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Inverted U-shaped association between total testosterone with bone mineral density in men over 60 years old

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Abstract

Background Aging often leads to changes in hormone levels, particularly testosterone, which is thought to significantly affect bone health in older males.

Objective This study aimed to explore the link between testosterone levels and bone mineral density in men aged 60 and above.

Methods Data from the National Health and Nutrition Examination Survey 2013–2014 were used. Weighted multivariable linear regression models were employed to study the association between testosterone and bone mineral density. Furthermore, a weighted generalized additive model and smooth curve fitting were used to address potential nonlinear patterns in the data.

Results The analysis included 621 elderly men. After accounting for various factors, the study uncovered a Inverted U-shaped correlation between testosterone levels and femoral neck density. Notably, a turning point was identified at the testosterone level of 406.4 ng/dL. Further examination, using different models, showed that testosterone levels in the third quartile (group Q3) were positively linked to bone density. However, contrasting trends were observed in the first (group Q1) and fourth quartiles (group Q4), where testosterone levels displayed a negative relationship with bone density.

Conclusion The results indicate a complex interplay between testosterone levels and bone mineral density in elderly men. The U-shaped trend suggests that both low and high testosterone levels could negatively impact bone health. These findings highlight the importance of maintaining testosterone levels within an optimal range to preserve bone health in aging men.

Keywords Testosterone, Bone mineral density, Men, NHANES, Cross-sectional study

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Background

Osteoporosis, recognized by the World Health Organization as one of the top 10 global health issues, affects over 200 million people worldwide [1, 2]. This condition is characterized by decreased bone mass and microstructural damage, leading to increased bone fragility and susceptibility to fractures [3]. The impact of osteoporosis goes beyond the physical, including frailty, chronic pain, and a decline in quality of life, often resulting in disability and, in severe cases, death. This widespread and debilitating nature makes osteoporosis a significant public health concern and a prominent topic in scientific research.

While osteoporosis can occur at any age, it is particularly common in postmenopausal women and older men [4]. The aging process, along with hormonal changes, significantly contributes to the risk of osteoporosis, especially in the elderly [5]. Although the sharp decline in sex hormones during perimenopause is well-known, the gradual reduction in sex hormones during male aging often leads to a lack of consideration of the hormonal impact on bone health in elderly men [6].

Among the various sex steroid hormones, testosterone is traditionally believed to play a crucial role in maintaining male skeletal integrity. However, the relationship between testosterone levels and bone mineral density (BMD) in men remains a topic of ongoing debate. Testosterone levels typically decrease by 0.4–2.6% annually in men as they age [7]. Numerous clinical studies have reached the consensus that a decline in testosterone levels is closely linked to a reduction in bone mineral density among middle-aged and elderly men. Moreover, these studies have established that men with low testosterone levels face an elevated risk of developing osteoporosis and experiencing fractures [8]. However, it is worth noting that a particular study has demonstrated an inverse association between testosterone levels in the proximal femur and lumbar spine with bone mineral density [9]. Furthermore, investigations have indicated that testosterone (T), dihydrotestosterone (DHT), and sex hormone-binding globulin (SHBG) do not exhibit a significant association with bone mineral density [10]. Consequently, the findings from these diverse studies yield inconclusive results, highlighting the need for further research in this area.

In contrast to previous studies, our research zeroes in on the specific age group of elderly men and makes use of a comprehensive dataset to examine the intricate interaction between testosterone and bone mineral density, with the aim of offering more targeted and practical insights for the management of osteoporosis in this particular group. This study intends to contribute to the existing body of knowledge by specifically delving into the link between testosterone and bone mineral density in elderly men, employing data from the National Health and Nutrition Examination Survey (NHANES). The objective is to establish a more accurate understanding of this relationship, which can steer future research and potentially facilitate the development of effective management and treatment strategies for osteoporosis in this population.

Materials and methods

Study design and population

The National Health and Nutrition Examination Survey (NHANES) stands as a comprehensive, ongoing cross-sectional survey designed to furnish objective insights into the health status and tackle emerging public health concerns within the broader population of the United States. Prior to its commencement, the survey protocol underwent scrutiny and approval by the Institutional Review Board of the National Center for Health Statistics. Each participant entering NHANES provided their consent for the use of data in subsequent studies. These pivotal cross-sectional investigations were overseen and executed by the National Center for Health Statistics (NCHS). For detailed insights into the methodologies employed in NHANES, refer to the website: http://www.cdc.gov/nchs/nhanes/.

In this specific study, data were amalgamated from NHANES spanning the years 2013 to 2014. Based on the World Health Organization (WHO)'s definition of the elderly and considering that physiological and hormonal changes become significant after age 60, it is possible that these changes may affect bone mineral density [11]. Therefore, this survey is limited to men aged 60 years and older, aiming to expand the study to include more individuals who may have begun to experience age-related health changes. Initially, the pool of eligible male participants numbered 874 individuals. Subsequently, exclusions were made: 165 participants were omitted due to missing femoral neck BMD data, 30 due to missing testosterone level data, and 58 due to missing covariate data. Ultimately, the analysis encompassed 621 participants(Fig. 1).

Bone Mineral Density Measurement

According to the guidelines set forth by the World Health Organization (WHO), the determination of osteoporosis or osteopenia relies on T-score assessments. T-scores are derived from the formula: (BMD measured − mean BMD reference) / SD reference. Osteoporosis is defined as a T-score of BMD ≤ -2.5, while osteopenia is defined as -2.5 < T-score ≤ -1. In this study, non-Hispanic white men aged 20–29 from NHANES III served as the reference group for calculating femoral neck BMD scores [12, 13]. The measurement of femoral neck BMD was conducted using dual-energy X-ray absorptiometry.

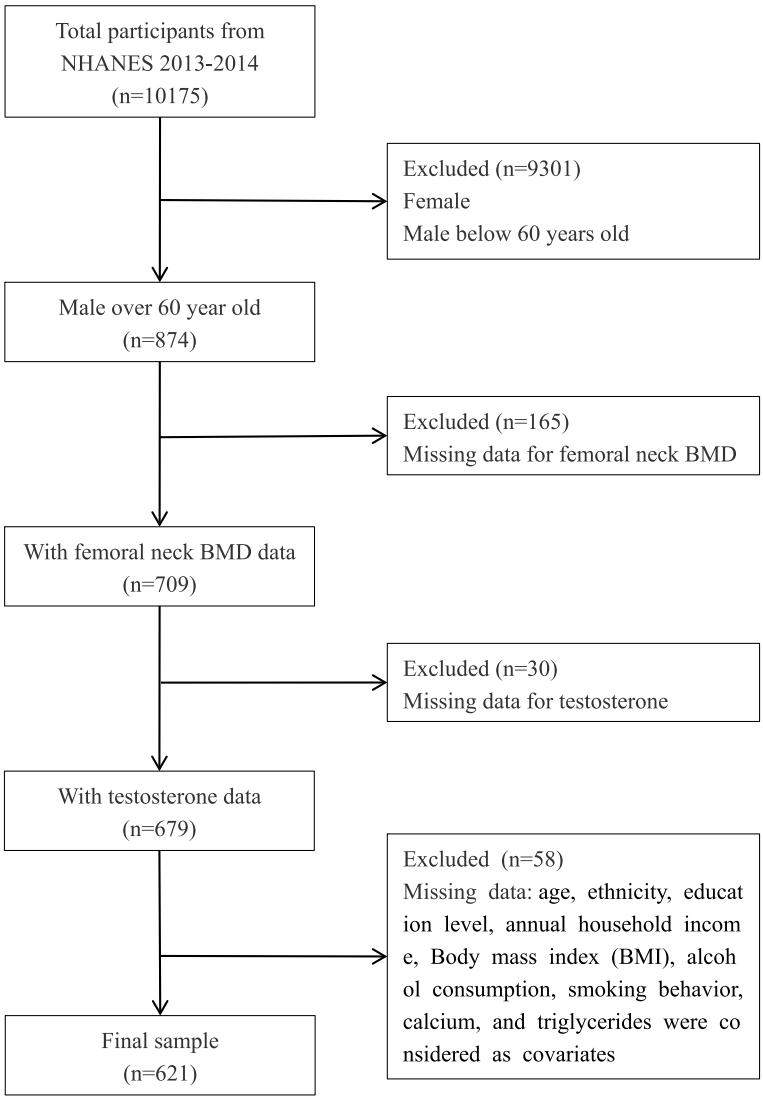


Fig. 1 Flow diagram of screening and selection process

Total testosterone

This study utilized a validated isotope dilution liquid chromatography tandem mass spectrometry (ID-LC–MS/MS) method for the routine quantitation of serum total testosterone. The method is based on the National Institute for Standards and Technology's (NIST) reference method, ensuring accuracy and reliability in the measurement process.

Variables

In this research, variables such as age, ethnicity, education level, annual household income, Body mass index (BMI), alcohol consumption, smoking behavior, calcium, and triglycerides were considered as covariates. These covariates were categorized into categorical variables like gender, education level, annual household income, BMI, alcohol consumption, smoking behavior, and continuous variables such as age, calcium, and triglycerides.

NHANES classifies race as Mexican American, non-Hispanic white, non-Hispanic black, and other Hispanics. Education qualifications were divided into High school or below, High school graduate, and More than high school. BMI was grouped as < 18.5, 18.5–25, 25–29.9, or ≥ 30 kg/m2, with obesity defined as a BMI of ≥ 30. Participants were asked about their smoking history, based on whether they had smoked more than 100 cigarettes in their lifetime, categorizing them as smokers or non-smokers accordingly. Those who reported consuming at least 12 alcoholic beverages in a year were identified as having a history of drinking.

Statistical analyses

The study categorized participants into quartiles based on their testosterone levels and utilized R software (version 4.2.3) for all analyses, maintaining a significance level of $P < 0.05$. Categorical variables were presented as frequencies or percentages, while continuous variables were expressed as means ± standard deviation.

To explore differences between groups, weighted linear regression models (for continuous variables) and weighted chi-square tests (for categorical variables) were employed. All calculations incorporated NHANES sample weights to ensure accurate representation.

For investigating the relationship between testosterone levels and femoral neck bone mineral density, a weighted multivariate linear regression model was applied. Following the Strengthening Epidemiological Observational Study Report (Control) statement [16], three models were executed: Model 1, without adjusting for covariates; Model 2, adjusted for BMI, calcium, and triglycerides; and Model 3, adjusted for all covariates. To account for potential nonlinearity in the association between testosterone levels and BMD, a weighted generalized additive model and smooth curve fitting were implemented, enhancing the study's ability to capture nuanced relationships in the data. P-overall indicates that the independent variables have a statistically significant overall effect on the dependent variables. P-non-linear is specifically employed to detect whether there are nonlinear relationships between the independent and dependent variables. When both are less than 0.05, it signifies that there is a significant nonlinear correlation between testosterone and bone mineral density. In addition, the multiple cross comparisons were carried out. When P is less than 0.05, if the $\beta > 0$, it indicates that the independent variable has a positive correlation with the dependent variable. Conversely, if the $\beta < 0$, it shows a negative correlation.

Results

A comprehensive analysis was conducted on 621 participants with complete data on testosterone levels and BMD. The number of cases with osteoporosis was 34, and that with osteopenia was 296. The incidence of osteoporosis was 5.48%, and that of osteopenia was 47.67%. These individuals were categorized into four groups based on their testosterone levels. In older men, significant differences in bone mineral density were detected at various testosterone levels ($P = 0.04$). The T Score was -1.13 ± 0.95 in Q1 and -1.31 ± 0.85 in Q4. These values were notably lower than normal. Importantly, there are differences in BMI ($P = 0.01$), calcium ($P = 0.01$), and triglyceride ($P = 0.01$) levels among the four groups. No other significant differences were identified (Table 1).

Following this, a smooth curve fitting analysis was conducted after adjusting for various factors including age, race, education level, annual household income, BMI, alcohol consumption, smoking behavior, calcium, and triglycerides. In model 1, model 2, and model 3, the differences in P-overall and P-nonlinear were all less than 0.05. This indicates that is, there is a significant nonlinear correlation between testosterone and bone mineral density (Fig. 2). Subsequently, a two-piecewise linear regression model was employed to ascertain the threshold effect of testosterone on bone mineral density based on the smoothing plot, pinpointing the inflection point at 406.4.

Moreover, logistic regression analysis was conducted by categorizing testosterone into quartiles (quartile 1: 1.44–281.54, quartile 2: 282.00–377.00, quartile 3: 377.98–505.30, quartile 4: 506.00–1260.00). Across model 1, model 2, and model 3, it was observed that testosterone levels in group Q3 exhibited a positive correlation with bone density(Model 1: $\beta = 0.21$, 95% CI: 0.01, 0.40, $P = 0.04$; Model 2: $\beta = 0.38$, 95% CI: 0.19, 0.57, $P = 0.01$; Model 3: $\beta = 0.38$, 95% CI: 0.06, 0.71, $P = 0.03$), while they displayed a negative correlation in groups Q1 (Model 1: $\beta = -0.21$, 95% CI: -0.40, -0.01, $P = 0.04$; Model 2: $\beta = -0.38$, 95% CI: -0.57, -0.19, $P = 0.01$; Model 3: $\beta = -0.38$, 95% CI: -0.71, -0.06, $P = 0.03$) and Q4 (Model 1: $\beta = -0.38$, 95% CI: -0.64, -0.12, $P = 0.01$; Model 2: $\beta = -0.28$, 95% CI: -0.55, -0.02, $P = 0.04$; Model 3: $\beta = -0.34$, 95% CI: -0.75, 0.07, $P = 0.08$) (Table 2).

Discussion

In our present study, we utilized data from NHANES (2013–2014) to investigate the relationship between testosterone and BMD in individuals aged 60 years and older. We discovered lower T-scores ranging between -0.9 and -1.3, in addition to an inverted U-shaped association between testosterone levels and bone mineral density.

The clinical insights gleaned from this research are multifaceted, holding significant implications for the management of skeletal health within the elderly male cohort. First and foremost, our study compellingly demonstrates the critical importance of considering serum testosterone levels as a key factor when evaluating bone health in elderly men. The identification of an inverted U-shaped relationship between testosterone and bone mineral density (BMD) in this population points to a subtle interplay: both excessively high and low testosterone levels could potentially harm bone health. This finding illuminates the complex dynamics between testosterone and BMD, emphasizing the necessity for a hormonal balance that maintains the structural and functional robustness of the skeletal system. Achieving this balance

Table 1 Weighted characteristics of study population based on total testosterone quartiles

Characteristic	Overall	Q1	Q2	Q3	Q4	*P*value
Age (years)	68.86 (6.51)	69.65 (6.47)	69.01 (6.80)	68.95 (6.71)	67.83 (5.97)	0.13
Race (%)						0.60
Mexican American	4.37	4.68	4.55	4.37	3.87	
Non-Hispanic White	79.54	78.20	81.24	82.13	76.57	
Non-Hispanic Black	7.66	8.19	5.64	6.80	10.03	
Other	8.43	8.93	8.57	6.71	9.53	
Education level (%)						0.40
High school or below	15.60	16.14	12.42	16.44	17.41	
High school graduate	20.90	25.97	22.60	14.30	20.73	
More than high school	63.50	57.88	64.99	69.25	61.85	
Body mass index (%)						0.01
Normal(18.5 to < 25)	20.61	7.35	16.60	21.00	37.69	
Obese(30 or greater)	34.40	50.07	46.22	22.18	17.02	
Overweight(25 to < 30)	43.79	42.58	34.52	55.31	42.64	
Underweight(< 18.5)	1.20	0.00	0.65	1.51	2.65	
Annual household income (%)						0.80
< 20,000	11.58	12.55	8.82	12.39	12.54	
≥ 20,000	88.42	87.45	91.18	87.61	87.46	
Had at least 12 alcohol drinks in a year (%)						0.20
Yes	84.72	91.88	84.56	83.89	78.48	
No	15.28	8.12	15.44	16.11	21.52	
Smoked at least 100 cigarettes in life (%)						0.30
Yes	59.45	62.47	64.08	52.68	58.58	
No	40.55	37.53	35.92	47.32	41.42	
Total calcium (mmol/L)	2.36 (0.09)	2.35 (0.08)	2.37 (0.09)	2.36 (0.08)	2.38 (0.08)	0.01
Triglycerides (mmol/L)	1.83 (1.24)	2.01 (1.23)	2.31 (1.50)	1.68 (1.14)	1.29 (0.71)	0.01
T Score	-1.08 (0.96)	-1.13 (0.95)	-0.95 (1.00)	-0.93 (0.99)	-1.31 (0.85)	0.04

is crucial for maintaining overall bone health and may significantly mitigate the risk of conditions like osteoporosis, which are often linked to hormonal imbalances. Furthermore, our findings underscore the pressing need for further research aimed at identifying the serum testosterone range that optimally supports bone health. Concurrently, there is a clear imperative for the development of individualized treatment protocols that are sensitive to the unique hormonal characteristics of each patient. The non-linear correlation between testosterone and BMD points towards the need for a sophisticated and tailored approach to hormone replacement therapy (HRT), particularly in individuals presenting with serum testosterone levels at the extremes of the spectrum. It is essential for medical practitioners to consider the bidirectional effects of testosterone on bone metabolism and to advocate for personalized HRT that navigates between the risks of hypogonadism and hypergonadism. Future inquiries should be directed towards pinpointing the precise testosterone levels that confer maximal bone health benefits and should also assess the enduring impact of HRT on bone remodeling and the incidence of osteoporotic fractures in the aging male population. Lastly, in light of the prevalent occurrence of osteoporosis and related fractures among the elderly, our findings advocate for the incorporation of regular testosterone level monitoring as a routine adjunct to BMD measurements in the clinical management of older men. This integrated approach to clinical assessment can pave the way for a more comprehensive and personalized treatment strategy, potentially reducing the incidence of osteoporotic fractures and their attendant morbidity in this susceptible demographic.

Bone mineral density is an important indicator to assess bone health, and its changes can reflect bone strength and stability. According to the criteria of the World Health Organization (WHO), a T value below -2.5 is typically utilized to diagnose osteoporosis. Although the T-score did not meet the criteria for osteoporosis, it is still noteworthy. This is because even though the differences in T values may appear insignificant in the short term, they may have cumulative effects on bone health

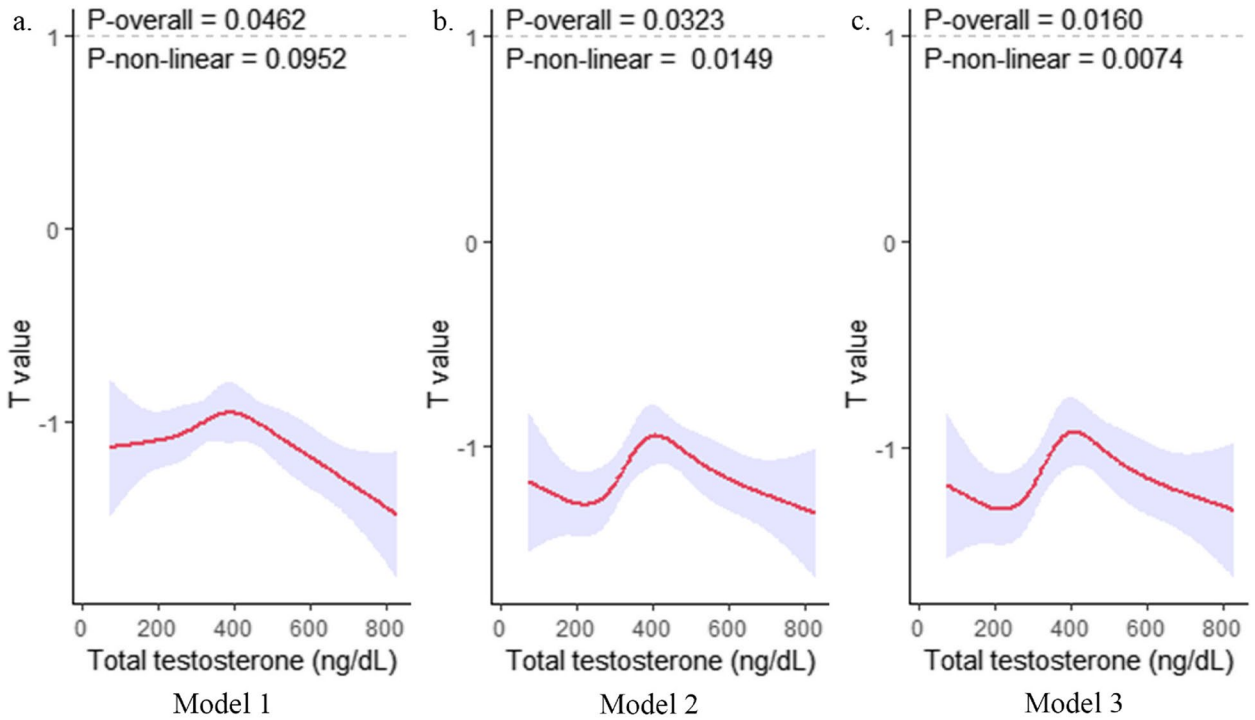


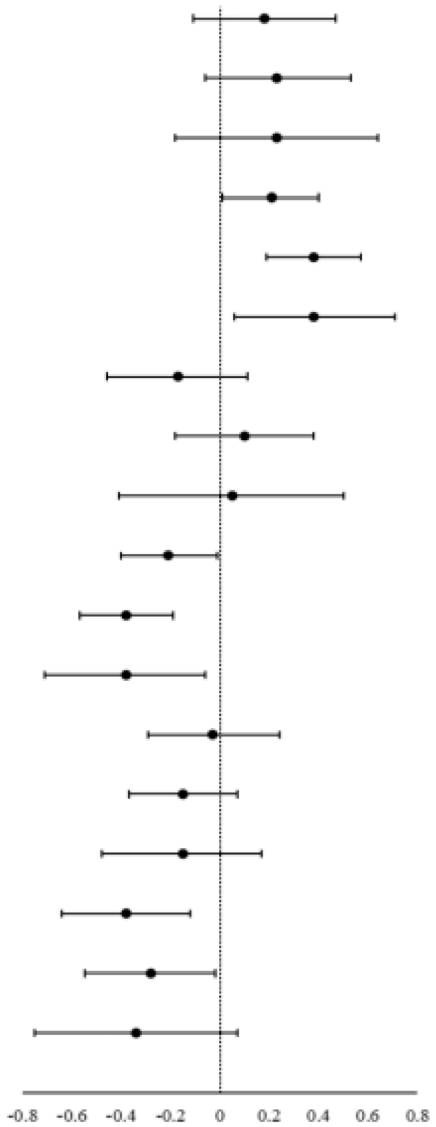
Fig. 2 The Nonlinear relationship between total testosterone with bone mineral density. Model 1: no covariates were adjusted; Model 2: BMI,total calcium,triglycerides were adjusted; Model 3: age, race, education, BMI annual household income, alcohol consumption, smoking behavior, total calcium, and triglycerides serum calcium were adjusted

over the long term. Studies indicate that small changes in BMD may accumulate over time, ultimately increasing the risk of fractures and impacting the microstructure and overall strength of the bone [14]. This means that the decrease in bone mineral density (BMD) increases the vulnerability and susceptibility to fractures, which is especially important for the elderly population. Osteopenia-related fractures can severely impact the quality of life, elevate the risk of complications, and potentially pose life-threatening consequences. Moreover, low BMD is linked to issues like chronic pain and spinal deformation, adversely affecting physical function and daily activities. Consequently, these small differences may have significant impacts on bone health, and bone density should be monitored regularly, and precautions should be taken to slow down bone loss.

Our study presents an inverted U-shaped association between testosterone levels and bone density in men over 60 years old. Specifically, we observed a positive correlation between testosterone levels in the third quartile (Q3) and bone density, while negative correlations were found in the first (Q1) and fourth quartiles (Q4). This suggests that both excessively high and low testosterone levels may adversely affect bone health in the elderly. A series of cohort study on older men have linked lower testosterone levels to decreased BMD and a higher fracture risk [15]. Low testosterone levels can lead to decreased bone mineral density, increasing the risk of osteoporosis. Interestingly, our research also revealed an inverse relationship between testosterone and BMD at high testosterone levels. This indicates that in older men, elevated plasma testosterone levels may not be enough to maintain optimal bone mass. However, the Bone sub-trial of the Testosterone trials demonstrated a higher bone mineral density (BMD) response when serum testosterone (T) levels reached approximately 500 ng/dL [16]. In contrast, the TRAVERSE trials, despite not providing BMD measurements, noted a higher incidence of fractures in men with lower serum T levels (~ 350 ng/dL) [17]. These discrepancies may be attributed to several factors that we will now discuss. Firstly, the study populations differ between the trials and our study. The Bone sub-trial of the Testosterone trials and the TRAVERSE trials included men with varying ages and health statuses, which could influence the relationship between testosterone and BMD. Additionally, our study exclusively focused on elderly men, a population that may exhibit different hormonal and bone metabolism dynamics compared to younger cohorts. Secondly, the study design plays a crucial role in the interpretation of results. While the Bone sub-trial of the Testosterone trials and the TRAVERSE trials were randomized, placebo-controlled trials, our study employed

Table 2 Association between total testosterone levels (ng/dL)) and femur bone mineral density (mg/cm2)

Total testosterone levels		β (95% CI)	*P* value
Q1 VS Q2	Model 1	0.18(-0.11, 0.47)	0.20
	Model 2	0.23(-0.06, 0.53)	0.10
	Model 3	0.23(-0.18, 0.64)	0.20
Q1 VS Q3	Model 1	0.21(0.01, 0.40)	0.04
	Model 2	0.38(0.19, 0.57)	0.01
	Model 3	0.38(0.06, 0.71)	0.03
Q1 VS Q4	Model 1	-0.17(-0.46,0.11)	0.20
	Model 2	0.1(-0.18, 0.38)	0.50
	Model 3	0.05(-0.41, 0.50)	0.80
Q3 VS Q1	Model 1	-0.21(-0.40, -0.01)	0.04
	Model 2	-0.38(-0.57, -0.19)	0.01
	Model 3	-0.38(-0.71, -0.06)	0.03
Q3 VS Q2	Model 1	-0.03(-0.29,0.24)	0.80
	Model 2	-0.15(-0.37, 0.07)	0.20
	Model 3	-0.15(-0.48, 0.17)	0.20
Q3 VS Q4	Model 1	-0.38(-0.64, -0.12)	0.01
	Model 2	-0.28(-0.55, -0.02)	0.04
	Model 3	-0.34(-0.75, 0.07)	0.08



Model 1: no covariates were adjusted.

Model 2: BMI, total calcium, triglycerides were adjusted.

Model 3: age, race, education, BMI, annual household income, alcohol consumption, smoking behavior, total calcium, and triglycerides serum calcium were adjusted.

a cross-sectional design. The cross-sectional nature of our research limits our ability to establish causality and may introduce biases that are not present in longitudinal, controlled trials. Thirdly, methodological differences in assessing BMD and testosterone levels could contribute to the contrasting findings. The TRAVERSE trials did not

provide BMD measurements, which makes direct comparison with our BMD data challenging. Furthermore, our use of weighted multivariate linear regression models and generalized additive models to account for potential nonlinearity may have unveiled a more nuanced relationship between testosterone and BMD that was not captured in the trials. While our findings appear to contrast with those of the trials mentioned, we believe these differences underscore the need for further research, particularly larger-scale, longer-term longitudinal studies to determine the long-term effects and safety of testosterone levels on bone health in the aging population.

The reasons for the inverted U-shaped association between testosterone levels and bone mineral density in men over the age of 60 may include the following: As individuals age, the hypothalamic-pituitary–testicular axis can weaken, resulting in a decline in testosterone production [18]. Low testosterone levels may reduce the stimulation of osteoblasts, leading to a decrease in bone formation [19]. At the same time, the process of testosterone conversion to estrogen may also be impaired, weakening the protective effect on bone mineral density [19].Testosterone affects osteocytes' androgen receptor directly and indirectly by converting osteocytes from the estrogen receptor to estradiol and dihydrotestosterone [20]. This results in reduced bone formation, increased bone resorption, shortened osteoblast lifespan, increased osteoblast death, and decreased mineralization capacity. Moreover, there is an increase in osteoclast formation, reduced apoptosis, and heightened osteoclast activity. Additionally, aging skeletal cells experience elevated reactive oxygen species (ROS) levels, which can harm proteins, lipids, and DNA, hindering osteoblast formation and contributing to osteoporosis development [15]. Conversely, an excess of testosterone can interfere with the feedback mechanisms of the hypothalamic-pituitary–gonadal axis, possibly affecting the bone remodeling process. This hormonal surplus may also modify the availability of free testosterone by affecting the levels of sex hormone-binding globulin (SHBG) [19]. It may also affect the activity of other hormones or signaling pathways involved in bone metabolism. Furthermore, high testosterone levels could potentially lead to an increase in oxidative stress, which can have detrimental effects on bone cells.

We incorporated age, ethnicity, education level, annual household income, Body mass index (BMI), alcohol consumption, smoking behavior, calcium, and triglycerides as covariates. The covariates were selected based on their known associations with bone health and potential confounding effects. Age, ethnicity, education level, and annual household income were included as they can influence lifestyle factors and access to healthcare, which in turn may affect bone density [21]. BMI is an important indicator of body composition and has been shown to be related to bone health [22]. Alcohol consumption and smoking behavior are known risk factors for various health conditions, including bone disorders [21]. Serum calcium is an essential mineral for bone formation and maintenance, and abnormal levels can impact bone mineral density [23]. Triglycerides were taken into consideration since they are associated with metabolic disorders which may exert an indirect effect on bone health. [24]. Each covariate was chosen to provide a more comprehensive understanding of the factors that could potentially influence bone mineral density in our study population.

Our study have highlighted the close relationship between BMI, triglycerides, calcium, and osteoporosis. Even after adjusting for these factors, testosterone remained significantly associated with BMD. Body Mass Index, a crucial indicator of body composition, has a profound and substantial impact on bone mineral density. Different levels of BMI can lead to varying degrees of changes in bone mineral density. Longitudinal analysis of 1,608 individuals completing a 5-year follow-up revealed that both low BMI (underweight) and high BMI (obesity) were correlated with an increased likelihood of developing osteoporosis [25]. Low BMI often correlates with malnutrition and inadequate protein intake, contributing to bone loss. Conversely, high BMI can exacerbate bone absorption, hinder bone formation, and predispose individuals to osteoporosis. Clinically, testing sex hormones in male obese osteoporosis patients may enhance diagnostic accuracy and guide treatment effectively. In our analysis, we identified significant variations in BMI distribution among the four testosterone quartiles. Notably, Q4 was characterized by the lowest combined proportion of individuals in the overweight and obese categories and conversely, the highest proportion of underweight individuals. This finding is particularly compelling as it suggests a complex interplay between BMI, testosterone levels, and bone health. Upon adjusting for BMI in our models 2 and 3, we observed that the significant associations were primarily evident when comparing with quartile Q1. This quartile, potentially comprising the largest subset of hypogonadal men, underscores the importance of testosterone in the context of low BMI and its implications for bone health. Given these observations, we acknowledge that once testosterone levels are within a normal range, BMI may indeed emerge as a predominant factor influencing low BMD. This suggests that while testosterone is crucial for maintaining bone integrity, particularly among hypogonadal men, BMI could be a significant factor of bone health in individuals with normal testosterone levels.

Triglycerides, a type of lipid molecule found in the bloodstream, have a profound and substantial influence

on bone mineral density. Changes in the level of triglycerides can lead to alterations in various physiological processes within the body. In a cross-sectional study involving 1,985 individuals aged 50 years and older, triglycerides showed a significant association with total lumbar BMD [26]. Further threshold effect analysis revealed an inverted U-shaped relationship between triglycerides and BMD. Triglyceride levels below 2.597 mmol/L were positively correlated with lumbar BMD, while levels above this threshold did not exhibit a statistically significant difference. Normal to moderately high triglyceride levels appeared to benefit bone health, whereas very high levels may not be associated with bone health. This may occur because triglycerides can act as energy reserves, providing energy support for the metabolic activities of osteocytes [27]. In older men, the body's energy requirements and metabolic levels may change as they age. Appropriate triglyceride reserves help maintain the normal function of osteocytes, promote bone formation, and maintain bone density. Additionally, triglycerides are not a simple indicator of obesity. Instead, they mainly reflect the state of lipid metabolism in the body. On the other hand, BMI primarily reflects an individual's overall degree of obesity. Although obese people are often accompanied by elevated triglycerides, elevated triglycerides are not entirely equivalent to obesity. Metabolic abnormalities in triglycerides may affect bone mineral density (BMD) independently of BMI.

Serum calcium levels significantly influence bone mineral density, serving as a crucial determinant in preserving the structural resilience and comprehensive health of our skeletal framework. Normal serum calcium levels are essential for maintaining the structure and strength of the bone. Two epidemiological analyses, encompassing 5,478 and 5,556 participants from the NHANES between 2003 and 2006, affirmed the causal and independent role of serum calcium in bone density through MR analysis [28]. This association remained statistically significant after adjusting for serum parathyroid hormone, 25 (OH) D, and phosphate levels. Testosterone can regulate calcium absorption, excretion, and deposition in bone through several pathways [29]. For instance, testosterone may promote the absorption of calcium in the gut and increase calcium reabsorption in the kidney, thereby affecting serum calcium levels [30]. Meanwhile, changes in serum calcium may in turn affect the effect of testosterone on BMD. For older men, reduced serum calcium levels due to inadequate dietary intake, decreased intestinal absorption function, or altered in renal excretion function. These age-related changes may occur simultaneously with decreases in testosterone levels and decreases in bone mineral density [31]. By including serum calcium as a covariate, controlling for these age-related changes in the analysis could more accurately assess the relationship between testosterone and BMD. In addition, Estradiol plays a crucial role in maintaining bone integrity in men, as evidenced by various studies. It acts on bone cells through estrogen receptors, influencing bone remodeling and mineralization. Low levels of estradiol in men are associated with decreased bone density and an increased risk of osteoporosis [32]. One study has indicated that an increase in serum estradiol concentrations during gender-affirming hormone therapy (GAHT) can significantly enhance both cortical and trabecular bone accrual, thereby improving bone strength [32]. Another study emphasized the key regulatory role of estrogen in bone metabolism in both men and women, noting that the loss of estrogens is linked to a decline in bone mineral density and that estradiol concentrations can predict the risk of fractures [33]. Future studies could explore the combined effects of testosterone and estradiol on bone health in older men to provide a more comprehensive understanding of the hormonal factors influencing bone metabolism. The bone matrix is an integral component of bone, essential for preserving bone strength and functionality. Its proper upkeep hinges on the equilibrium and stability of the assorted constituents it contains. Principally, these constituents are categorized into organic and inorganic materials [34]. The bone matrix's composition shifts with age, with the inorganic content becoming predominant. In the elderly, the inorganic fraction can surpass 75%, leading to enhanced bone brittleness and an increased risk of fractures [35]. Beyond monitoring hormone levels, it is imperative to take into account the multitude of factors that influence the bone matrix. Adopting a more holistic set of interventions and management strategies will be instrumental in safeguarding and promoting bone health more effectively.

The NHANES provides nationally representative data on the US civilian population, ensuring accuracy, consistency, and reliability of study data and results through standardized and uniform protocols for data collection and screening. This quality control framework contributes to the reliability of our current study. However, our research does have limitations. Firstly, due to the cross-sectional design, establishing a causal relationship between testosterone and bone mineral density is challenging. To address this, further longitudinal follow-up studies with a larger sample size are necessary. Secondly, while our study used a nationally representative sample in the United States focusing on men aged over 60, caution must be exercised in generalizing the results to all men, as demographic variations may influence the findings. Thirdly, there are limitations in the data from the NHANES database. Although we made every effort to minimize the impact of missing data by excluding those

with missing femoral neck BMD data, testosterone level data, or covariate data, the remaining missing data may still have introduced some bias. We are aware that this could potentially affect the generalizability and reliability of our results. Fourthly, there is a lack of adjustment for vitamin D levels, creatinine, liver dysfunction, and estradiol in the models. While these factors are known to potentially have a direct impact on bone density, there is a significant absence of data regarding these variables in the existing datasets. Fifthly, we are unable to obtain information on the exact number of men in the study who are taking testosterone. Therefore, we cannot determine the number of people with low bone mineral density who are actually taking testosterone. This may have a certain impact on the interpretation and application of the research results. Nevertheless, our study still provides valuable insights into the relationship between testosterone levels and BMD in elderly men.

Conclusion

Our findings unveiled an inverted U-shaped association between testosterone and BMD, indicating that for older American men, both excessively high and excessively low testosterone levels can have adverse effects on bone health. In conclusion, maintaining an optimal level of androgen is crucial for preserving bone integrity in elderly men. The nuanced relationship between testosterone and bone mineral density highlights the importance of a balanced hormonal milieu in supporting the structural and functional aspects of the skeletal system. It is the careful regulation of these levels that may contribute to the overall bone health, potentially mitigating the risks associated with imbalances that could lead to conditions such as osteoporosis.

Abbreviations

BMD	Bone mineral density
T	Testosterone (T)
DHT	Dihydrotestosterone
SHBG	Sex hormone-binding globulin
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
WHO	World Health Organization
ID-LC–MS/MS	Isotope dilution liquid chromatography tandem mass spectrometry National
BMI	Body mass index
NIST	Institute for Standards and Technology's
ROS	Reactive oxygen species

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Authors' contributions

JiMa, Jian Zhao, Ning Wu contributed equally to this work as joint first authors. They were responsible for designing the study, collecting and analyzing the data, interpreting the results, and drafting the manuscript. Minghua Han provided critical insights into the interpretation of the findings and revised the manuscript for important intellectual content. Zhuojing Yang assisted in data collection and contributed to the manuscript preparation. Qian Zhao and Haoyang Chen supervised the entire project, including study conception, design, data analysis, interpretation of results, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability

The National Health and Nutrition Examination Survey (NHANES) maintains comprehensive data for all analyses undertaken throughout the study period, and these datasets are accessible upon request through the official website: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The survey protocol received ethical clearance from the Ethics Review Board of the National Center for Health Statistics. Prior to their participation in the study, every individual participant provided their written informed consent, ensuring adherence to ethical principles.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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