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Correlation between low testosterone levels and the risk of osteoarthritis: a cross-sectional analysis of NHANES data (2011–2016)

Ning Ma[1] and Fang Gao[1*]

Abstract

Background Osteoarthritis (OA) is a common degenerative joint disease that significantly impacts the quality of life, especially among older adults. Testosterone, a critical hormone for musculoskeletal health, has been suggested to influence OA pathogenesis. However, the relationship between low testosterone levels and OA risk remains underexplored in large, representative populations. This study aimed to investigate the association between low testosterone levels and OA risk using data from the National Health and Nutrition Examination Survey (NHANES, 2011–2016).

Methods This cross-sectional analysis included 4,548 participants from NHANES, a nationally representative U.S. dataset. Testosterone levels were categorized as low or normal, with low testosterone defined as < 300 ng/dL for men and population-based cutoffs for women. The presence of OA was determined through self-reported physician diagnosis. Multivariable logistic regression models were used to examine the association between testosterone levels and OA risk, adjusting for demographic, socioeconomic, lifestyle, and clinical factors. Restricted cubic spline (RCS) analysis was conducted to evaluate non-linear relationships. Subgroup analyses were performed to assess consistency across key demographic and clinical strata.

Results Among the 4,548 participants, 812 (17.9%) were diagnosed with OA. Participants with OA were older, more likely to be female, and exhibited higher rates of obesity and hyperlipidemia. In fully adjusted models, low testosterone levels were significantly associated with increased OA risk (OR, 1.22; 95% CI, 1.02–1.46; $P = 0.028$). RCS analysis indicated a non-linear relationship, with a steep increase in OA risk at lower testosterone levels, suggesting a threshold effect. Subgroup analyses demonstrated consistent associations across demographic and clinical groups without significant interactions.

Conclusion Low testosterone levels are independently associated with an increased risk of OA in the U.S. population. These findings underscore the potential role of hormonal health in OA pathogenesis and highlight the need for longitudinal studies to clarify causal pathways. The observed non-linear relationship suggests that maintaining optimal testosterone levels may be important for joint health, and testosterone replacement therapy could be explored as a preventative strategy for individuals with testosterone deficiency.

*Correspondence:
Fang Gao
csbg521@126.com

Full list of author information is available at the end of the article

Keywords Osteoarthritis, Testosterone, NHANES, Hormonal health, Joint disease, Cross-sectional analysis, Testosterone replacement therapy

Introduction

Osteoarthritis (OA) is one of the most prevalent degenerative joint diseases worldwide, affecting millions of individuals and leading to significant morbidity and impaired quality of life, especially among older adults [1, 2]. It is characterized by the progressive breakdown of joint cartilage, bone remodeling, and synovial inflammation, resulting in pain, stiffness, and reduced joint function [3, 4]. As the global population ages, the incidence of OA is projected to increase, making it a significant public health challenge [5].

The etiology of OA is complex and multifactorial, with various risk factors including age, genetics, obesity, joint injury, and mechanical stress [6, 7]. Recently, there has been increasing interest in the role of systemic hormonal factors, particularly sex hormones, in the pathogenesis of OA [8, 9]. Testosterone, a key sex hormone in both males and females, plays a critical role in musculoskeletal health, influencing bone density, muscle mass, and cartilage integrity [10, 11]. Testosterone deficiency, particularly in men, has been associated with increased risk of several age-related conditions, including osteoporosis, sarcopenia, and cardiovascular diseases [12, 13].

Emerging evidence suggests that testosterone may also play a protective role in joint health. Testosterone receptors have been identified in articular cartilage, and animal studies have shown that testosterone exerts anabolic effects on cartilage, promoting matrix synthesis and inhibiting degradation [14, 15]. Furthermore, testosterone has anti-inflammatory properties that may mitigate the chronic low-grade inflammation observed in OA [16, 17]. Conversely, low testosterone levels have been linked to increased levels of pro-inflammatory cytokines and oxidative stress, which are key contributors to the pathophysiology of OA [18, 19].

Several observational studies have reported an association between low serum testosterone levels and an increased risk of OA, particularly in men [20, 21]. For example, a cross-sectional analysis of older men from the Osteoporotic Fractures in Men (MrOS) study found that lower testosterone levels were significantly associated with a higher prevalence of radiographic knee OA [22]. Similarly, data from the European Male Ageing Study (EMAS) demonstrated that men with testosterone deficiency were more likely to report symptoms of OA and had higher levels of cartilage degradation markers [23].

The National Health and Nutrition Examination Survey (NHANES) provides a valuable dataset for investigating the relationships between hormone levels and chronic diseases. NHANES collects comprehensive health data from a representative sample of the U.S. population, including serum testosterone levels and self-reported diagnosis of OA [24]. Recent studies using NHANES data have explored the associations between sex hormones and various musculoskeletal disorders, such as osteoporosis and sarcopenia, but the specific relationship between testosterone levels and OA has not been extensively examined [25–27]. Given the potential links between hormonal health and joint integrity, further analysis of testosterone levels in relation to OA using large, population-based data like NHANES could provide new insights into the role of hormonal factors in OA development and progression.

In this study, we aim to examine the relationship between testosterone levels and OA risk using NHANES data, considering several key covariates that are known to influence both testosterone levels and OA risk. These covariates, which include demographic factors such as age, sex, race/ethnicity, and education level, as well as lifestyle and clinical factors like body mass index (BMI), smoking, alcohol consumption, hypertension, and comorbidities, are central to understanding the multifactorial nature of OA (Figure S1). Understanding these associations may have important implications for identifying individuals at higher risk of OA and could help guide future preventive and therapeutic strategies.

Methods

Study population

This study utilized data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2016. NHANES is a stratified multistage probability survey designed to collect nationally representative data on the non-institutionalized civilian population of the United States. The National Center for Health Statistics (NCHS) Research Ethics Review Committee reviewed and approved the survey, confirming that informed consent was obtained from all participants.

The initial sample included 24,133 participants. After excluding individuals with missing testosterone measurements (n=2,541), the remaining sample consisted of 21,592 participants. We further excluded participants without osteoarthritis data, reducing the sample to 8,693. Lastly, after excluding participants with missing covariates, the final analytic sample included 4,548 participants, of whom 3,736 did not have osteoarthritis, and 812 had osteoarthritis (Fig. 1).

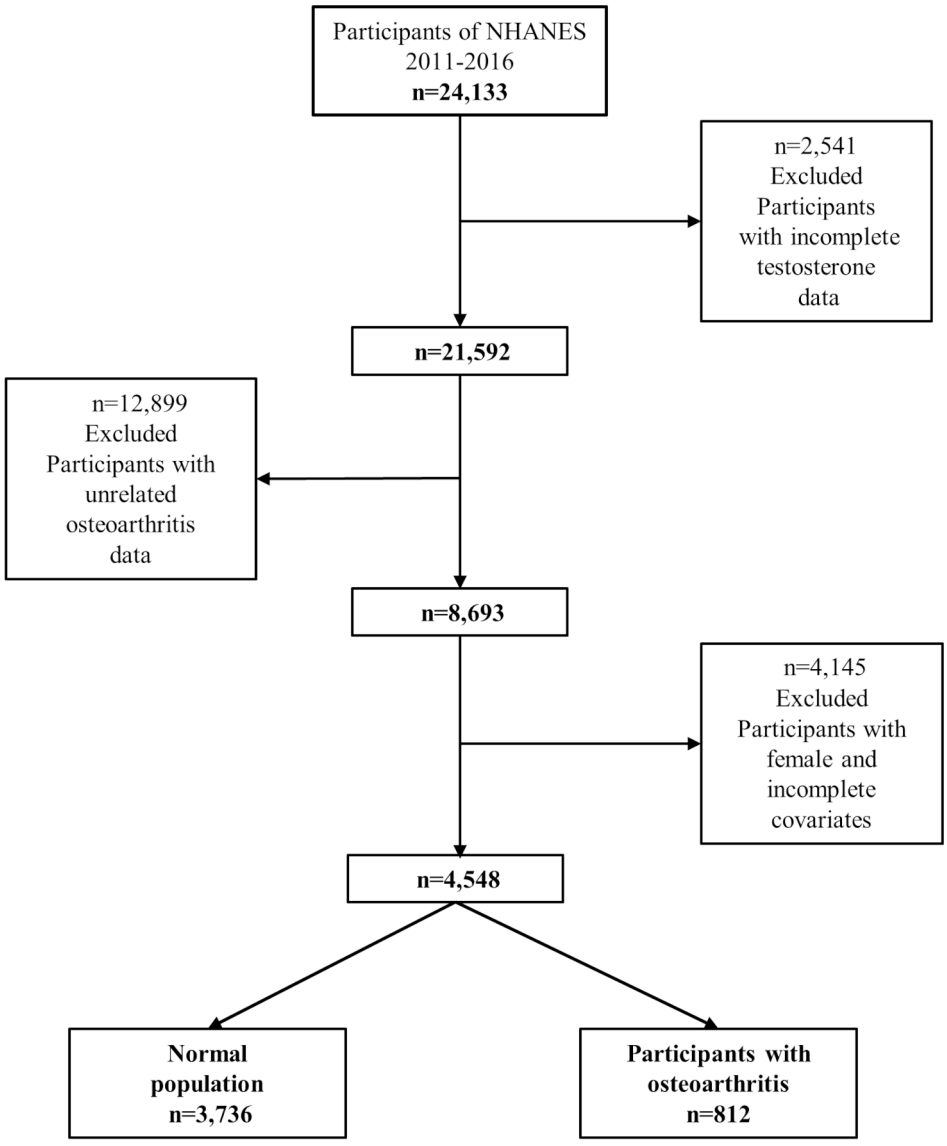

Fig. 1 Flow chart of participant selection

Diagnosis of osteoarthritis

In this study, the diagnosis of osteoarthritis (OA) as the primary outcome variable, was based on self-reported data from the NHANES dataset, specifically from the "Medical Conditions" section. Participants were first asked, "Has a doctor or other health professional ever told you that you had arthritis?" If the answer was "yes," participants were subsequently asked, "What type of arthritis was it?" The response options included "Rheumatoid arthritis," "Osteoarthritis," "Psoriatic arthritis," "Other," "Refused," and "Don't know." Participants who identified as having "Osteoarthritis" were classified into the OA group, while those reporting other types of arthritis or unspecified responses were excluded from the OA analysis [28].

Variables

All covariates were assessed using standardized NHANES questionnaires and laboratory measurements. These covariates were then categorized into four groups: demographic, socioeconomic, lifestyle and clinical factors. These factors are known to influence both osteoarthritis (OA) and testosterone levels, and were selected based on their relevance to both conditions. Specifically, the demographic factors included age (<50 or ≥50 years), sex (male, female), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, other race). Socioeconomic factors, such as education level (less than high school, high school or equivalent, more than high school) and marital status (married/cohabitating, widowed/divorced/separated, never married), were also included. Lifestyle factors,

including smoking status (ever smoked at least 100 cigarettes) and alcohol consumption (≥12 drinks in the past year or not), were accounted for. Clinical factors included the presence of hypertension, diabetes, hyperlipidemia, and body mass index (BMI: <25, 25-29.9, ≥30 kg/m²). A visual diagram (Fig. 2) was developed to illustrate the relationships between these variables and their potential effects on testosterone levels and OA risk.

Testosterone assessment

The primary exposure of interest was testosterone level, categorized as low or normal based on reference ranges specific to male and female participants. Testosterone levels were measured using mass spectrometry assays from morning blood samples collected during NHANES laboratory examinations. The testosterone levels were categorized into two groups: low testosterone, defined as levels below the 2.5th percentile of the population distribution, and normal testosterone levels. For men, low testosterone was defined as less than 300 ng/dL, while in women, a low testosterone threshold was used based on population norms [29].

Statistical analysis

All analyses accounted for NHANES's complex, multistage probability sampling design. Descriptive statistics were used to summarize participant characteristics, with continuous variables presented as mean±standard deviation (SD) and categorical variables as frequencies and percentages. Normality tests were conducted to justify the use of mean±SD for continuous variables. Differences between participants with and without osteoarthritis were compared using independent t-tests for continuous variables and chi-square tests for categorical variables.

We used multivariable logistic regression models to examine the association between testosterone levels and osteoarthritis. Three models were developed: Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was additionally adjusted for race/ethnicity, education level, marital status, PIR, smoking status, alcohol use, hypertension, diabetes, hyperlipidemia, and BMI. To ensure the validity of the regression analysis, Variance Inflation Factor (VIF) was calculated for all predictors to ensure no significant multicollinearity (VIF<2 for all variables). Box-Tidwell transformations were applied to verify the linearity of continuous predictors with the logit of the dependent variable. Cook's distance was used to identify and address influential data points.

To assess potential non-linear relationships between testosterone levels and osteoarthritis, we used restricted cubic splines with testosterone levels as the continuous variable. Restricted cubic splines with 3 knots, determined using the Akaike Information Criterion (AIC), were applied to model potential non-linear relationships between testosterone levels and osteoarthritis risk. The knots were placed at the 10th, 50th, and 90th percentiles of the testosterone distribution. This approach was chosen to ensure flexibility in capturing the relationship

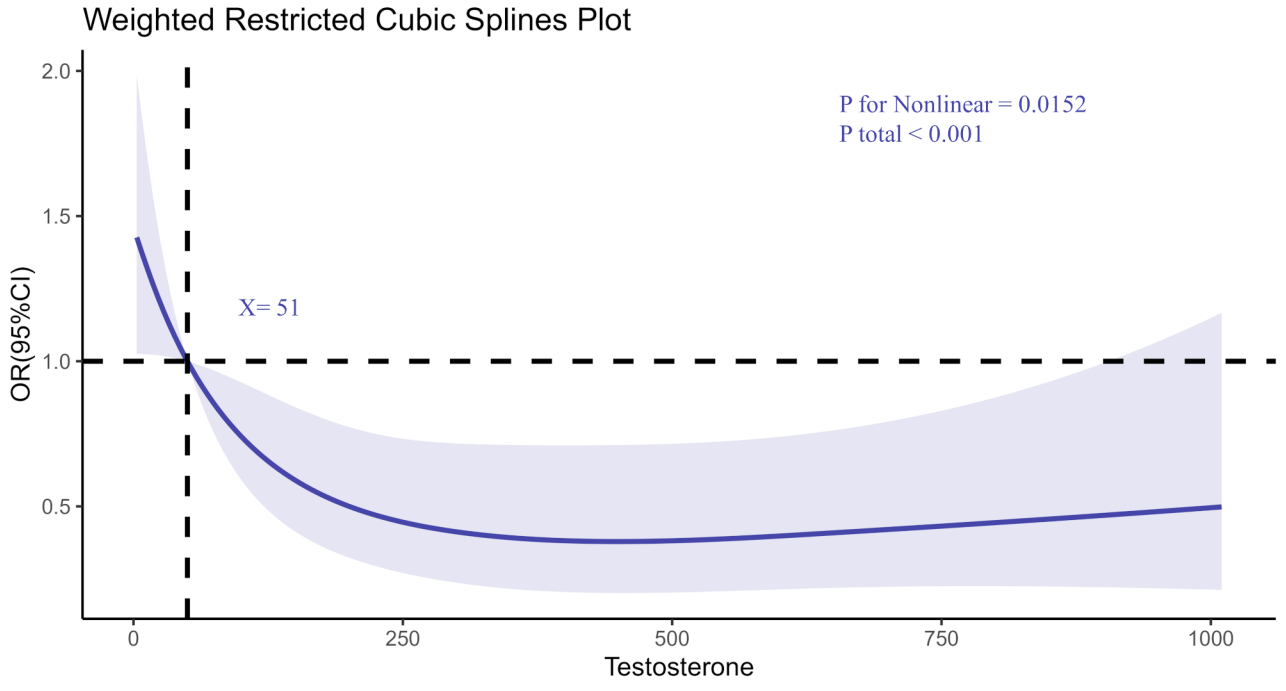

Fig. 2 Determination of the association between testosterone and osteoarthritis by restricted cubic spline (RCS) regression analysis

across the full range of testosterone levels while avoiding overfitting.

Subgroup analyses were performed to evaluate the consistency of associations across demographic (e.g., age, sex) and clinical categories (e.g., BMI). Interaction terms were included in regression models to test for significant modifications of the association between testosterone levels and OA risk. A two-sided p-value of <0.05 was considered statistically significant for all analyses. All analyses were performed using SPSS 27.0 (IBM Corp., Chinese localization by Beijing Easy Scientific, Beijing, China) and R 4.4.1 (Chinese mirror site of the R Foundation for Statistical Computing, maintained by Tsinghua University, Beijing, China) software, considering the complex survey design of NHANES.

Results

Baseline characteristics of the study population

The baseline characteristics of the 4,548 participants included in the study are presented in Table 1. Of the total participants, 812 (17.9%) were diagnosed with osteoarthritis (OA). Significant differences were observed between participants with and without OA across several demographic and clinical variables. Participants with OA were older compared to those without OA (60.26±15.06 years vs. 44.92±16.88 years, $P<0.001$) and were more likely to be female (71.4% vs. 49.2%, $P<0.001$). Higher rates of obesity, hyperlipidemia, and smoking were observed in the OA group compared to the non-OA group (all $P<0.001$).

Regarding racial/ethnic distribution, non-Hispanic Blacks constituted a larger proportion of OA cases (10.8%) compared to the control group (32.3% non-Hispanic Black). Educational attainment was also significantly associated with OA, with a higher percentage of participants with less than a high school education having OA ($P=0.001$).

In terms of lifestyle factors, a larger proportion of individuals with OA were smokers ($P<0.001$), and fewer consumed alcohol compared to those without OA ($P=0.020$). Clinical characteristics showed significant differences, with higher proportions of individuals with OA having hyperlipidemia (54.0% vs. 28.9%, $P<0.001$) and obesity (BMI≥30: 43.6% vs. 28.7%, $P<0.001$).

Association between testosterone and osteoarthritis

The results of the multivariable logistic regression analysis assessing the association between testosterone levels and osteoarthritis are presented in Table 2. In the unadjusted model (Model 1), low testosterone levels were significantly associated with an increased risk of OA (odds ratio [OR], 2.22; 95% confidence interval [CI], 1.90–2.59; $P<0.001$). After adjusting for age and gender in Model 2, the association remained significant, though attenuated (OR, 1.25; 95% CI, 1.05–1.48; $P=0.012$). In the fully adjusted model (Model 3), which accounted for additional covariates such as race/ethnicity, marital status, education, poverty-income ratio, smoking status, alcohol use, hypertension, diabetes, hyperlipidemia, and BMI, low testosterone levels were still associated with a higher risk of OA (OR, 1.22; 95% CI, 1.02–1.46; $P=0.028$).

Non-linear relationship between testosterone levels and osteoarthritis

The restricted cubic spline analysis indicated a non-linear association between testosterone levels and the risk of OA, with an inflection point of 51 ng/dL ($P<0.001$) (Fig. 2). As testosterone levels decreased, the risk of OA increased, suggesting a potential threshold effect at lower testosterone levels. This relationship plateaued at moderate testosterone levels, but the risk sharply increased as testosterone levels fell below the identified threshold.

Subgroup and interaction analyses

Subgroup analyses showed that the association between low testosterone levels and increased OA risk was consistent across key demographic and clinical strata (e.g., age, sex, BMI categories) (Fig. 3). No significant interactions were observed between testosterone levels and covariates such as age or BMI (P for interaction>0.05 for all). For example, among participants with BMI≥30 kg/m², low testosterone was significantly associated with OA risk (adjusted OR, 1.30; 95% CI, 1.05–1.61). A similar pattern was observed for participants aged≥50 years (adjusted OR, 1.24; 95% CI, 1.03–1.50). These findings suggest that low testosterone levels independently contribute to OA risk, with no significant modification of this relationship by demographic or clinical factors.

Model fit and statistical assumptions

Model diagnostics confirmed the absence of significant multicollinearity (all VIFs<2), and the linearity assumption for continuous covariates was met based on Box-Tidwell transformations. Additionally, Cook's distance values indicated no influential outliers that could unduly affect the regression results. Models incorporating non-linear terms provided a better fit based on lower Akaike Information Criterion (AIC) values compared to purely linear models (ΔAIC=12.5).

Discussion

In this study, we explored the relationship between low testosterone levels and the risk of osteoarthritis (OA) using data from NHANES (2011–2016). Our findings suggest that low testosterone levels are significantly associated with an increased risk of OA, even after adjusting for multiple demographic, socioeconomic, lifestyle, and clinical covariates. The results also reveal a non-linear

Table 1 Characteristics of the study population based on the rheumatoid arthritis people

Characteristics	Overall	Osteoarthritis		*P*-value
		No	Yes	
n	4548	3736	812	
Gender, *n* (%)				< 0.001
Male	2129(46.8%)	1897(41.7%)	232(5.1%)	
Female	2419(53.2%)	1839(40.4%)	580(12.8%)	
Age, years	47.66 ± 17.58	44.92 ± 16.88	60.26 ± 15.06	< 0.001
Race, *n* (%)				< 0.001
Mexican American	518(11.4%)	443(9.7%)	75(1.6%)	
Other Hispanic	408(9.0%)	356(7.8%)	52(1.1%)	
Non-Hispanic Black	1961(43.1%)	1469(32.3%)	492(10.8%)	
Non-Hispanic White	911(20.0%)	775(17.0%)	136(3.0%)	
Other races	750(16.5%)	693(15.2%)	57(1.3%)	
Education, *n* (%)				0.001
Less than 9th grade	277(6.1%)	220(4.8%)	57(1.3%)	
9-11th grade	564(12.4%)	470(10.3%)	94(2.1%)	
High school graduate	994(21.9%)	832(18.3%)	162(3.6%)	
Some college or AA degree	1460(32.1%)	1174(25.8%)	286(6.3%)	
College graduate or above	1253(27.5%)	1040(22.9%)	213(4.7%)	
Marital Status, *n* (%)				0.756
Married	2404(52.9%)	1958(43.1%)	446(9.8%)	
Widowed	302(6.6%)	184(4.0%)	118(2.6%)	
Divorced	491(10.8%)	372(8.2%)	119(2.6%)	
Separated	119(2.6%)	99(2.2%)	20(0.4%)	
Never married	919(20.2%)	836(18.4%)	83(1.8%)	
Living with partner	313(6.9%)	287(6.3%)	26(0.6%)	
PIR, *n* (%)				0.767
<=1	946(20.8%)	803(17.7%)	143(3.1%)	
1–3	1779(39.1%)	1444(31.8%)	335(7.4%)	
> 3	1823(40.1%)	1489(32.7%)	334(7.3%)	
Smoke, *n* (%)				< 0.001
Yes	1748(38.4%)	1392(30.6%)	356(7.8%)	
No	2800(61.6%)	2344(51.5%)	456(10.0%)	
Alcohol Use, *n* (%)				0.020
Yes	3132(68.9%)	2578(56.7%)	554(12.2%)	
No	1416(31.1%)	1158(25.5%)	258(5.7%)	
Hypertension, *n* (%)				0.179
Yes	1510(33.2%)	1074(23.6%)	436(9.6%)	
No	3038(66.8%)	2662(58.5%)	376(8.3%)	
Hyperlipidemia, *n* (%)				< 0.001
Yes	1517(33.4%)	1079(23.7%)	438(9.6%)	
No	3031(66.6%)	2657(58.4%)	374(8.2%)	
Diabetes, *n* (%)				0.946
Yes	521(11.5%)	362(8.0%)	159(3.5%)	
Borderline	97(2.1%)	69(1.5%)	28(0.6%)	
No	3930(86.4%)	3305(72.7%)	625(13.7%)	
BMI				< 0.001
< 25	1580(34.7%)	1366(30.0%)	214(4.7%)	
25–30	1541(33.9%)	1297(28.5%)	244(5.4%)	
>=30	1427(31.4%)	1073(23.6%)	354(7.8%)	

Table 2 Weighted logistic regression analyses of association between testosterone and osteoarthritis

	Model 1		Model 2		Model 3	
	OR 95%CI	*P* value	OR 95%CI	*P* value	OR 95%CI	*P* value
Normal	Reference		Reference		Reference	
Low testosterone	2.22(1.90,2.59)	< 0.001	1.25(1.05,1.48)	0.012	1.22(1.02,1.46)	0.028

Model 1: Unadjusted

Model 2: Adjusted for gender and age

Model 3: Additionally, adjusted for race, marital status, education, poverty-income ratio smoke, alcohol Use, hypertension, hyperlipidemia, diabetes, BMI, and sleep time

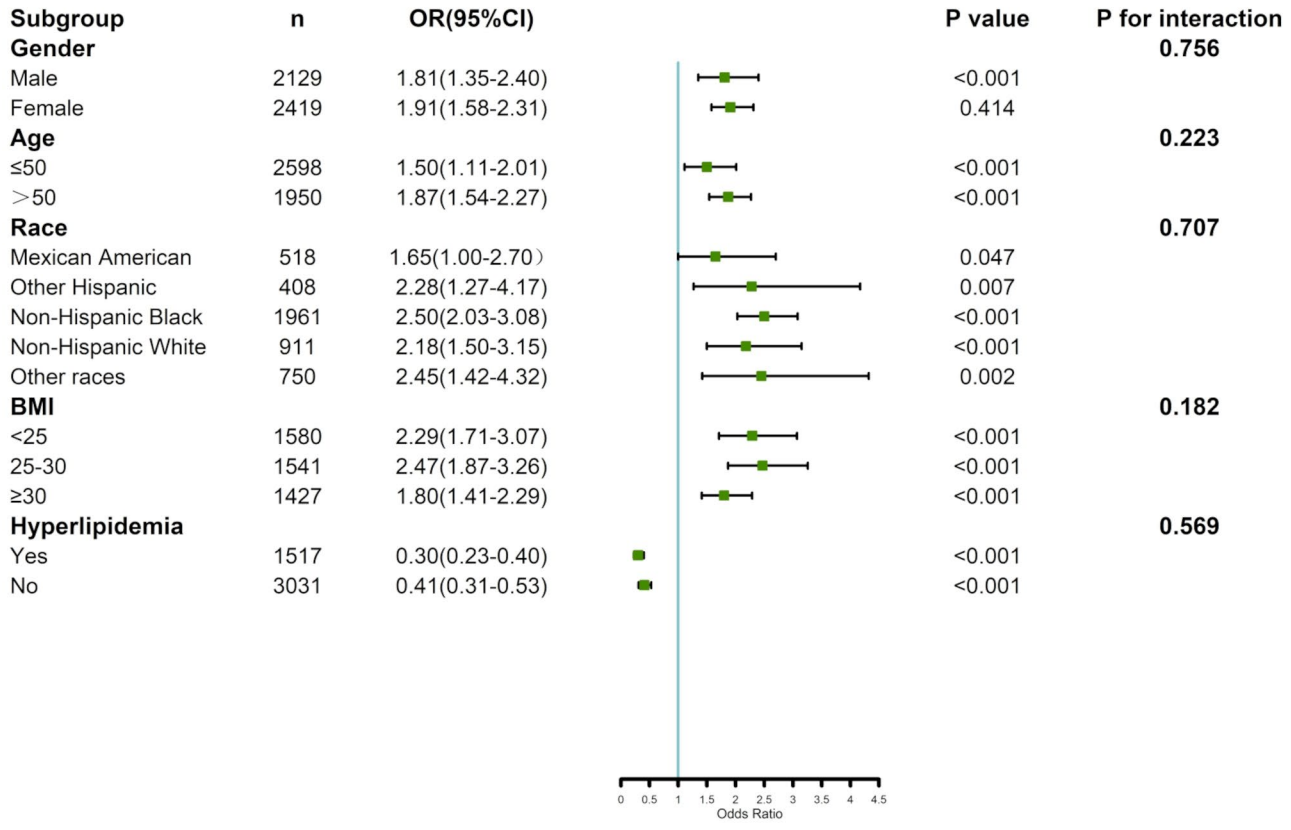

Fig. 3 Verification of the association between testosterone and osteoarthritis by subgroup analyses and interaction analyses

relationship between testosterone levels and OA risk, suggesting a potential threshold effect. These findings contribute to the growing body of evidence linking hormonal health to musculoskeletal disorders.

Comparison with previous studies

Our results are consistent with previous research that has demonstrated a link between low testosterone and musculoskeletal disorders. For instance, Freystaetter et al. (2020) found that low levels of testosterone were associated with an increased risk of developing osteoarthritis, particularly in older men [30]. Similarly, Schwanbeck (2020) observed that lower testosterone levels were associated with reduced muscle mass and strength, which are important factors in the development of OA [31]. Moreover, several studies have highlighted the role of testosterone in maintaining muscle mass and joint health, with reduced levels contributing to sarcopenia and joint deterioration [32, 33]. Our study extends these findings by showing that the relationship between testosterone and OA is not only linear but also remains robust across different subgroups, including age and BMI categories [34].

Interestingly, our restricted cubic spline analysis revealed a non-linear relationship between testosterone levels and OA risk, with a significant inflection point at 51 ng/dL. Below this threshold, testosterone levels were strongly associated with increased OA risk, but the relationship plateaued as testosterone levels rose above this threshold. This threshold effect is consistent with previous research that found a similar pattern between testosterone levels and fracture risk [35]. These findings

suggest that testosterone's protective effects on joint and bone health may be most pronounced at lower ranges, and once a certain threshold is crossed, the risk of OA increases sharply [36].

Mechanisms of testosterone and osteoarthritis

The exact mechanisms underlying the relationship between low testosterone and OA are complex and multifactorial. Testosterone is known to have anabolic effects on muscle and bone tissue and plays a critical role in maintaining cartilage health by modulating chondrocyte activity and reducing inflammation [37, 38]. Testosterone deficiency has been linked to cartilage degradation and joint dysfunction, increasing the susceptibility to OA [39]. One of the key mechanisms through which testosterone influences OA risk is its modulation of inflammatory cytokines [40]. Low testosterone levels are associated with increased systemic inflammation, a well-established risk factor for OA and other musculoskeletal conditions [41]. Specifically, testosterone deficiency has been shown to increase levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [42], which play a central role in the pathogenesis of OA by promoting cartilage breakdown and joint inflammation. Elevated IL-6 and TNF-α levels are known to disrupt cartilage homeostasis and enhance the catabolic processes that contribute to joint damage [43].

In addition to pro-inflammatory cytokines, recent studies have identified other pro-inflammatory markers, such as C-reactive protein (CRP) and interleukin-1β (IL-1β), as being crucial in driving OA progression. Elevated CRP levels are strongly associated with increased OA severity and pain [44], while IL-1β exacerbates cartilage degradation by inducing chondrocyte apoptosis and inhibiting matrix synthesis [45]. These findings underscore the importance of targeting inflammatory cytokines in the treatment of OA. Furthermore, testosterone deficiency has been linked to a reduction in the production of anti-inflammatory cytokines like interleukin-10 (IL-10), which normally act to suppress inflammation and protect cartilage [46]. The imbalance between pro-inflammatory and anti-inflammatory cytokines in individuals with low testosterone could thus further exacerbate cartilage degradation and OA progression [47]. In light of these mechanisms, emerging research suggests that restoring testosterone levels may potentially help rebalance the inflammatory response, offering a therapeutic approach to mitigate OA risk, offering a promising therapeutic avenue to mitigate OA risk [17].

Testosterone also plays a critical role in cartilage repair. For instance, testosterone influences the expression of growth factors such as insulin-like growth factor 1 (IGF-1) and transforming growth factor-beta (TGF-β), which are critical for cartilage regeneration [48, 49]. Reduced levels of these factors in individuals with low testosterone may hinder cartilage repair, leading to accelerated OA progression [50]. Furthermore, testosterone deficiency has been linked to elevated oxidative stress, which exacerbates cartilage damage and accelerates joint tissue degradation. Increased oxidative stress leads to the generation of reactive oxygen species (ROS), which directly harm chondrocytes and facilitate the breakdown of the extracellular matrix, contributing to the progression of OA [51].

In addition to direct effects on cartilage and inflammation, testosterone deficiency often coexists with obesity and metabolic syndrome, both of which are known contributors to OA development. Both obesity and metabolic syndrome can exacerbate the inflammatory environment, with elevated adipokines such as leptin and adiponectin promoting systemic inflammation. These metabolic disturbances may synergize with testosterone deficiency to increase OA risk, particularly in individuals with central obesity or those who have developed insulin resistance. The interplay between low testosterone, increased adiposity, and systemic inflammation may create a vicious cycle, further accelerating cartilage degradation and OA progression.

Subgroup analysis and lack of interaction effects

In addition to testosterone levels, several other factors were included in our analysis to adjust for potential confounding effects. These factors, such as age, sex, BMI, and lifestyle habits, not only influenced by testosterone levels but also independently affect OA risk [52, 53]. For example, the association between low testosterone and OA risk may differ by age or sex, as older adults and men tend to have lower testosterone levels and higher OA risk [53]. Additionally, obesity and metabolic conditions like diabetes and hypertension are known to contribute to OA pathogenesis [54], and their interaction with testosterone levels may exacerbate the overall risk. Our study demonstrated that the association between low testosterone and OA was consistent across various demographic and clinical subgroups, with no significant interaction effects observed. This lack of significant interactions suggests that the impact of testosterone on OA risk is relatively uniform across different populations. Specifically, no substantial modifications in the testosterone-OA association were found based on factors such as age or BMI. These findings highlight the robustness and generalizability of the relationship between low testosterone and OA risk, suggesting that the impact of testosterone on OA risk is largely independent of these factors.

Prior studies have similarly found that testosterone deficiency is a risk factor for OA in both men and women, although the association tends to be stronger in men due to their higher baseline testosterone levels [55].

However, the lack of significant interaction effects in our study contrasts with some earlier research that suggested metabolic syndrome or obesity may amplify the negative effects of low testosterone on joint health [56, 57]. Despite this, our findings align with recent research by Han et al. (2021), which found that while both low testosterone and high BMI independently increase the risk of OA, their combined effect does not appear to be synergistic [58]. These findings suggest that while both factors contribute to OA risk, their mechanisms may operate in parallel rather than interacting directly [59]. This discrepancy may be attributed to differences in study designs, sample sizes, or the specific population studied, but it also underscores the need for future research to clarify the mechanisms through which testosterone interacts with other metabolic factors to influence OA risk.

Implications for clinical practice

Our findings have important clinical implications for the prevention and management of OA, particularly in populations at risk for testosterone deficiency. Given the non-linear relationship between testosterone levels and OA risk, as identified in our study, it is essential to consider not only the presence of low testosterone but also the optimal range of testosterone levels for minimizing OA risk. Screening for low testosterone in middle-aged and older adults could be a valuable strategy for the early identification of individuals at high risk for OA [60], especially those whose testosterone levels fall below the identified threshold of 51 ng/dL. This threshold effect suggests that testosterone levels below this threshold may significantly increase OA risk, while levels above it may not provide additional benefit.

Testosterone replacement therapy (TRT) has shown promise in improving musculoskeletal health in hypogonadal men, and our study suggests that TRT may also help reduce OA risk in individuals with low testosterone [61, 62]. However, the threshold effect implies that TRT may be particularly beneficial for individuals whose testosterone levels fall below the optimal threshold, whereas those with testosterone levels above this threshold may not see significant improvements in OA risk from TRT. This underscores the importance of individualized treatment strategies tailored to specific testosterone levels rather than a one-size-fits-all approach.

Furthermore, our results underscore the importance of addressing modifiable risk factors such as obesity and metabolic syndrome, which are common comorbidities in individuals with low testosterone and OA [63]. Interventions targeting both hormonal imbalances and metabolic health, including weight management and lifestyle modifications, may be particularly effective in reducing OA risk [64]. Since both testosterone deficiency and obesity independently contribute to OA, combining TRT with weight management and metabolic interventions could offer a more comprehensive strategy for OA prevention and management.

Strengths and limitations

One of the key strengths of our study is the use of a large, nationally representative sample from NHANES, which enhances the generalizability of our findings. Additionally, we controlled for a wide range of potential confounders, and the use of restricted cubic splines allowed us to explore the non-linear relationship between testosterone levels and OA risk.

While our study provides valuable insights, several limitations of this study must be considered. First, the cross-sectional design of the NHANES data limits causal inferences, as it captures a snapshot of testosterone levels and osteoarthritis (OA) risk at a single time point, precluding the ability to determine the directionality of the association. It remains unclear whether low testosterone contributes to OA development or whether OA leads to lower testosterone levels, potentially through mechanisms such as chronic inflammation. Second, while NHANES aims to represent the U.S. population, certain groups, particularly individuals with severe OA who may face mobility challenges, could be underrepresented, limiting the generalizability of the findings to individuals with advanced stages of OA. Third, testosterone measurements can fluctuate due to various factors, such as time of day and health status, which may impact the reliability of individual testosterone levels. Although NHANES employs standardized protocols, these fluctuations could introduce measurement error. Furthermore, NHANES measures testosterone levels using a single morning blood sample, which may not account for daily fluctuations in hormone levels. Although this method is practical within a large, nationally representative dataset, it may not fully reflect the dynamic nature of testosterone secretion, and repeated measures could provide a more comprehensive view. Additionally, it is essential to note that NHANES primarily measures total testosterone, rather than free testosterone, which more accurately reflects biologically active hormone levels. Future studies should specify the type of testosterone measured and consider dynamic testing approaches where feasible. Fourth, despite controlling for several potential confounders, including age, BMI, and comorbidities, residual confounding remains a concern, as other unmeasured factors, such as physical activity or dietary habits, may influence both testosterone levels and OA risk. Moreover, using the 2.5th percentile of the population distribution as the cutoff for low testosterone may not be clinically meaningful across all age groups. Given the natural age-related decline in testosterone, we suggest that future research should explore age- and sex-specific thresholds

to better identify individuals who could benefit from TRT. This would allow for more personalized treatment approaches that are better suited to individuals' unique hormonal profiles. Lastly, the reliance on self-reported data for OA diagnosis and testosterone deficiency introduces the potential for recall bias and misclassification, which may obscure the true nature of the relationship.

Future directions

Future studies should prioritize longitudinal designs, objective clinical measurements, and more comprehensive data collection are necessary to overcome the limitations of current research and provide a clearer understanding of the complex interactions between testosterone and OA. Long-term studies tracking testosterone levels alongside OA progression will be crucial for elucidating the causal pathways involved. Additionally, mechanistic studies that explore the biological effects of testosterone on cartilage and bone health will provide valuable insights into potential therapeutic targets for OA [14, 65].

Furthermore, future research should address specific questions regarding the optimal timing and duration of TRT for OA prevention and the long-term effects of TRT on OA progression. Identifying biomarkers that predict individual responsiveness to TRT is another critical area, enabling more personalized treatment strategies. Future studies should also explore the interplay between testosterone deficiency and factors such as obesity and metabolic syndrome, which may synergize to exacerbate OA risk. Given the complex interplay between hormonal and metabolic factors in OA, future interventions should consider both testosterone supplementation and lifestyle modifications aimed at improving metabolic health and reducing OA risk [66, 67].

Conclusion

In conclusion, our study provides strong evidence that low testosterone levels are associated with an increased risk of OA, independent of other risk factors. These findings highlight the importance of hormonal health in the development and progression of OA and suggest tahat testosterone replacement therapy may be a potential strategy for reducing OA risk in individuals with testosterone deficiency. Further research is needed to elucidate the mechanisms underlying this association and to identify effective interventions for preventing OA in at-risk populations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-024-08272-6.

Supplementary Material 1

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NM was a major contributor to the writing of the manuscript and was involved in the design of the study. GF contributed to the data analysis and interpretation, and critically revised the manuscript for important intellectual content.

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Data availability
This study analyzed publicly available datasets and can be found at https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and informed consent statement
All protocols were approved by the NCHS Ethics Review Board and conducted in accordance with the Declaration of Helsinki, with all NHANES participants providing written informed consent. The Institutional Review Board at our institution classified this analysis as exempt, as the dataset employed was entirely de-identified.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Author details
[1]Department of Orthopedic Trauma, Norinco General Hospital, Xi'an, Shaanxi Province, China

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