variables: Age, SHBG (Sex Hormone-Binding Globulin), PIR (Poverty-to-Income Ratio). Categorical variables: Ethnicity: Non-Hispanic White, Non-Hispanic Black, Hispanic, Other.Education: Less than High School, High School Graduate, Some College, College Graduate or higher. Hypertension: Yes/No. CVD treatment: Yes/No

Table 4 Association between low serum testosterone levels and all-cause mortality in female CVD patients

	Unadjusted Model		Adjusted Model	
	HR (95% CI)	P value	HR (95% CI)	P value
Testosterone levels				
Normal	Ref		Ref	
Low	1.53 (1.01–2.31)	0.042	1.23 (0.80–1.90)	0.341

CVD Cardiovascular disease, *HR* Hazard ratio, *CI* Confidence interval, *Ref* Reference

Unadjusted model: Univariate COX regression model. Continuous variables: Age, SHBG (Sex Hormone-Binding Globulin), Estradiol. Categorical variables: Ethnicity: Non-Hispanic White, Non-Hispanic Black, Hispanic, Other. Education: Less than High School, High School Graduate, Some College, College Graduate or higher. Hypertension: Yes/No. Drinking: Yes/No. CVD treatment: Yes/No

Table 5 Association between low serum testosterone levels and all-cause mortality of CVD patients in different age and the history of hypertension

	Subgroups	HR (95% CI)	P value
Male			
	Age		
	≥ 65 years	1.45 (1.09–1.93)	0.010
	< 65 years	1.39 (1.01–1.90)	0.041
	Hypertension		
	Yes	1.35 (1.06–1.71)	0.015
	No	1.93 (1.25–2.96)	0.003
Female			
	Age		
	≥ 65 years	0.97 (0.72–1.32)	0.858
	< 65 years	1.14 (0.84–1.54)	0.410
	Hypertension		
	Yes	1.02 (0.80–1.30)	0.866
	No	0.83 (0.53–1.32)	0.440

CVD Cardiovascular disease, *HR* Hazard ratio, *CI* Confidence interval. In subgroups of age: Ethnicity, education level, hypertension, SHBG and CVD treatment were adjusted in male patients; Ethnicity, education level, hypertension, SHBG, estradiol and CVD treatment were adjusted in female patients. Continuous variables: Male patients: Age, SHBG (Sex Hormone-Binding Globulin). Female patients: Age, SHBG (Sex Hormone-Binding Globulin), Estradiol. Categorical variables: Ethnicity: Non-Hispanic White, Non-Hispanic Black, Hispanic, Other. Education level: Less than High School, High School Graduate, Some College, College Graduate or higher. CVD treatment: Yes/No

improves or does not worsen cardiovascular outcomes and mortality [22–24]. The present study focused on patients with CVD, including males and females. Although a relationship between low testosterone levels and patient outcomes was observed in males, no association was observed in females, which could be related to the need to define a threshold for low testosterone in females.

In middle-aged and elderly males, total circulating testosterone levels decrease by around 0.8% per year, while sex hormone-binding globulin (SHBG) levels increase by 1.6% per year, which may decrease the bioavailable testosterone concentrations in elderly males [43]. Normal testosterone levels play an important role in maintaining cardiovascular health. Boden et al. [44] postulated that low testosterone levels may interact with traditional CVD risk factors such as diabetes, obesity, and metabolic syndrome to increase the risk of developing overt heart and vascular disease. Similar to previously proposed mechanisms, testosterone could impact cardiovascular health through effects on insulin resistance, fat mass accumulation, inflammation, and ischemia in the setting of coronary heart disease (CHD). Additionally, it has been reported that males with hypergonadotropic hypogonadism are more prone to ischemic heart disease. This susceptibility may be due to luteinizing hormone (LH) potentially exerting a direct effect on vascular tissue or the heart through the LH receptor in extragonadal sites [45]. Testosterone replacement therapy in males with low testosterone levels may be a promising method to improve the survival of male patients with CVD.

The current literature on the association between testosterone level and all-cause mortality in females is inconclusive. Some studies suggest a U-shaped relationship with the implication that those with the lowest or highest levels have impaired survival [46], while other investigations are devoid of any prognostic association [47, 48]. The main results from a recent report from the Multi-Ethnic Study of

Atherosclerosis showed that higher total testosterone was associated with an increased risk of cardiovascular disease in females [49]. However, no significant association was observed in this study between serum testosterone levels and all-cause mortality in female CVD patients across all subgroups. The impact of testosterone in female patients remains undecided and necessitates further research. Interestingly, the results from the current study showed that age and estradiol were significantly associated with an increased risk of all-cause mortality in female CVD patients. Previous studies have also found that higher estradiol levels [50] and early onset of menopause [51] were associated with a higher risk of CVD mortality. In women, the aromatase enzyme can convert testosterone into estradiol. Therefore, low testosterone levels may be associated with high estradiol levels, which could partially explain the relationship between low testosterone levels and CVD in women [11]. Aromatase-knock-out mice display high testosterone and low estradiol levels, as well as less severe myocardial damage after ischemia–reperfusion injury [52]. Therefore, further studies are needed to confirm the association between testosterone levels and all-cause mortality in female CVD patients, considering age, estradiol, and menopause as confounding factors.

A strength of this study is the use of the large NHANES database. In addition, the study included only patients with CVD, decreasing confounding. On the other hand, the study has some limitations. This study is a retrospective study, so it was difficult to adjust for potential confounders, such as lifestyle changes. In addition, hormone levels may be affected by circadian rhythm fluctuations. Finally, since the present study aimed to examine the impact of low testosterone on CVD, participants were dichotomized into low vs. physiological/high groups, as done in previous studies [30, 31]. However, this approach limits the examination of the impact of high testosterone levels on CVD, which remains controversial [7, 42]. Further research is necessary to better understand the role of testosterone levels in the prognosis of CVD patients.

In conclusion, the present study found that low serum testosterone levels were associated with a higher risk of all-cause mortality in male CVD patients. However, this association was not significant in female CVD patients. Our results emphasize the importance of focusing on testosterone levels and their changes in the clinical work-up of male patients with CVD, which may provide some evidence-based support for the use of hormone replacement therapy in CVD treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12012-025-09973-7.

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Author Contributions Jiang Rui: Data analysis and Writing. Yongchen Wang: review and editing.

Data Availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interests The authors declare no competing interests.

Ethical Approval The database protocol was approved by the National Center for Health Statistics institutional review board (NCHS IRB/ERB). All the participants provided informed consent. No ethical approval of our Institutional Review Board was required since these survey data were publicly available.

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