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The causal impact of bioavailable testosterone levels on osteoarthritis: a bidirectional Mendelian randomized study

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Abstract

Background It has been shown that low testosterone levels are associated with the development of osteoarthritis (OA). In our study, we aimed to investigate a bidirectional causal relationship between bioavailable testosterone levels and OA using Mendelian randomization (MR) analysis.

Methods In our study, the datasets from publicly available genome-wide association study (GWAS) were adopted, including the OA-related dataset (ukb-b-14486) and the bioavailable testosterone levels-related dataset (ebi-a-GCST90012104). The UKB-B-14,486 dataset contains 462,933 samples in total, including 38,472 OA samples, 424,461 control samples, and 9,851,867 SNPs, all collected from the European population in 2018. Additionally, the EBI-A-GCST90012104 dataset includes 382,988 samples and 16,137,327 SNPs, which reflect data from the European population in 2020. In total, five methods were utilized, namely MR Egger, Weighted median, Inverse variance weighted (IVW), Simple mode, and Weighted mode. Among them, IVW was the main analytical method. Additionally, the sensitivity analysis was carried out through the heterogeneity test, the horizontal pleiotropy test, and the Leave-One-Out (LOO) method.

Results The result of forward MR analysis demonstrated that bioavailable testosterone levels were considerably relevant to OA, and were a risk factor for OA (OR = 1.01, 95% CI: [1.00, 1.02], $P = 0.02$). However, through reverse MR analysis, we did not find a causal relationship between OA and bioavailable testosterone levels. Moreover, the results of the sensitivity analysis suggested that our results were reliable.

Conclusion The results of our study supported a causal relationship between bioavailable testosterone levels and OA.

Keywords Bioavailable testosterone levels, Osteoarthritis, Mendelian randomization, Bidirectional

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Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by chronic inflammation of the joints and their appendages, resulting in pain, swelling, and limited functional activity [1–3]. At present, the pathogenesis of OA is not clear, but it is known that factors such as obesity, trauma, and lifestyle are all risk factors for the onset of OA [4–6]. but even if these risk factors are avoided, the incidence rate of OA is still high. Preventing cartilage degeneration remains the key to preventing and treating OA [7, 8]. However, there are currently no reliable biochemical biomarkers that can prevent the occurrence of OA [9, 10]. Studies have shown that hormone replacement therapy has a clear effect on the treatment of OA and can effectively reduce joint replacement rates [11], indicating that sex steroids may play an important role in the development of OA.

Testosterone is mainly a steroid hormone secreted by the male testes and female ovaries. It is transported to the target tissues in the body through binding of sex hormone binding globulin (SHBG) in the blood to function [12]. It is an important androgen that promotes human growth and development, and maintains normal organ function [13, 14]. There have been numerous reports linking testosterone to the risk of OA [15, 16]. In middle-aged and elderly men, with increasing age, testosterone deficiency leads to a progressive decline in muscle mass and strength, and central body fat increases, resulting in obesity and insulin resistance. Testosterone treatment can inhibit fat deposition and reduce insulin resistance [17], Testosterone also inhibits the endoplasmic reticulum (ER) stress mechanism and inflammatory response and cell apoptosis, and reduces the concentration of extremely low density lipoprotein and susceptibility to OA. Androgen receptors are present in human knee joint chondrocytes, synovial tissue and bone cells, and are expressed in both male and female patient chondrocytes [18], indicating a close correlation between chondrocytes and androgens [19]. There are androgen receptors in articular chondrocytes, which have the ability to synthesize androgens, and testosterone can affect the internal environment of bones by binding to receptors, which further indicates that androgens may be related to the pathogenesis of OA [20].

Mendelian Randomization (MR) is an analytical method for exploring causal relationships by introducing genome-wide association studies (GWAS) data represented by single nucleotide polymorphisms (SNPs) as mediating instrumental variables. Genetic variation is a random allocation of fixed alleles at conception, which can effectively overcome potential confounding factors and reverse the effects of causality [20]. Currently widely used in research on exposure and outcomes of various diseases, it can help us analyze and understand the causal relationship between exposure factors and diseases more conveniently and accurately. At present, a research has found a causal relationship between testosterone with hip osteoarthritis and the risk of hip replacement. However, the causal relationship between testosterone and overall OA, as well as who causes and effects OA and testosterone, is remains unclear [15]. Bidirectional MR evaluates whether there is a reverse causal relationship between exposure and outcome, that is, whether the outcome can lead to the occurrence of exposure, and conducts two double sample MR analyses to better understand the causal relationship between instrumental variables.

Therefore, based on publicly available GWAS data, this study conducted a bidirectional MR analysis using bioavailable testosterone levels and OA as exposure factors or outcomes, providing a new reference for the causal relationship between bioavailable testosterone levels and OA.

Materials and methods

Study design

MR studies must satisfy the following three assumptions. Firstly, genetic variants selected as instrumental variables (IVs) are strongly correlated with exposure factors. Secondly, SNPs in genetic variants are independent of confounding factors that are related to exposure and outcome. Thirdly, genetic variants affect outcomes only through exposure and not through other biological pathways [21]. The study used data from published public databases, and therefore, this study did not require any additional ethical approval.

Data source and pre-processing

The IEU OpenGWAS database (Institute of Epidemiology and Health's Open Genomics Wide Association Studies Database, https://gwas.mrcieu.ac.uk/) was utili zed to download OA-related dataset (ukb-b-14486) and bioavailable testosterone levels-related dataset (ebi-a-GCST90012104). The ukb-b-14486 dataset collected population data from Europe in 2018, containing a total of 462,933 samples, including 38,472 OA samples, 424,461 control samples, and 9,851,867 SNPs. Meanwhile, the ebi-a-GCST90012104 dataset collected data from the European population in 2020, containing a total of 382,988 samples and 16,137,327 SNPs [22]. Afterwards, SNPs selected as IVs were screened via "TwoSampleMR" R package (version 0.5.6) with $P < 5 \times 10^{-8}$, and linkage disequilibrium analysis (LDA) was performed to ensure independence ($r^2 = 0.001$ and kb = 10,000).

Statistical analyses

After the IVs were filtered, MR analyses were performed by combining the MR function with five methods: MR Egger, Weighted Median, Inverse Variance Weighted

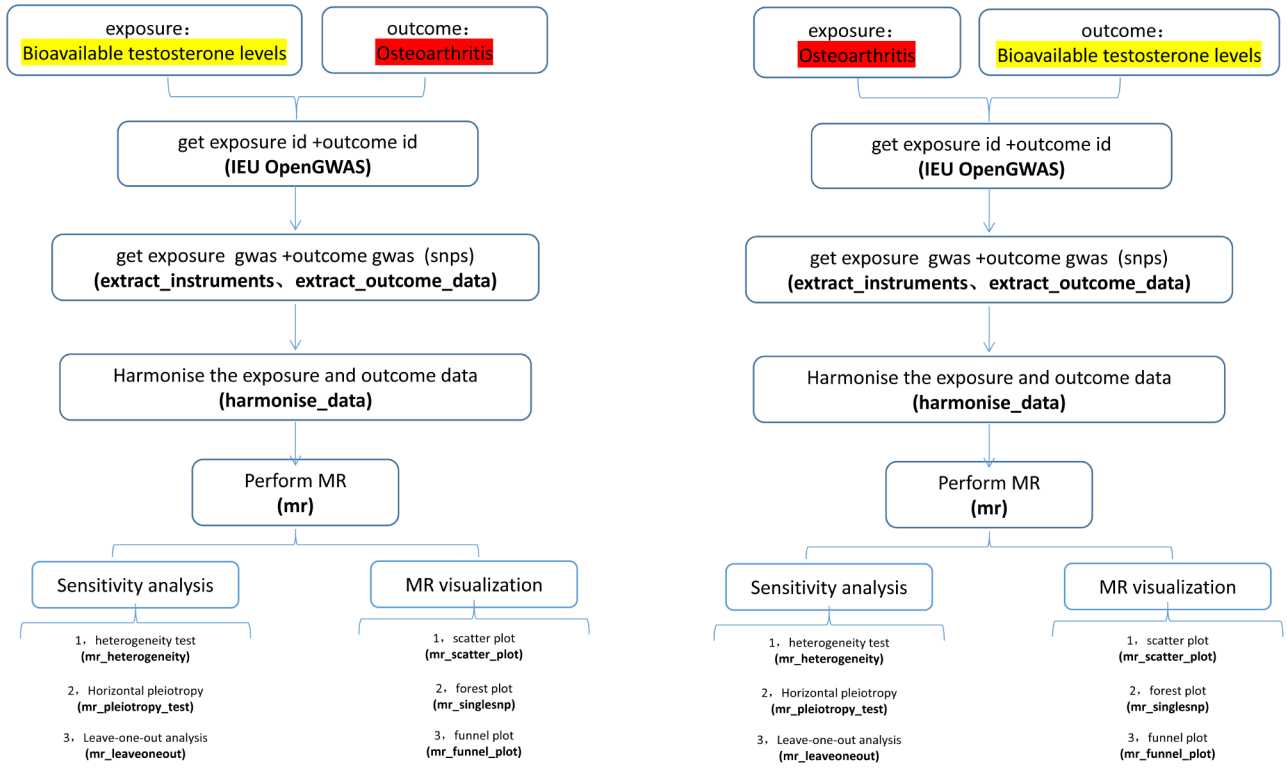

Fig. 1 Flowchart

Table 1 MR analysis results of bioavailable testosterone levels for OA

Exposure	Outcome	Method	Nsnp	*P*-value	OR(95% CI)
Bioavailable testosterone levels	Osteoarthritis	MR Egger	98	0.76	1.00(0.99–1.02)
		Weighted median	98	0.03	1.01(1.00-1.02)
		Inverse variance weighted	98	0.02	1.01(1.00-1.02)
		Simple mode	98	0.56	1.01(0.98–1.03)
		Weighted mode	98	0.19	1.01(1.00-1.02)

(IVW), Simple Mode, and Weighted Mode. Since the IVW method provides more precise causation and its results are unbiased, the results are mainly referred to the IVW. Then, odds ratios (ORs) were calculated, with an OR equal to 1 indicating no correlation between exposure and outcome; an OR greater than 1 indicating that exposure promotes the outcome; and an OR less than 1 indicating that exposure inhibits the occurrence of the outcome event. The results were presented using scatter plots, forest plots, and funnel plots.

To determine the reliability of the results of the analysis, a sensitivity analysis was conducted via heterogeneity test, the Horizontal pleiotropy test, and the Leave-One-Out (LOO) method. In the heterogeneity test, we used the mr_heterogeneity function ("TwoSampleMR" R package, version 0.5.6) to check for heterogeneity and interpret the results based on the Q value, where a value greater than 0.05 indicates the absence of heterogeneity. A *P* value greater than 0.05 indicates that there is no horizontal pleiotropy in the Horizontal Pleiotropy Test. The Leave-One-Out (LOO) method is used to detect outliers in the effect of each SNP. An overview of the study design is shown in Fig. 1.

Results

Causal effect of bioavailable testosterone levels on OA

After screening, 105 SNPs were obtained that were strongly relevant to bioavailable testosterone levels but not associated with OA. As shown in Table 1, there was a causal relationship between bioavailable testosterone levels and OA ($P = 0.02$), and bioavailable testosterone levels were a risk factor for OA (OR = 1.01, 95% CI: [1.00, 1.02]). The results of the scatter plot showed that the slopes of the lines were positive, further validating bioavailable testosterone levels as a risk factor for OA (Fig. 2A). Of the forest plot results, the point of IVW was on the right, which supported the view that bioavailable testosterone levels increase risk of OA (Fig. 2B). The funnel plot

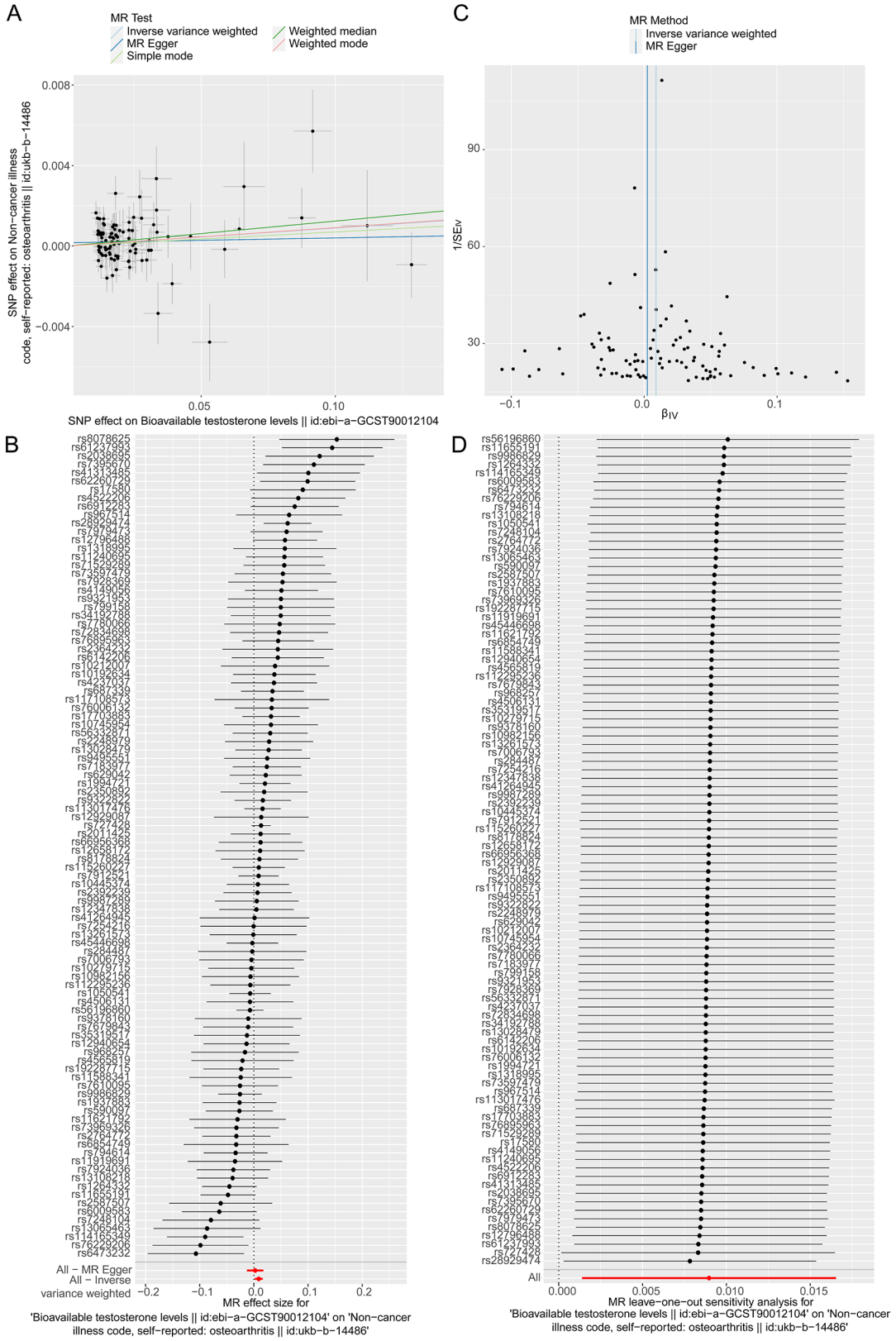

Fig. 2 The results of a Mendelian randomization analysis with bioavailable testosterone levels as the exposure factor and osteoarthritis as the outcome. (**A**) Scatter plot, (**B**) Forest plot, (**C**) Funnel plot, (**D**) Leave-one-out (LOO) analysis forest plot

Table 2 MR analysis results of OA on bioavailable testosterone levels (Reverse MR)

Exposure	Outcome	Method	Nsnp	P-*value*	OR
Osteoarthritis	Bioavailable testosterone levels	MR Egger	6	0.52	0.62(0.16–2.34)
		Weighted median	6	0.99	1.00(0.57–1.74)
		Inverse variance weighted	6	0.78	0.93(0.55–1.57)
		Simple mode	6	0.86	0.93(0.41–2.07)
		Weighted mode	6	0.93	1.03(0.51–2.08)

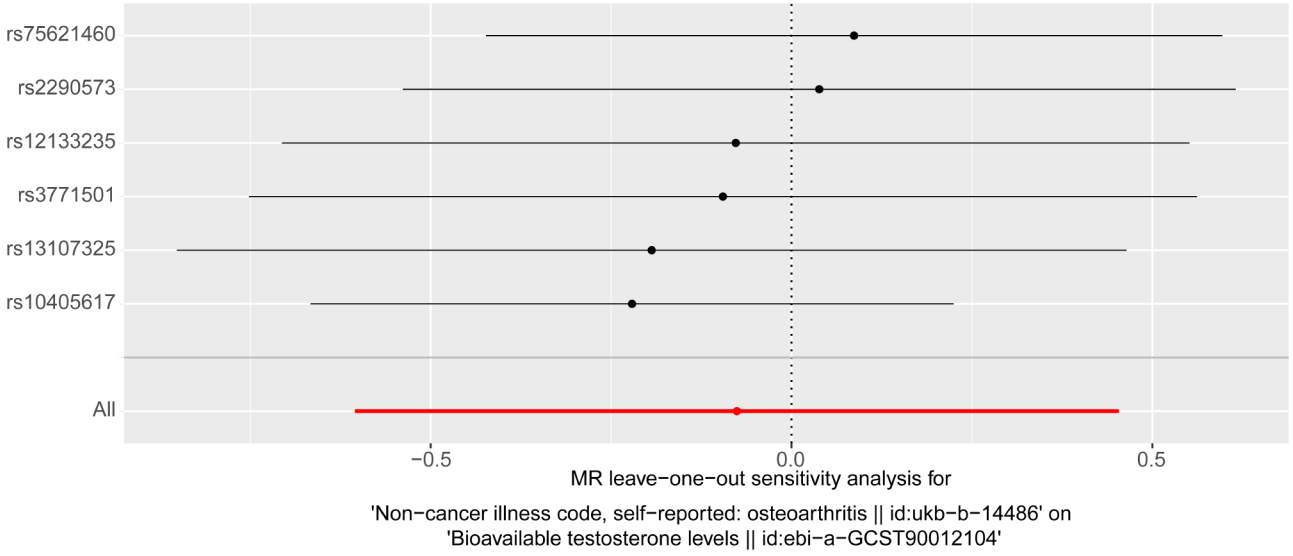

Fig. 3 The leave-one-out forest plot of the Mendelian randomization analysis with osteoarthritis as the exposure factor and bioavailable testosterone levels as the outcome

showed that MR conformed to Mendel's second law of random grouping (Fig. 2C).

Evaluation of the reliability of the results, we then did a sensitivity analysis. Firstly, the Q value of IVW was less than 0.05, suggesting that there was heterogeneity (Supplementary Table 1). At the same time, for factors with heterogeneity, we applied the random-effects IVW method for subsequent analysis to reduce the impact of heterogeneity on the results and ensure the reliability of the findings. Then, according to the horizontal pleiotropy test, there were no confounding factors in this study ($P = 0.33$) (Supplementary Table 2). Thereafter, the LOO method suggested that there were no points of deviation (Fig. 2D). In conclusion, the results that we obtained were reliable, and there was a causal relationship between bioavailable testosterone levels and OA.

Causal effect of OA on bioavailable testosterone levels

To illustrate the exact causal relationship between bioavailable testosterone levels and OA, we performed a reverse MR analysis, with OA as the exposing factor and bioavailable testosterone levels as the outcome. A total of six independent SNPs were obtained with the same screening criteria. Under the IVW model, OA was not significantly associated with bioavailable testosterone levels ($P = 0.78$, OR = 0.93, 95% CI: [0.55, 1.57]) (Table 2). Moreover, the remaining four models demonstrated the same results. Furthermore, the sensitivity analysis results manifested that our results were reliable (Fig. 3; Supplementary Tables 3–4).

Discussion

There have been reports on the relationship between bioavailable testosterone levels and OA, but the causal relationship between them is still unclear. In this study, we conducted a bidirectional two sample MR analysis using the maximum GWAS data of genetic variation to evaluate the causal relationship between testosterone and OA, demonstrating strong genetic evidence. We found a positive causal relationship between bioavailable testosterone levels and the risk of OA.

Sex steroid play an important role in the occurrence and development of osteoarthritis [23]. Sex steroid can affect the metabolism and function of tissues such as articular cartilage, bone, and synovium through various mechanisms. Firstly, sex steroid can regulate cartilage metabolism. There are estrogen receptors (ER α and ER β) in articular cartilage, and estrogen regulates the growth, differentiation, and apoptosis of chondrocytes through these receptors [24]. Estrogen can promote the

synthesis of cartilage matrix proteins such as collagen and proteoglycans, while inhibiting the expression of matrix metalloproteinases (MMPs) and reducing cartilage degradation [25]. Secondly, sex steroid can inhibit the production of inflammatory factors such as tumor necrosis factor - α (TNF - α) and interleukin-6 (IL-6), reducing inflammation in the joints and producing anti-inflammatory effects. At the same time, sex steroid affect the function of immune cells, regulate the infiltration and activity of inflammatory cells, and thus affect the inflammatory state of OA [26, 27]. Finally, estrogen promotes the survival of chondrocytes, reduces apoptosis, maintains the integrity of cartilage tissue, and upregulates the expression of anti apoptotic factors such as Bcl-2 by activating mechanisms such as the PI3K/Akt signaling pathway, further protecting chondrocytes from the effects of apoptosis [28]. From this, it can be seen that sex hormones play an important decisive role in the progression of OA.

Research on OA mainly focuses on estrogen, while research on androgens is relatively scarce. Biologically available testosterone is one of the most important androgens in the human body, and its concentration varies in a peak line with age [29, 30]. After the age of 40, there is a linear decline in testosterone levels in males and postmenopausal females [31]. Under normal circumstances, testosterone binds to specific receptors in the cell to form a testosterone receptor complex, and the active testosterone receptor complex binds to specific androgen response sheets (ARE) on the target gene to regulate gene expression. Studies have shown that both estrogen and androgen receptors exist in osteoblasts [32, 33]. In addition to its direct effects on bone and cartilage, testosterone not only binds to androgen receptors, but also to estrogen receptors to affect bone calcium metabolism balance [20]. In addition, testosterone can aromatise and convert into estradiol, which then binds to estrogen receptors and participates in the physiological regulation of bone and cartilage [34]. The decrease in testosterone levels affect cartilage metabolism through androgen receptors and ion channels, as well as leading to decreased in estradiol conversion rate, which leading to cartilage degeneration and the formation of OA [35]. When testosterone is at normal levels in men but there is an aromatase deficiency in the body, most of the androgens cannot be converted into estrogen, which often results in lower levels of estrogen in the body, which leads to joint cartilage degeneration and the development of OA [36]. This indicates a significant correlation between androgens, especially testosterone, and OA. In a study of male calf knee joint cartilage, it was found that testosterone increased the content of glycosaminoglycans in the extracellular matrix of chondrocytes, promote the coverage of type II collagen on the cartilage surface and the growth of cartilage fiber structure in joint cartilage [37]. Currently, clinical studies on the correlation between testosterone levels and OA are mainly case reports. A study of the correlation between hormone levels and hand OA in 573 premenopausal women found a significant correlation between lower levels of serum testosterone and the prevalence of hand OA [38]. In another study targeting men, serum testosterone levels were found to be positively correlated with cartilage thickness [39]. Testosterone can increase male muscle strength and is often recommended for the treatment of male musculoskeletal pain, its also can effective to reduce fat content and inhibit inflammatory reactions [40, 41]. In the study of serum testosterone levels and OA symptoms, it was found that higher levels of serum testosterone can reduce the joint osteoarthritis index (WOMAC) [42]. In a Mendelian study on the relationship between sex steroids and OA risk, it was also found that testosterone levels were positively correlated with OA, which is consistent with our research findings [15]. In summary, our research suggests a causal relationship between bioavailable testosterone levels and OA from a genetic perspective, providing a theoretical basis and research foundation for the prevention and treatment of OA. Previous studies have shown that men with rheumatoid arthritis have lower levels of bioavailable testosterone, which is largely attributed to hypogonadism [43]. The results of this study indicate a clear causal relationship between bioavailable testosterone levels and the occurrence of OA, suggesting that genes related to bioavailable testosterone levels have the potential to serve as biomarkers.

In this study, we had sufficient samples for MR analysis to explore the causal relationship between bioavailable testosterone levels and OA, and found a causal relationship between bioavailable testosterone levels and OA. This study has several advantages. Firstly, the data is sourced from the GWAS database, which can exclude the interference of confounding factors. Secondly, we use bidirectional MR analysis to study the impact of causal relationships on causal inference. We also used sensitivity analysis using multiple methods to exclude bias caused by related and unrelated pleiotropy.

In summary, we demonstrate a potential causal relationship between bioavailable testosterone levels and OA, whereas OA is the cause and bioavailable testosterone levels are the result, and there is no causal relationship between the two. However, our research still has certain limitations. Firstly, the study population is of European ancestry, and the scope of the study is relatively limited. At the same time, there are currently additional databases on testosterone levels in other races, which makes our results unable to further explain the causal relationship between testosterone and OA among different races. Secondly, this study used data from European

populations in public databases from 2018 to 2020, but there may be differences in gene distribution, lifestyle, environmental factors, and other aspects among cohorts from different countries, which may affect the generalizability and extrapolation of the research results. However, when using MR analysis methods, it is impossible to avoid the offset caused by such problems, but starting from the selected instrumental variables, these offsets cannot affect the robustness of the final results. Thirdly, due to the lack of raw data from the GWAS database, subgroup analysis was not conducted. Finally, we only found a causal relationship between bioavailable testosterone levels and OA from a genetic perspective, and the mechanism of its occurrence is still unclear. Nevertheless, this study provides new insights into the causal relationship between bioavailable testosterone levels and OA from a genetic perspective, thereby providing new insights into the study of OA. In future research, we look forward to studying the correlation between OA and available testosterone levels through data covering multiple countries or regions, in order to ensure that the research results have a certain degree of universality and reference significance as much as possible. In addition, in future research, we have further research expectations for biomarkers related to available testosterone levels in OA. In the future, we will focus on further exploration of biomarkers related to testosterone levels in OA, in order to obtain biomarkers with early diagnostic value, and deeply analyze the biological functions and pathways involved in the progression of OA by biomarkers, in order to gain a deeper understanding of the molecular mechanisms of OA progression and provide a certain research basis and new perspectives for the prevention and treatment of OA.

Conclusion

Our research suggests a positive causal relationship between testosterone levels and OA, which may provide effective biomarkers for the prevention and treatment of OA.

Abbreviations

OA	Osteoarthritis
MR	Mendelian randomization
GWAS	Genome-wide association study
IVW	Inverse variance weighted
SNP	Single nucleotide polymorphism
IV	Instrumental variable
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08626-8.

Supplementary Material 1: **Supplementary Table 1**: Heterogeneity test(Forward MR); **Supplementary Table 2**: Horizontal pleiotropy test (Forward MR); **Supplementary Table 3**: Heterogeneity test (Reverse MR); **Supplementary Table 4**: Horizontal pleiotropy test (Reverse MR).

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Author contributions

Conceptualization, Z.J. and X.L.; methodology, Y.Z.; software, W.Y.; validation, Z.J., L.X. and Y.Z.; formal analysis, X.M.; investigation, F.T.; resources, W.K.; data curation, F.T.; writing—original draft preparation, Z.J.; writing—review and editing, F.T.; visualization, X.M.; supervision, W.K.; project administration, F.T.; funding acquisition, W.K. All authors have read and agreed to the published version of the manuscript.ding acquisition, F.T. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data analyzed in this research was downloaded from IEU database (https://gwas.mrcieu.ac.uk/).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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