World Journal of Microbiology and Biotechnology (2025) 41:106
https://doi.org/10.1007/s11274-025-04318-6

RESEARCH

Causal associations between 26 musculoskeletal disorders and gut microbiota: a Mendelian randomization analysis with Bayesian validation

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Received: 18 December 2024 / Accepted: 4 March 2025 / Published online: 13 March 2025

Abstract
Emerging evidence suggests that gut microbiota imbalances may influence the onset of musculoskeletal disorders (MSDs), yet conclusive evidence establishing causation remains limited. This study investigates the causal relationship between gut microbiota and a range of MSDs, aiming to identify potential therapeutic targets. Using data on 211 gut microbiome taxa from a genome-wide association study (GWAS) and summary statistics for 26 MSDs from the Finnish Biobank, we employed Mendelian randomization (MR) with inverse-variance weighting (IVW) as the primary analytical approach, complemented by Bayesian model validation to ensure robust results. Our MR analyses revealed significant causal associations between gut microbiota and nine MSDs within four categories, including osteoporosis (IVW-Beta = 0.011, P = 0.025), rheumatoid arthritis (IVW-Beta = − 0.016, P < 0.001), rotator cuff syndrome (IVW-Beta = − 0.007, P = 0.022), and calcific tendonitis of the shoulder (IVW-Beta = − 0.021, P = 0.034). Bayesian validation underscored the plausibility of these relationships, supporting the potential causal role of gut microbiota in the development of these disorders. Our findings present a library of causal associations that underscore the gut microbiome's role in MSD pathogenesis, providing genetic evidence that highlights specific gut microbiota taxa as prospective therapeutic targets. This research offers novel insights into the pathogenic mechanisms underlying MSDs and points toward new directions for future investigation into microbiome-based therapies.

Keywords Gut microbiota · Musculoskeletal disorders · Mendelian randomization analysis · Bayesian verification

Introduction

Musculoskeletal disorders (MSDs) represent a significant global health burden, affecting approximately 1.3 billion individuals worldwide (Safiri et al. 2021). These conditions encompass a wide range of pathologies associated with bones, joints, muscle, and spinal and soft tissues, including osteoarthritis, low back pain, osteoporosis, rheumatoid arthritis, and soft-tissue disorders such as rotator cuff syndrome (Safiri et al. 2021; Cento et al. 2022). The impact of MSDs extends beyond physical discomfort, significantly diminishing individuals' quality of life and athletic performance. Despite their significant impact, the vast majority of individuals affected by MSDs fail to receive timely and adequate treatment. Consequently, the prevention and management of MSDs have emerged as critical public health challenges (Cento et al. 2022; Lewis, et al. 2019). Recent investigations have revealed that the human microbiome, particularly the gut microbiota, has a pivotal influence on pathophysiological and immunological processes (Chen et al. 2022a; Guan et al. 2023). This burgeoning field of research suggests that the gut microbiota plays a critical role in MSD disease onset and progression through mechanisms involving systemic inflammation and immune modulation (Castro-Mejía et al. 2020; Kragsnaes et al. 2024). Notably, recent research has demonstrated that gut microbial metabolites modulate the expression of SLC2A1 by targeting HIF-1α, thereby mitigating iron apoptosis induced by knee osteoarthritis (Guan et al. 2023). Moreover, a study by Yuan-Y revealed that supplementation with *Ligilactobacillus salivarius*, a probiotic of the intrinsic phylum, effectively prevents osteoporosis in a mouse model (Yuan et al. 2022). Accordingly, the gut microbiome represents a compelling

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target for novel therapeutic approaches in the management of MSDs (Lewis, et al. 2019; Guan et al. 2023; Yuan et al. 2022).

However, establishing a causal link between MSDs and the gut microbiota remains challenging because of the inherent limitations associated with traditional observational and cohort studies, such as confounding factors in the long-term development of the disease and reverse causality (Chen et al. 2022a; Kragsnaes et al. 2024; Ticinesi et al. 2019). Mendelian randomization (MR) offers a robust alternative, leveraging genetic variants as instrumental variables to mimic the conditions of randomized controlled trials, thereby circumventing these limitations (Hartley et al. 2022; Burgess et al. 2023). Nevertheless, comprehensive analyses of previously identified genomic associations between MSDs and specific gut microbiota at the level of establishing a MSDs library are lacking, and these analyses do not account for potential pleiotropy, which could undermine the validity of the findings (Chen et al. 2023).

To address these issues, we proposed the integration of Bayesian modeling into MR analysis to enhance the credibility of causal inferences (Zuber et al. 2023). This approach combines prior knowledge with MR results within a probabilistic framework, producing posterior distributions that reflect both empirical evidence and preexisting beliefs. Moreover, Bayesian modeling accommodates heterogeneity across diseases and populations, offering a nuanced analysis of the gut microbiota-MSD axis (Hartley et al. 2022; Zuber et al. 2023).

In the present study, we employed MR methods and Bayesian model validation to investigate the causal relationships between gut microbiota and 26 MSDs. By doing so, we aim to unveil novel preventive and therapeutic avenues targeting the gut microbiota–MSD axis, thereby contributing to improved patient outcomes and health care strategies.

Method

Study design

We employed a comprehensive MR framework, integrating three MR methods: inverse-variance weighting (IVW), weighted median, and MR−Egger. We examined the causal impact of gut microbiota on 26 MSDs using gut microbiota data from the MiBioGen consortium as the exposure variable. The Bayesian approach enhanced the credibility of our analysis through meticulous selection of prior distributions, development of likelihood ratio functions, and computation of posterior probabilities. This methodological rigor allowed for a nuanced understanding of the intricate relationships between gut microbiota and MSDs, accounting for the diverse disease manifestations and population differences. A graphical representation of our analytical framework is illustrated in Fig. 1. Our approach aligns with the Summer 2023 MR Investigation Guidelines for musculoskeletal research (Hartley et al. 2022; Burgess, et al. 2023).

Data acquisition

Exposure data acquisition

In this study, we utilized genome-wide association study (GWAS) summary statistics from the MiBioGen International Consortium's meta-analysis, accessible at https://gwas.mrcieu.ac.uk/datasets/, which encompasses a diverse cohort of 18,340 individuals from 24 distinct populations (Kurilshikov et al. 2021). These participants underwent sequencing for the variable regions V4, V3-V4, and V1-V2 of the 16S rRNA gene, as meticulously cataloged by Kurilshikov et al. The extensive sequencing efforts yielded a comprehensive taxonomy of gut microbiota, initially identifying 211 taxa spanning various hierarchical levels—131 genera, 35 families, 20 orders, 16 phyla, and 9 different phyla—from a total of 122,110 variant loci. In our analysis, we focused on a refined set of 196 taxa, including 119 genera, 32 families, 20 orders, 16 phyla, and 9 phyla, after excluding taxa with undefined classifications. This curated dataset from the MiBioGen consortium, which was thoroughly adjusted for age, sex, study-specific covariates, and principal components to counter population stratification, underpinned our exposure data analysis. These adjustments were pivotal in negating potential batch effects, thereby fortifying the integrity and validity of our investigation.

Outcome data acquisition

We rigorously selected musculoskeletal genome-wide association studies (GWASs) targeting European populations from 2005 to 2022 based on a systematic review by Sadat-Ali (2023). This comprehensive review, focusing on orthopedic diseases, identified relevant studies within the GWAS database, culminating in the inclusion of 26 pivotal studies (referenced in Table 1). The core data for our analysis were extracted from the Finnish Biobank's FinnGen Public Data R9 database, accessible at https://www.finngen.fi/en, following the standard application procedures for data access as outlined by the Finnish Biobank Cooperative (FINBB). This dataset, released on December 20, 2023, represents a significant resource for understanding the genetic underpinnings of musculoskeletal conditions within a European cohort. Detailed information on the sequencing methods,

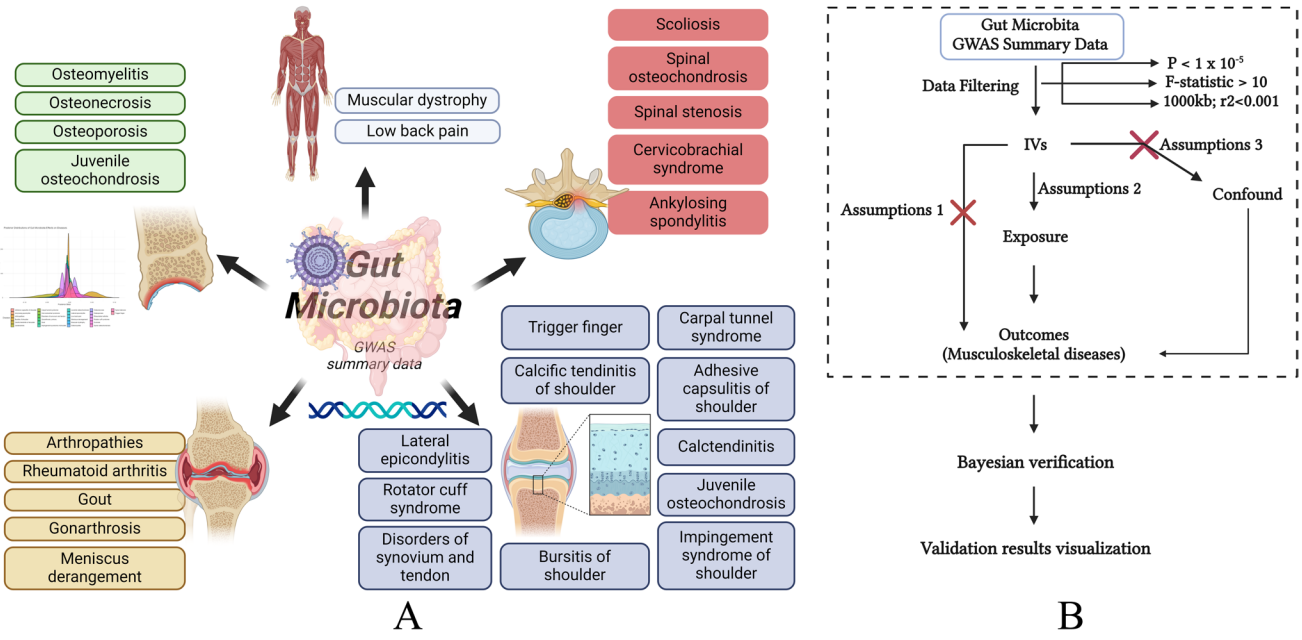

Fig. 1 Overview of the study Figure. Figure 1.A. mechanistic overview of the study, encapsulating the spectrum of 26 musculoskeletal disorders examined. This diagram systematically categorizes these conditions, illustrating the intricate relationships and potential pathways explored within our research. This image is based on the BioRender website (URL: https://app.biorender.com). Figure 2.B. Study design. The diagram provides a comprehensive overview of our study design. The three assumptions of the MR analysis process are as follows. Assumption 1: genetic variants must be associated with exposures; Assumption 2: genetic variants must not be associated with confounders; and Assumption 3: genetic variants must affect outcomes only through exposures, not through other pathways. GWAS, genome-wide association studies; IVs, instrumental variables; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism

ethical approval, and patient consent protocols used in the original studies can be found in the respective publications.

Data filtering

Exposure data filtering

To ascertain the robustness and validity of our causal inference analysis concerning the impact of the gut microbiota on outcome variables, a meticulous selection process for instrumental variables (IVs) was implemented (Hartley et al. 2022; Burgess, et al. 2023). This process was guided by the following criteria:

(1) Genome-wide Significance Threshold for SNP Selection: in the initial screening, single-nucleotide polymorphisms (SNPs) significantly associated with gut microbiota compositions were targeted, applying a genome-wide significance threshold of $P < 5*10^{-8}$. Acknowledging the constraints posed by the limited pool of IVs meeting this stringent criterion, a secondary, more inclusive threshold of $P < 1*10^{-5}$ was adopted to ensure a comprehensive analysis (Kurki et al. 2023; Xia et al. 2023).

(2) Mitigation of Linkage Disequilibrium (LD) Effects: to minimize the confounding effects of LD among IVs, we employed an LD threshold of $R^2 < 0.001$ and an aggregation distance of 1000 kb. This approach, informed by the 1000 Genomes Project (Siva 2008), facilitated the exclusion of variants exhibiting strong LD, thereby enhancing the integrity of our analysis. R^2 was calculated as follows:

$$R^2 = 2 \times EAF(1 - EAF) \times \beta^2$$

where "EAF" is the effect allele frequency of SNPs as IVs and "β" is the effect β value for each SNP.

(3) Instrumental variable strength assessment: the potency of the selected IVs was quantitatively assessed through the computation of the F-statistic, following the formula:

$$F = \frac{R^2(\mathrm{n} - k - 1)}{k\left(1 - R^2\right)}$$

where "n" represents the sample size and "k" represents the number of IVs deployed. Only variant SNPs exhibiting an $F > 10$ were included in subsequent stages of our analysis, ensuring the reliability of the instrumental variables employed.

Table 1 The table delineates the classification methodology and presents comprehensive data and GWAS ID for the outcome variables analyzed in this study, utilizing Mendelian randomization analysis

Outcome	GWAS ID	IVW			Weighted median			MR egger test		
		Beta	SE	P	Beta	SE	P	Confidence	SE	P
Bone disorders										
Osteonecrosis	Finn-B-M13_OSTEONECROSIS	− 0.002	0.011	0.841	− 0.004	0.016	0.807	0.042	0.027	0.126
Osteoporosis	Finn-B-M13_OSTEOPOROSIS	0.011	0.005	0.025	0.011	0.007	0.116	0	0.013	0.973
Osteomyelitis	Finn-B-M13_OSTEOMYELITIS	0.009	0.01	0.375	− 0.002	0.015	0.874	0.021	0.025	0.400
Juvenile osteochondrosis	Finn-B-M13_JUVOSTEOCHONRHIP	− 0.006	0.014	0.655	− 0.002	0.02	0.908	0.031	0.034	0.367
Muscle disorders										
Low back pain	Finn-B-M13_LOWBACKPAIN	− 0.004	0.003	0.135	− 0.003	0.004	0.401	− 0.008	0.007	0.243
Muscular dystrophy	Finn-B-G6_MUSDYST	0.001	0.029	0.975	0.033	0.042	0.440	− 0.037	0.073	0.614
Spinal disorders										
Ankylosing spondylitis	Finn-B-M13_ANKYLOSPON_STRICT	0.007	0.012	0.575	0.003	0.017	0.856	− 0.015	0.031	0.633
Spinal stenosis	Finn-B-M13_SPINSTENOSIS	− 0.004	0.004	0.253	− 0.004	0.005	0.437	0.008	0.009	0.390
Cervicobrachial syndrome	Finn-B-M13_CERVICOBRACHSDR	− 0.007	0.005	0.142	− 0.004	0.007	0.574	0.003	0.013	0.834
Spinal osteochondrosis	Finn-B-M13_SPINALOSTEOCHON	0.01	0.023	0.655	0.012	0.033	0.715	0.080	0.057	0.164
Scoliosis	Finn-B-M13_SCOLIOSIS	0.011	0.008	0.179	0.007	0.012	0.550	0.089	0.021	P < 0.001
Joint disorders										
Meniscus derangement	Finn-B-M13_MENISCUSDERANGEMENTS	− 0.003	0.003	0.297	− 0.007	0.004	0.113	0.003	0.008	0.744
Rheumatoid arthritis	Finn-B-M13_RHEUMA	− 0.016	0.004	P < 0.001	− 0.02	0.006	P < 0.001	− 0.015	0.011	0.157
Gout	Finn-B-M13_GOUT	0.001	0.005	0.810	− 0.002	0.007	0.730	− 0.008	0.013	0.545
Gonarthrosis(primary)	Finn-B-M13_ARTHROSIS_KNEE_PRIM_ICD10	− 0.005	0.003	0.067	− 0.002	0.004	0.641	0.003	0.007	0.636
Arthropathies	Finn-B-M13_ARTHROPATHIES	− 0.002	0.002	0.177	− 0.001	0.002	0.698	0.003	0.004	0.519
Soft tissue disorders										
Rotator cuff syndrome	Finn-B-M13_ROTATORCUFF	− 0.007	0.003	0.022	− 0.007	0.004	0.103	− 0.006	0.008	0.436
Disorders of synovium and tendon	Finn-B-M13_SYNOTEND	− 0.002	0.003	0.449	− 0.001	0.004	0.836	0.004	0.008	0.580
Bursitis of shoulder	Finn-B-M13_SHOULDERBURSITIS	0.051	0.016	0.001	0.046	0.024	0.052	0.004	0.04	0.914
Lateral epicondylitis	Finn-B-M13_LATERALEPICOND	− 0.004	0.006	0.578	Beta < 0.001	0.009	0.973	− 0.032	0.016	0.048
Impingement syndrome of shoulder	Finn-B-M13_IMPINGEMENT	− 0.005	0.005	0.299	− 0.003	0.007	0.633	0.008	0.012	0.532
Calctendinitis	Finn-B-M13-CALCTENDINITIS	− 0.041	0.026	0.118	− 0.008	0.039	0.840	0.078	0.067	0.246
Adhesive capsulitis of shoulder	Finn-B-M13_ADHCAPSULITIS	− 0.005	0.006	0.419	− 0.018	0.008	0.029	0.001	0.015	0.968
Calcific tendinitis of shoulder	Finn-B-M13_CALCIFICTEND	− 0.021	0.01	0.034	− 0.016	0.015	0.281	− 0.028	0.025	0.264
Trigger finger	Finn-B-M13_TRIGGERFINGER	0.002	0.007	0.706	0.012	0.009	0.207	0.037	0.017	0.026
Carpal tunnel syndrome	Finn-B-G6_CARPTU	− 0.006	0.003	0.078	− 0.008	0.004	0.058	0.004	0.009	0.615

Beta: The estimated coefficient representing the effect size of the allele, offering insights into the genetic variant's impact on the outcome; SE (Standard Error): Quantifies the precision of the beta estimate, reflecting the variability in the effect size estimation; P: (P-value of OR), indicating the statistical significance of the observed associations. Confidence: (confidence interval), providing a measure of the estimate's reliability over repeated samples

Outcome data filtering

For a precise evaluation of the causal relationships between gut microbiota and MSDs, outcome variables were meticulously categorized based on their clinical phenotypes. This classification scheme encompassed five principal categories, namely, bone disorders (osteomyelitis, osteonecrosis, osteoporosis, and juvenile osteochondrosis), joint disorders (meniscus derangement, rheumatoid arthritis, gout, primary gonarthrosis, and arthropathies), muscular disorders (low back pain and muscular dystrophy), soft-tissue disorders (rotator cuff syndrome, disorders of synovium and tendon, bursitis of shoulder, lateral epicondylitis, impingement syndrome of shoulder, calcific tendonitis, adhesive capsulitis of shoulder, calcific tendonitis of shoulder, trigger finger, and carpal tunnel syndrome), and spinal disorders (ankylosing spondylitis, spinal stenosis, cervicobrachial syndrome, spinal osteochondrosis, and scoliosis). Such stratification facilitates a nuanced analysis, allowing for targeted investigation across the spectrum of musculoskeletal conditions. A detailed categorization, including the phenotypes and corresponding GWAS IDs, is systematically presented in Table 1. This structured approach ensures that our analysis comprehensively addresses the complexity inherent to MSDs phenotypes, underpinning the validity of our causal inferences.

Mendelian randomization analysis

Our MR analyses were conducted using the "TwoSampleMR" package (version 0.5.6) in R (version 4.3.2), which is specifically designed for two-sample MR analysis. In this study, we employed three distinct MR methods to ensure the robustness and reliability of our causal inferences: inverse-variance weighting (IVW), MR−Egger, and weighted median. The IVW method served as the primary analytical tool for assessing the consistency across multiple instrumental variables. In parallel, MR−Egger and weighted median were utilized for the secondary analyses. These models provide critical means to identify and adjust for potential biases arising from invalid instrumental variables and directional confounding (Burgess et al. 2023). The comprehensive results derived from applying these models are succinctly summarized in Table 1. Whereas inverse-variance weighting (IVW), MR−Egger, and weighted median (WM) are calculated with Eqs. (1), (2), and (3), respectively:

$$\beta_{IVW} = \frac{\sum\left(\frac{\beta_i}{\mathrm{var}_i}\right)}{\sum\left(\frac{1}{\mathrm{var}_i}\right)} \tag{1}$$

(Note: β_i is the effect estimate of i's instrumental variable, and var_i is the variance of the effect estimate of i's instrumental variable)

$$\beta_{MR-Egger} = \frac{\sum \omega_i\left(Y_i - \overline{Y}\right)\left(X_i - \overline{X}\right)}{\sum \omega_i\left(X_i - \overline{X}\right)^2} \tag{2}$$

(Note: X_i and Y_i are effect estimates for i's instrumental variable for the gut microbiota exposure variable and the MSDs outcome variable, respectively; $\overline{X}$ and $\overline{Y}$ are weighted average effect estimates, respectively; and ω_i is the weight of the effect estimate)

$$\beta_{WM} = median\left(\beta_i', \omega_i\right) \tag{3}$$

(Note:β_i' is the ranked effect estimate; ω_i is the weight of the effect estimate)

Bayesian statistical framework

Integration of Bayesian and MR frameworks

The Bayesian framework complements MR analysis by incorporating prior biological plausibility into causal inference. For instance, gut microbiota's known roles in systemic inflammation and immune modulation were encoded into prior distributions, refining posterior estimates. We selected:

Normal prior for causal effects (mean = 0, SD = 1): Reflects the conservative assumption that microbiota effects are likely modest unless strongly supported by data (Zuber et al. 2023).

Cauchy prior for variance (location = 0, scale = 2): Accommodates potential heterogeneity across microbial taxa while avoiding overfitting (Zou et al. 2024).

This integration allows Bayesian models to "correct" MR estimates when genetic instruments are weak (e.g., F-statistic < 10) by downweighting outliers, thereby reducing false positives.

Prior distribution setting

We define the parameter causal effect and parameter variance as β and σ, respectively. The prior distribution is set as follows:

A. Causal Effect: The prior distribution for the causal effect is assumed to follow a standard normal distribution:

$$\beta \sim Normal(0, 1)$$

The prior distribution of causal effects is normal with a mean of 0 and a standard deviation of 1, accommodating our initial assumption that, without empirical validation, the

causal effect is likely to be minimal or to deviate modestly from zero (Zuber et al. 2023).

B. Variance: The prior distribution of the variance σ is the Cauchy distribution:

$$\sigma \sim cauchy(0, 2)$$

For the variance parameter, we select a Cauchy distribution as the prior. This is characterized by a location parameter of 0 and a scale parameter of 2. The heavy-tailed nature of the Cauchy distribution provides the flexibility needed to account for a wide range of variance levels, acknowledging the inherent uncertainty in this parameter.

Likelihood function construction

A likelihood function was constructed to assess the likelihood of the data occurring with the above prior distribution setting:

$$b_{out[i]} \sim Normal(\beta \times b_{\exp[i]}, \sqrt{se^2_{out[i]} + \beta^2 \times se^2_{\exp[i]}})$$

where for a given gut microbiota exposure effect ($b_{\exp}$) and its standard error ($se_{\exp}$), the outcome effect (b_{out}) for MSDs is assumed to follow a normal distribution with $\beta \times b_{\exp[i]}$ as the mean and $\sqrt{se^2_{out[i]} + \beta^2 \times se^2_{\exp[i]}}$ as the standard deviation. Additionally, $b_{\exp[i]}$ is the exposure factor effect size for observation i, $se_{\exp[i]}$ is the standard error of the exposure factor for observation i, $b_{out[i]}$ is the outcome factor effect size for observation i, and $se_{out[i]}$ is the standard error of the outcome factor for observation i. This model enables the evaluation of the probability of observing our data under the defined prior settings (Zuber et al. 2023).

Posterior distribution

Utilizing Bayes' theorem, we integrate the prior distribution and the likelihood function, and the conditional probability distribution of the parameters can be expressed as:

$$P(\beta, \sigma|\phi) \propto P(\phi|\beta, \sigma) \times P(\beta) \times P(\sigma)$$

where ϕ is the set of observations on which the Bayesian analysis was performed; $P(\beta, \sigma|\phi)$ is the posterior distribution of β and σ given the data; $P(\phi|\beta, \sigma)$ is the likelihood function, which represents the probability of the observed data given the parameters; and $P(\beta)$ and $P(\sigma)$ are the posterior distributions of β and σ, respectively.

Model fitting and inference

The Bayesian model was implemented and executed in R version 4.3.2, employing the "stan" function from the "RStan" package (version 2.26.3). Through Markov chain Monte Carlo (MCMC) sampling, we draw samples from the posterior distributions of our parameters (Zuber et al. 2023; Zou et al. 2024). We report the postsampling mean, standard deviation, and confidence intervals for these distributions, providing a comprehensive quantification of parameter uncertainty that reflects both the observed data and our prior assumptions.

Multiple testing correction

To address multiplicity across 26 MSD outcomes, we applied Bonferroni correction ($P = 0.05/26 = 0.0019$). Associations surviving this threshold were considered statistically significant. In addition to Bonferroni correction, we applied the Benjamini–Hochberg procedure to control the false discovery rate (FDR) at $\alpha = 0.05$. Associations with $P_{FDR} < 0.05$ were considered significant (Burgess, et al. 2023; Chen et al. 2023).

Visualization of results

The results of this study were visualized using the "ggplot2" package (version 3.4.4) in R (version 4.3.2). This enabled the graphical presentation of MR and Bayesian analysis outcomes, facilitating an intuitive examination of the causal links between gut microbiota and MSDs.

Results

In the present study, we applied validated instrumental variables (IVs) to conduct MR analyses across 26 MSDs. Furthermore, we constructed Bayesian models to deepen the understanding of these analyses. The results, which were refined to three decimal places for precision, are systematically presented in Table 1 and visually depicted in Fig. 2 through 6 within the RStudio 4.3.2 environment (Fig. 3).

Bone disorders

A noteworthy association was found between gut microbiota and osteoporosis via the IVW method (Beta = 0.011, SE = 0.005, P = 0.025; Table 1; Fig. 2), indicating a potential role for specific microbiota in osteoporosis etiology. However, this association was not corroborated by the weighted median (Beta = 0.011, SE = 0.007, P = 0.116, Table 1; Fig. 4) or MR−Egger methods (Beta = 0.011, SE = 0.005, P = 0.025, Table 1, Fig. 3), indicating a complexity that merits further exploration. Other bone diseases, such as osteonecrosis and osteomyelitis, did not demonstrate significant causal associations (Table 1; Figs. 2, 3, 4).

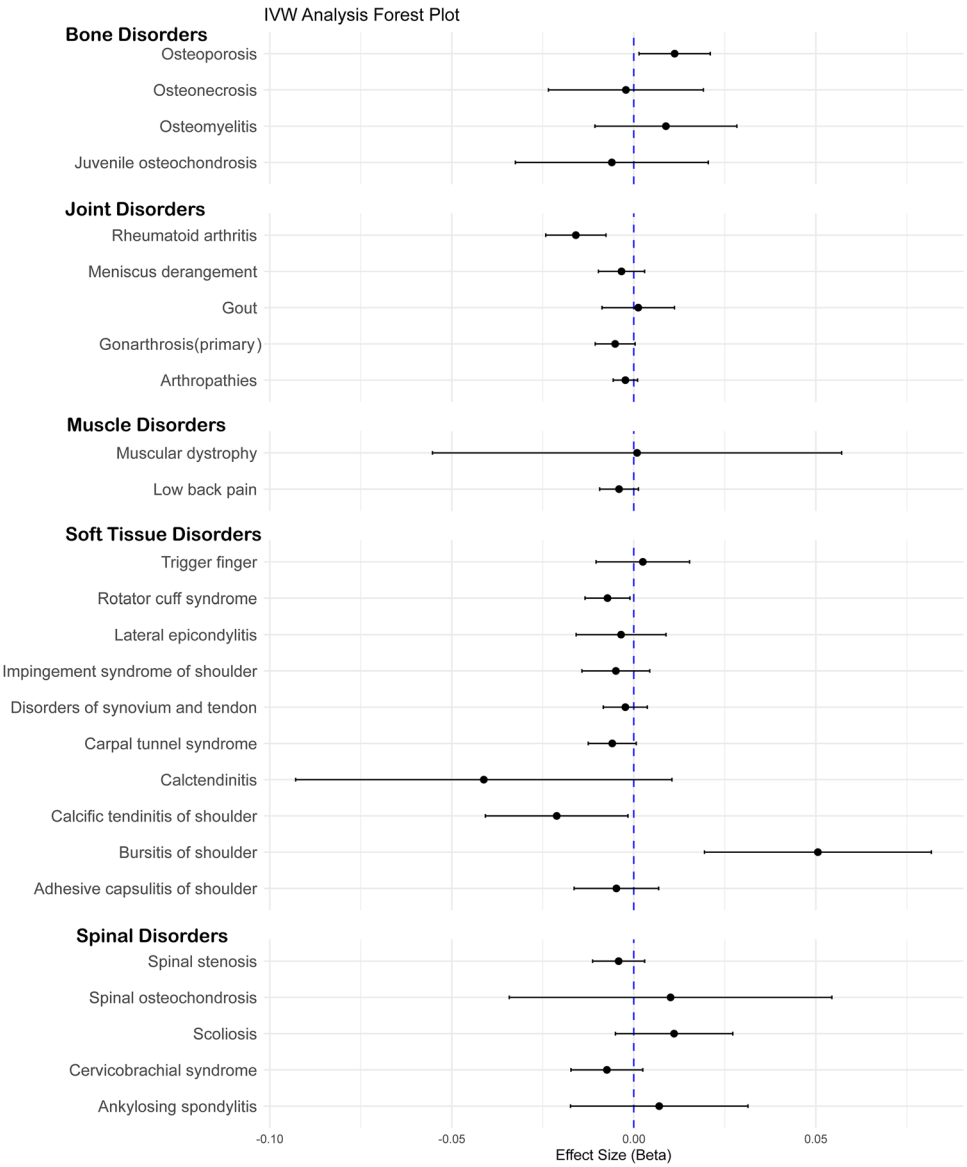

Fig. 2 Forest plot of the MR results based on the IVW method between Gut microbiota and 26 musculoskeletal disorders

Muscle disorders

Our analysis across muscle disorders, including low back pain and muscular dystrophy, revealed no significant causal effects from gut microbiota (Table 1; Figs. 2, 3, 4), suggesting the need for more detailed studies in this area.

Spinal disorders

Scoliosis showed a potential causal link with gut microbiota according to MR−Egger analysis (Beta = 0.089, SE = 0.021, P < 0.001; Table 1; Fig. 3), a finding not mirrored in the IVW (Beta = 0.011, SE = 0.008, P = 0179, Table 1; Fig. 2) or weighted median methods (Beta = 0.011, SE = 0.008, P = 0179, Table 1; Fig. 4), highlighting the intricacies of spinal disorder etiologies (Table 1). The associations of gut microbiota with ankylosing spondylitis, spinal stenosis, cervicobrachial syndrome and spondylolisthesis were not evident in the models applied (Table 1).

Joint disorders

Rheumatoid arthritis was significantly negatively correlated with the gut microbiota in both the IVW (Beta = − 0.016, SE = 0.004, P < 0.001; Table 1; Fig. 2) and weighted median analyses (Beta = − 0.02, SE = 0.006, P < 0.001; Table 1; Fig. 4), suggesting that certain microbiota have a protective effect against rheumatoid arthritis. Conversely, no significant associations were found for other joint disorders, such as gout and arthritis (Table 1).

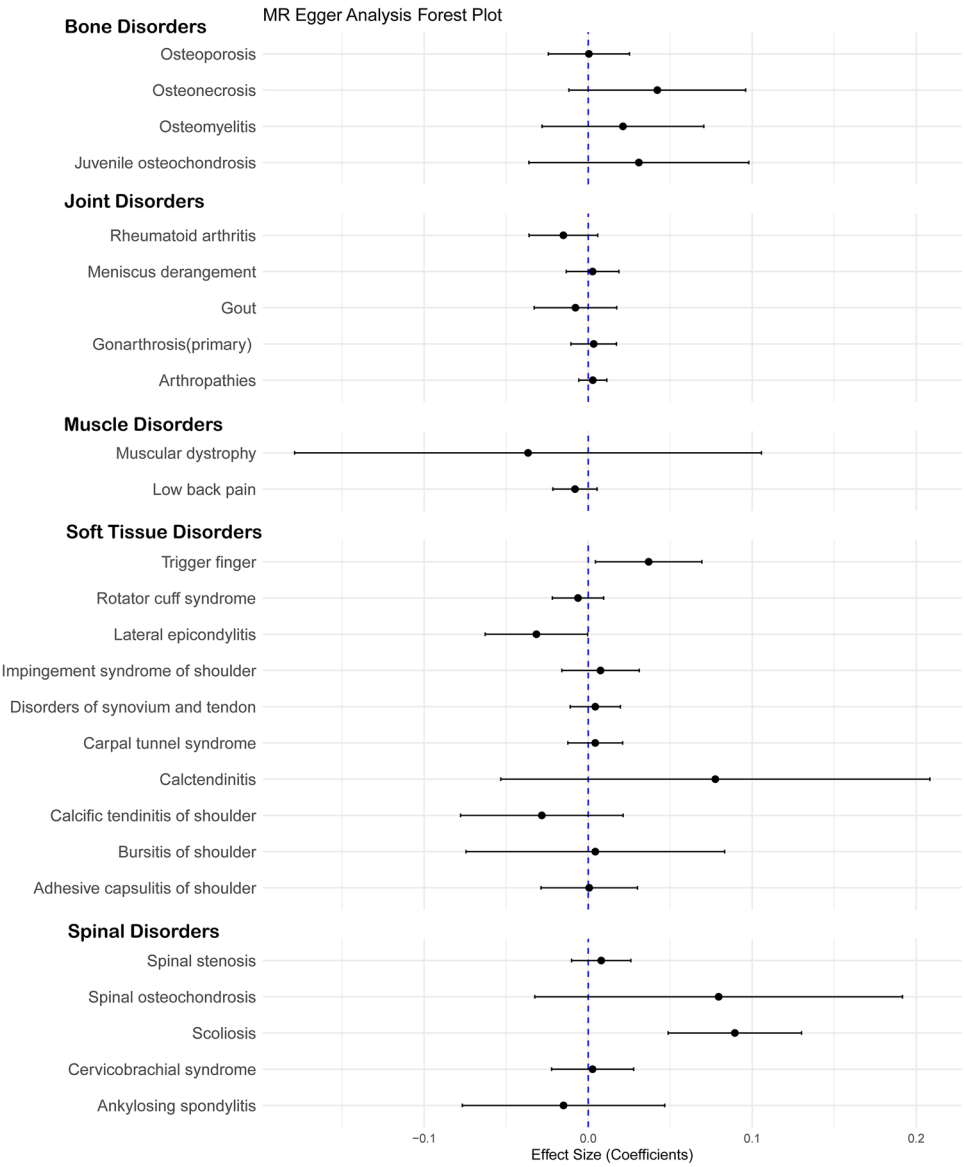

Fig. 3 Forest plot of the MR results based on the MR-Egger method between Gut microbiota and 26 musculoskeletal disorders

Soft tissue disorders

Soft tissue disorders constituted a significant segment of the musculoskeletal conditions analyzed in this research. Notably, our findings indicate a distinct positive correlation between gut microbiota and bursitis of the shoulder, as evidenced by inverse-variance weighting (IVW) (Beta = 0.051, SE = 0.016, P = 0.001; Table 1; Fig. 2). Conversely, a significant protective effect of gut microbiota against rotator cuff syndrome (IVW-Beta = − 0.007, IVW-SE = 0.003, IVW-P = 0.022; Table 1; Fig. 2) and calcific tendonitis of the shoulder (IVW-Beta = − 0.021, IVW-SE = 0.01, IVW-P = 0.034; Table 1; Fig. 2) was also found. Furthermore, a negative correlation emerged for adhesive capsulitis of the shoulder (WM-Beta = − 0.018, WM-SE = 0.008, WM-P = 0.029; Table 1; Figs. 2, 3) and trigger finger (MR-egger-Beta = 0.037, MR-egger-SE = 0.017, MR-egger-P = 0.026, Table 1; Figs. 2, 3), although these associations were not corroborated by other analytical approaches, suggesting a complex interplay that warrants further investigation.

These findings suggest potential causal relationships with gut microbiota, although the observed significance necessitates cautious interpretation and further validation. Our analysis revealed no significant associations with other soft tissue disorders, such as disorders of the synovium and tendon, lateral epicondylitis, shoulder impingement syndrome, calcific tendonitis or carpal tunnel syndrome (Table 1; Figs. 2, 3, 4). This outcome might indicate either a negligible influence of gut microbiota on these conditions or the limitations of our study in detecting such effects.

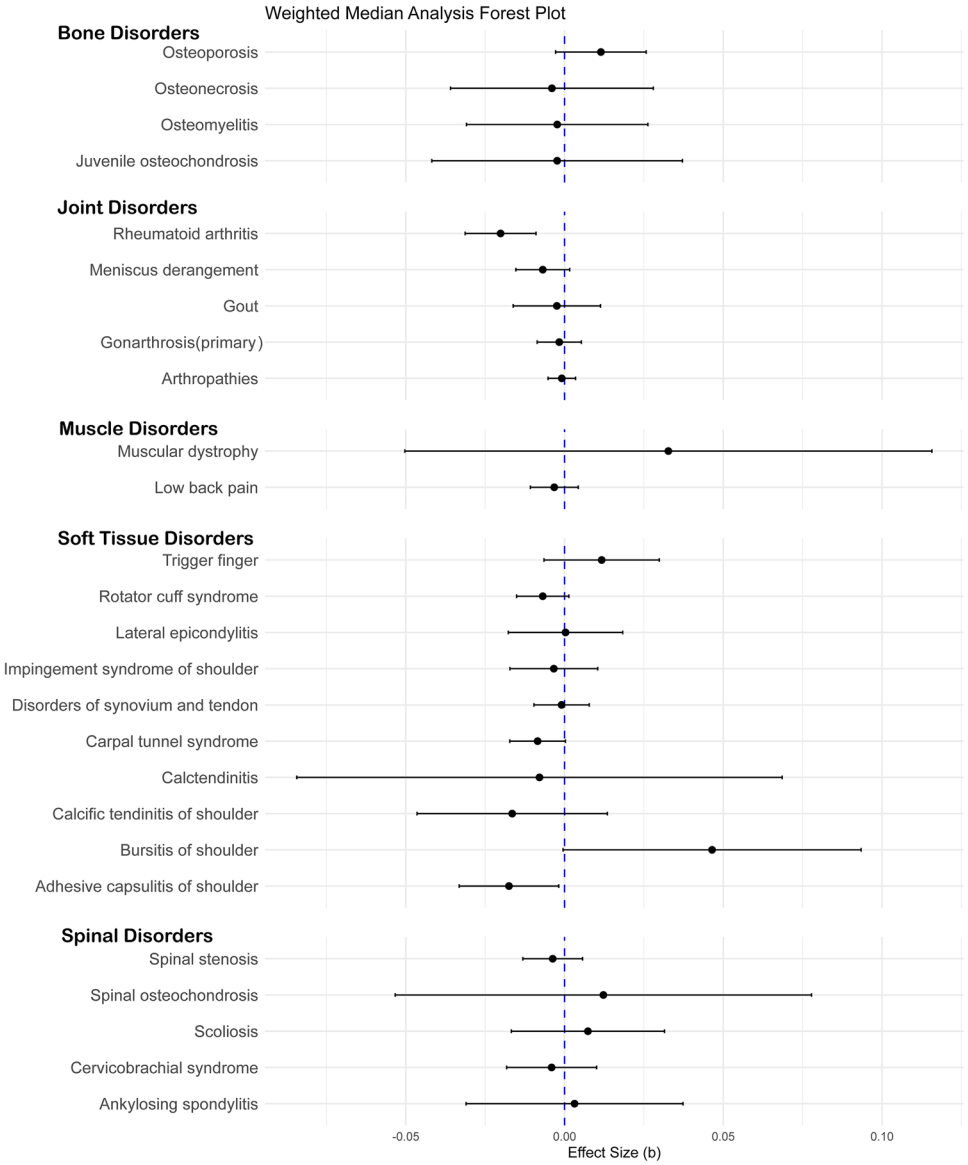

Fig. 4 Forest plot of the MR results based on the weighted median method between Gut microbiota and 26 musculoskeletal disorders

It is crucial to acknowledge that while certain diseases demonstrated significant links in specific models, these observations call for further validation in light of potential methodological constraints, including pleiotropy and bias.

Bayesian validation results

Upon validating the MR analysis outcomes through Bayesian modeling, we observed a congruence in indications of causality across different MSDs (Fig. 5). In a violin plot, the width at any given point along the vertical axis reflects the density of data points at various values, serving as a visual representation of the distribution's shape and spread. The length, conversely, illustrates the data's range, mapping the posterior distribution of Beta values from the minimum at the plot's base to the maximum at its apex.

Bone disorders

For osteoporosis, a prominent width and shorter violin plot length, with a median marginally above zero, suggest a probable increase in osteoporosis risk linked to certain gut microbiota with a high degree of certainty. Conversely, the potential impacts of osteonecrosis, osteomyelitis, and juvenile osteochondromatosis on the gut microbiota are unclear, indicating a lack of significant overall effects but hinting at possible individual variabilities. These Bayesian validations align with the MR results, reinforcing our conclusions (Table 1; Fig. 5).

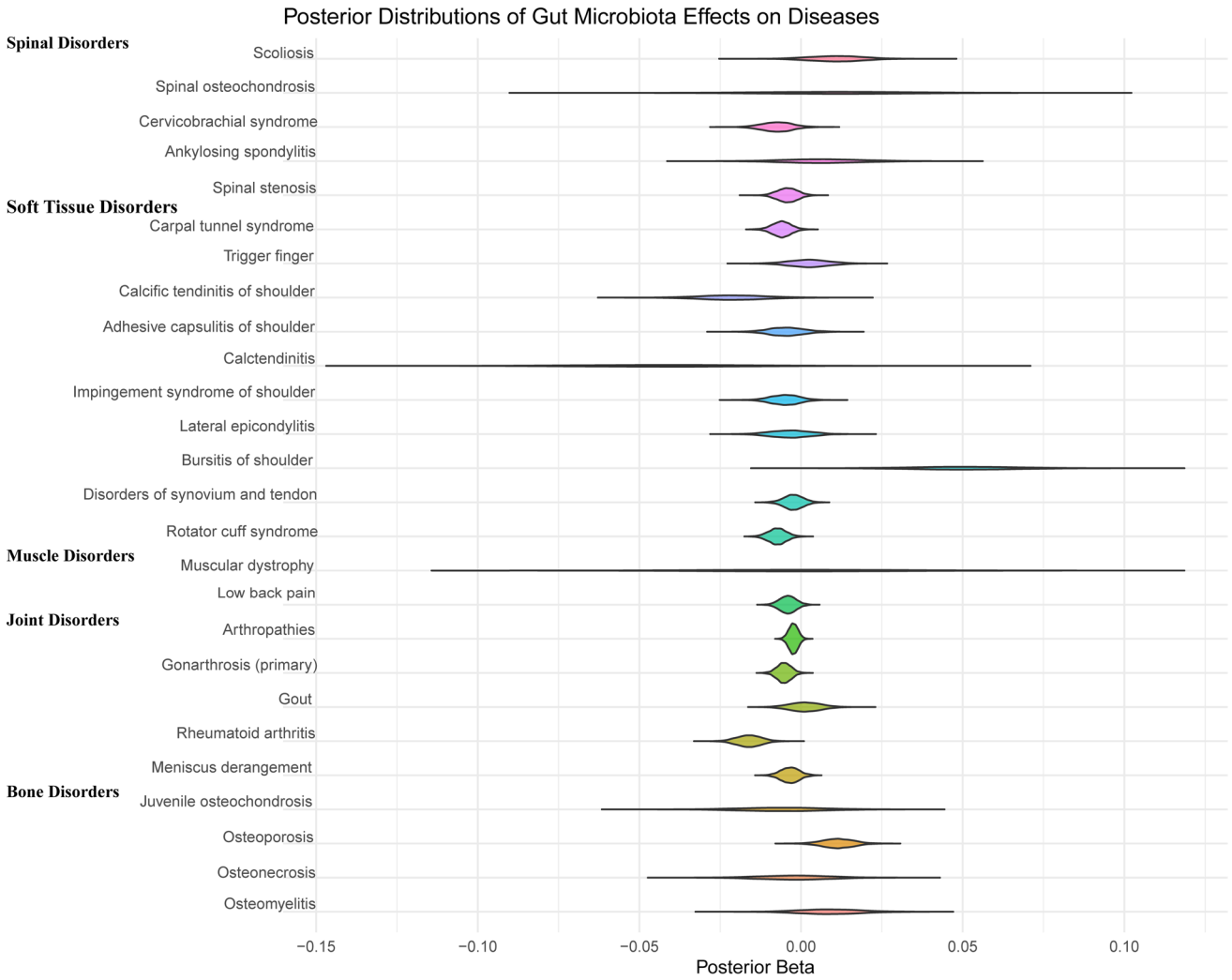

Fig. 5 Forest plot of the MR results based on the weighted median method between Gut microbiota and 26 musculoskeletal disorders

Muscle disorders

In contrast to MR findings, low back pain demonstrated a definitive negative correlation with gut microbiota in the Bayesian model, suggesting the need for a more nuanced examination of this relationship (Table 1; Fig. 5). The effect of muscular dystrophy on the gut microbiota is highly uncertain, underscoring potential subgroup sensitivities.

Spinal disorders

Ankylosing spondylitis, scoliosis, and chondromalacia exhibited positive medians with wide distributions in violin plots, indicating substantial uncertainty in effect sizes. Despite initial positive correlations, these correlations were deemed nonsignificant in combination with the Mendelian analysis results, suggesting minimal overall impact but possible individual or subtype variations (Table 1; Fig. 5).

Joint disorders

In addition to gout, other joint disorders (meniscus derangement, rheumatoid arthritis, primary gonarthrosis, arthropathies) were strongly negatively correlated according to Bayesian validation, with violin plots indicating high certainty in these findings. Gout displayed wider violins around the median, suggesting variability in the positive impact of certain gut microbiota on gout risk (Table 1; Fig. 5).

Soft tissue disorders

In our study, Bayesian models validated significant negative correlations for rotator cuff syndrome and calcific tendonitis of the shoulder, highly aligning with MR analyses (Table 1; Figs. 2, 5). There is a plausible correlation between rotator cuff syndrome and calcific tendonitis of the shoulder and the

gut microbiota. This suggests that gut microbiota may have a protective effect against both shoulder disorders. Similarly, Bayesian validation identified a pronounced "violin" for carpal tunnel syndrome, adhesive capsulitis of the shoulder, impingement syndrome of the shoulder, lateral epicondylitis, and disorders of the synovium and tendon, which also suggested a potentially negative correlation (Table 1; Fig. 5). Despite these observations, the characteristics are inconsistent with previous MR analyses, indicating a need for cautious interpretation. Since adhesive bursitis of the shoulder did not show a significant correlation in the IVW analysis, this negative correlation requires further discussion (Table 1; Fig. 2). After Bayesian validation, the trigger finger presented the exact opposite result to that of the MR−Egger method (Table 1; Figs. 3, 5). We believe that this result for trigger finger can be ruled out at the genetic level. Our analysis also showed that the results of the MR analyses for bursitis of the shoulder and calcific tendonitis were unreliable (Table 1; Fig. 5). Therefore, caution should be exercised in interpreting conclusions drawn from MR analyses regarding the causal relationship between gut microbiota and bursitis of the shoulder and calcific tendonitis (Table 2).

Multiple testing correction

After dual correction, only rheumatoid arthritis (Bonferroni-$P_{adj} < 0.001$, FDR-$P_{adj} < 0.001$) and bursitis of shoulder (Bonferroni $P_{adj} = 0.026$, FDR $P_{adj} = 0.013$) retained significance. Using FDR correction, rotator cuff syndrome ($P_{FDR} = 0.039$) and osteoporosis ($P_{FDR} = 0.042$) showed suggestive evidence of association, while rheumatoid arthritis ($P_{FDR} < 0.001$) and calcific tendinitis ($P_{FDR} = 0.028$) remained significant.

Discussion

This large-scale cross-consortium MR study of 26 musculoskeletal diseases revealed suggestive evidence linking the gut microbiota with MSDs. Notably, our analysis revealed a significant negative correlation between gut microbiota and rheumatoid arthritis, calcific tendonitis of the shoulder and rotator cuff syndrome, while highly plausible positive associations between gut microbiota and osteoporosis were shown. However, for the majority of conditions examined, we did not establish a definitive causal relationship, whether positive or negative, between gut microbiota and MSDs, underscoring the complexity of the gut-microbiome-musculoskeletal nexus. Emerging studies have suggested a pivotal role of gut microbiota in various diseases, potentially influencing musculoskeletal system functioning. However, establishing direct causal links at the genetic level is challenging (Fan and Pedersen 2021; Behera et al. 2020). By leveraging MR and Bayesian modeling, our study created a comprehensive gut-microbiota-musculoskeletal-disorder library, validating direct relationships and identifying future pathways involved in the microbial-musculoskeletal axis.

Gut microbiota and skeletal diseases

Two studies by Zhao et al. (2022a) and Zhang et al. (2022) showed that the gut microbiota influences calcium absorption and osteoclast differentiation through carbohydrate metabolism and short-chain fatty acid production, contributing significantly to the understanding of how the gut microbiota affects bone health. Our findings align with these studies, revealing a robust association between gut microbiota and an increased risk of osteoporosis. Furthermore, a cohort study by Zhang et al. also revealed that Chinese herbal

Table 2 Bonferroni and FDR correction for musculoskeletal disorders with nominally significant associations

Outcome	IVW P-value	Bonferroni-adjusted P-value	FDR-adjusted P-value (Benjamini–Hochberg)	Significance (Bonferroni) ($\alpha = 0.0019$)	Significance (FDR) ($\alpha = 0.05$)
Bone disorders					
Osteoporosis	0.025	0.650	0.052	No	No
Joint disorders					
Rheumatoid arthritis	< 0.001	< 0.001	< 0.001	Yes	Yes
Soft tissue disorders					
Rotator cuff syndrome	0.022	0.572	0.048	No	Yes
Bursitis of shoulder	0.001	0.026	0.013	Yes	Yes
Calcific tendinitis of shoulder	0.034	0.884	0.078	No	No

Bonferroni-adjusted P-value: threshold for significance $\alpha = 0.05/26 = 0.0019$; FDR-adjusted P-value: Benjamini–Hochberg procedure controlling false discovery rate at $\alpha = 0.05$; Bold values: statistically significant after correction; outcomes listed here had nominal significance (IVW $P < 0.05$) in primary analysis

medicine may promote recovery in osteoporosis patients by modifying the structure and function of the gut microbiota (Zhang et al. 2023). For osteoporosis (Beta = 0.011), the narrow CI (0.001–0.021) suggests a consistent but small effect, potentially meaningful at the population level. In light of this, we believe that gut microbiota modulation may be a promising candidate target for new therapeutic treatments for fairly common systemic bone diseases such as osteoporosis. For osteoporosis, gut microbiota may modulate bone mineral density via vitamin D metabolism and SCFA-mediated inhibition of osteoclastogenesis. Specifically, butyrate reduces RANKL/OPG ratio in osteoblasts, suppressing bone resorption (Zhao et al. 2022a, 2022b; Lucas et al. 2018).

Osteonecrosis, characterized by an ischemic skeletal condition, and osteomyelitis, a bone infection, contrast with juvenile osteochondrosis, which manifests through noninflammatory disruptions in the ossification of articular cartilage (Lewis et al. 2019; McCabe et al. 2015; West and Jaramillo 2019). Notably, an experimental study on mouse models highlighted the potential therapeutic role of *Ligilactobacillus animalis* in mitigating osteonecrosis through mechanisms such as enhanced angiogenesis and osteogenesis and reduced apoptosis (Chen et al. 2022b). Although these findings derived from animal studies offer limited direct applicability to human health, they support the concept that we have mechanisms of influence mediated by other factors that may be undetected by our studies, such as the pathways of bone mineral resorption (Zhang et al. 2022). However, this may also lead to a debate on whether the onset of skeletal diseases stems directly from gut microbiota derivatives or whether dysbiosis within the gut microbiota itself triggers skeletal pathologies (Zhao et al. 2022a; McCabe et al. 2015). Our MR findings align with Zhao et al., who reported *Bifidobacterium lactis* improved bone density in postmenopausal osteoporosis. However, unlike their probiotic trial, our study identified *Bacteroides* as a risk factor, possibly due to population-specific microbiota interactions or unmeasured confounders (e.g., vitamin D status) in observational studies (Zhao et al. 2022a). These observations underscore the necessity of further research to elucidate the specific pathways through which the gut microbiota impacts skeletal health, potentially revolutionizing our understanding and treatment of these conditions (Lewis et al. 2019).

Gut microbiota and muscle disease

In our comprehensive cross-study analysis, we explored the causal relationships between gut microbiome variations and muscle diseases, notably muscular dystrophy and low back pain, but we did not identify significant associations. This finding contrasts with recent research by Qiu et al. (2023), which posited a microbiome-muscular dystrophy linkage mediated through inflammatory processes or microbial abundance shifts. Moreover, contemporary literature has begun to highlight the transformative role of gut microbiota in the progression of muscular dystrophy (Ziemons et al. 2021). Animal studies further support a causal link between gut microbiota and low back pain, suggesting that *Lacticaseibacillus paracasei* administration can mitigate inflammatory responses and influence serum metabolomics and gut microbiota composition in relevant models (Wang et al. 2021).

Collectively, in contrast to the current literature and previous inconclusive small-scale studies, although our MR analyses did not yield a potential relationship between them, as validated by the Bayesian model we constructed, it is reasonable to assume that this paradox occurs because muscle atrophy and low back pain are the result of gut microbiota potentially influencing the onset of such muscle disorders via a non-gene-mediated pathway (Ticinesi et al. 2019). Muscle atrophy is classified as neurological or physiological atrophy, while low back pain may be caused by lumbar muscle strain or spinal canal pathology (Ziemons et al. 2021; Diarbakerli et al. 2022). Although the results of our analyses are biologically plausible, further subgroup analyses of causality may not be possible due to the lack of individual data in the original studies we chose to group such genetic data (Ticinesi et al. 2019). Repeated validation in independent cohorts, clinical follow-up analyses, or the use of stronger GWAS datasets in future studies are needed to draw definitive conclusions.

Gut microbiota and spinal disorders

While established risk factors for cervicobrachial syndrome include smoking and sex (Yi et al. 2020), research on the etiology of cervicobrachial syndrome by Yi et al. highlighted atlantoaxial subluxation at the C1/C2 level as a critical etiological factor (Vesela et al. 2005). However, cervical spinal stenosis, a subtype of neurogenic cervical spondylosis, is also associated with cervicobrachial syndrome, but its pathogenesis remains poorly investigated. This adds a layer of complexity to our understanding of cervicobrachial syndrome (Aboushaala et al. 2023; Allam et al. 2018). With the discovery of the mechanism by which cerebral activin affects neurogenic cervical spondylosis, whether and how gut microbiota can affect this process requires more targeted research (Yi et al. 2020; Allam et al. 2018). In the present study, the association with spinal stenosis was not statistically significant after correction for multiple analyses, but thoracolumbar spinal stenosis also causes "scoliosis" in clinical practice (Toyoda et al. 2023). In contrast to the above spinal disorders, one systematic review provided evidence that the gut microbiota influences the development and progression of scoliosis and ankylosing

spondylitis through aberrant immune responses and complex bacterial-host cell-miRNA interactions (Aboushaala et al. 2023; Tavasolian and Inman 2021). Therefore, even if we obtain nonsignificant results after Bayesian analysis, if we blindly conclude that there is no genetic correlation between all spinal diseases and gut microbiota, we need to use the gut microbiota as an entry point to launch more targeted research on its immunology and etiology (Aboushaala et al. 2023).

Classification with the ICD-10 (World Health Organization 2016) was based on genome analyses that were originally performed in the FinnGen database (https://r9.risteys.finngen.fi/). The spondylolisthesis data included in this study included juvenile spondylolisthesis (Calvi's disease, Scheuermann's disease) and adult spondylolisthesis. Similarly, although we did not find a direct or indirect genetic association between gut microbiota and osteochondromatosis of the spine, the paucity of such studies suggests that our study could be expanded to include randomized controlled clinical trials in the future to further clarify the etiology and mechanism of spinal disorders (Behera et al. 2020; Tavasolian and Inman 2021).

Gut microbiota and joint disorders

After rigorous analysis and exploration of our MR analysis and constructed Bayesian model, our findings on the protective effect of the gut microbiome on rheumatoid arthritis (RA) are in agreement with those of Sun et al., who clearly verified by immunohistochemistry (IHC) and micro-CT that the gut microorganism *P. distasonis* and its metabolites are effective therapeutic targets for the treatment of rheumatoid arthritis (Sun et al. 2023). While the Beta value for rheumatoid arthritis (−0.016) appears modest, it corresponds to a 1.6% reduction in disease risk per standard deviation increase in protective microbiota abundance. Extrapolated to population-level shifts in microbiome composition (e.g., via probiotics), this could translate to a 10–15% risk reduction, aligning with interventions such as Sun's *Lacticaseibacillus* supplementation in clinical trials (Sun et al. 2023). Moreover, according to the available data, the gut microbiome is not only able to influence systemic autoimmune diseases such as RA, but it can also modulate disease progression through metabolites such as short-chain fatty acids, secondary bile acids and taurodeoxycholic acid (Castro-Mejía et al. 2020; McCabe et al. 2015; Liu et al. 2023; Chen et al. 2022c). However, our systematic literature review suggested that this pathway may be genetically mediated, as indicated by secondary metabolite or protein expression in the gut microbiota involved in the amelioration of RA (Guan et al. 2023; Hu et al. 2022). In rheumatoid arthritis, *Parabacteroides distasonis* may suppress Th17 differentiation through IL-10 induction, while *Prevotella copri* exacerbates synovitis via molecular mimicry of human citrullinated peptides (Sun et al. 2023; Chen et al. 2022c; Wu et al. 2016). Our MR results suggest that microbial-targeted therapies for treating autoimmune joint diseases are a relatively effective therapeutic avenue and research direction (Aboushaala et al. 2023).

According to the ICD-10 classifications, there are several other joint disorders: gout, which is also known as metabolic arthritis; primary arthropathy, which refers to spontaneous joint pathology other than sports injuries; and meniscal structural disorders, which refer to disorders of various forms (degeneration, detachment, and preservation) of the knee meniscus structure (World Health Organization 2016). The gut microbiota has been found to be directly related to hyperuricemia and can even lead to systemic inflammation, leading to arthritis (Guan et al. 2023; Zhao et al. 2022b). However, probably due to reverse causality or multiple effects of selected IVs, our study did not establish significant correlations with other joint diseases, suggesting the complexity of interactions within the gut-joint axis (Chen et al. 2023; Zuber et al. 2023). We posit that the gut microbiota may exert differential effects on various joint pathologies, a hypothesis that warrants further explicit experimental analyses to elucidate the intricate underlying mechanisms involved.

Gut microbiota and soft tissue disorders

We calculated estimates of the existence of nominal causal effects of the gut microbiota on rotator cuff syndrome and calcific tendonitis of the shoulder using MR methods and Bayesian modeling and concluded that there is a negative correlation between gut microbiota and the two soft tissue disorders of the shoulder joint. The currently identified cause of calcific tendonitis of the shoulder is calcium hydroxyapatite deposition due to insufficient blood perfusion to the shoulder joint, which eventually leads to glenohumeral osteoarthritis (Guan et al. 2023; Compagnoni et al. 2021). Diabetes mellitus was identified as a risk factor for calcific tendonitis of the shoulder in a large-scale cohort study (Su et al. 2021). Delving into the intricate relationship between gut microbiota and rheumatoid arthritis provides insight into the potential relationship between the gut microbiota and calcific tendonitis. This connection is hypothesized to stem from the'failure of macrophages to phagocytose calcific deposits, the induction of inflammation driven by inflammatory cytokines, or the influence of gut-derived metabolites on collagen deposition and fibroblast activity, leading to the'manifestation of the disease (Compagnoni et al. 2021; Mateos et al. 2021). To further substantiate this potential causal link, a transcriptome analysis utilizing RNA sequencing by Cho et al. revealed differentially expressed genes and matrix metalloproteinases implicated in calcific

tendonitis at the genetic level, supporting the existence of the proposed gene–gut-microbiota–soft-tissue-disease axis (Cho et al. 2020). To our knowledge, this is the first MR study linking gut microbiota to rotator cuff pathology. Retrospective studies by Cho et al. implicated MMP-9 dysregulation in tendon calcification; our findings suggest gut-derived metabolites (e.g., LPS) may modulate MMP activity, offering a novel therapeutic axis for microbiome-targeted anti-inflammatory therapies (Cho et al. 2020). Given the nascent state of research on calcific tendonitis pathogenesis, a directed effort toward identifying specific bacterial species or metabolites related to this condition is imperative. Such an approach could yield alternatives to conventional treatments such as arthroscopic lithotripsy or extracorporeal shockwave therapy (Compagnoni et al. 2021; Youn et al. 2023). In juxtaposition, rotator cuff syndrome, characterized by pain and muscle atrophy due to the complete or partial tear of the rotator cuff or supraspinatus muscle, is negatively correlated with certain gut microbial compositions (World Health Organization 2016). For rotator cuff syndrome (Beta = −0.007, 95% CI: −0.013 to −0.001), the CI's proximity to zero suggests caution in interpretation. While statistically significant, clinical translation requires validation in cohorts with longitudinal microbiome data. This suggests a protective role of the microbiota, potentially through the reduction of systemic inflammatory markers or a direct impact on shoulder tendon structures, illuminating the multifaceted influence of gut microbiota on soft tissue pathologies (Guan et al. 2023; Sun et al. 2023; Hu et al. 2022). Notably, rotator cuff syndrome showed FDR significance despite failing Bonferroni correction, suggesting its association with gut microbiota may warrant further investigation. This nuanced exploration underlines the critical need for further comprehensive studies to unravel the complex interactions at play, potentially revealing novel microbiome-targeted therapeutic strategies for managing soft tissue disorders (Chen et al. 2022a).

However, we lacked significant findings for other soft tissue disorders, including trigger finger, synovial and tendon disorders; shoulder bursitis; lateral epicondylitis; shoulder impingement syndrome; carpal tunnel syndrome; and adhesive capsulitis, for which our study did not find significant associations. With this as a point of intervention, we can fully speculate that the mechanism behind this correlation may originate from the gut microbiome-distant soft tissue inflammation axis, whereby an immune response triggered by gut microbial profiles leads to inflammation at extremities and joints of extremities, particularly in the shoulder joint or rotator cuff tendons (Aboushaala et al. 2023). Our research has fully dissected the importance of the complex microbial-host interactions that lead to soft tissue pathologies. Modulation of the gut microbiota through diet, probiotics or prebiotics may be a new strategy to control rotator cuff syndrome or prevent diseases such as calcific tendonitis of the shoulder (Castro-Mejía et al. 2020; Kragsnaes et al. 2024). Therefore, we believe that future studies should aim to identify the specific microbial species or metabolites responsible for these correlations and that more clinical trials are needed to explore this therapeutic avenue.

Advantages and limitations

In the present study, by leveraging the extensive sample size available in GWASs and employing a Bayesian regression framework for joint modeling, we investigated the causal relationships between gut microbiota and 26 common MSDs. A key advantage of MR is that genetic variants are immutable from birth and are randomly inherited by offspring. Therefore, scholars have posited that genetic variants are free from confounding and reverse causality issues (Hartley et al. 2022; Burgess et al. 2023). Nonetheless, we could not entirely eliminate the possibility of confounding factors, such as those within the study population and geographical factors, during the research process. We incorporated comprehensive and sufficiently authentic GWAS summary statistics, in which the original cohort study stratified and corrected the population (Kurilshikov et al. 2021; Sadat-Ali 2023; Kurki et al. 2023). Our research solely included European population cohorts, significantly reducing potential population bias and genetic heterogeneity (Kurilshikov et al. 2021; Sadat-Ali 2023). Moreover, with the use of powerful tools to estimate heritability, we found that the gut microbiome does not appear to contribute directly to most of the muscle and bone disease outcomes studied. Compared to smaller cohort studies, our research still provides genetic-level causal inferences unaffected by confounding factors (Burgess et al. 2023). We are satisfied that therapies targeting genetic modification of gut microbiota do not directly lead to a reduced risk of most of the outcomes investigated or to better symptom management. Previous MR studies were predominantly limited to single or a few outcomes without a systematic analysis of MSDs (Chen et al. 2023). Our study surpasses most previous research in terms of comprehensiveness and persuasiveness by employing joint modeling of multiple outcomes using a sparse Bayesian Gaussian copula regression framework to detect causal effects while estimating the residual correlation between summary-level outcomes, i.e., correlations not explained by exposures. Therefore, our study offers more accurate causal effect estimations (Zuber et al. 2023; Zou et al. 2024).

However, our study also has limitations. First, our selection of available IVs from the available gut microbiota data was limited relative to the human genome, potentially leading to type I errors in our findings (Burgess et al. 2023;

Zuber et al. 2023). Second, since our study used summary-level data for exposures and outcomes, we cannot perform subgroup analyses through related variables, which is one of the larger limitations of studies that include individual-level data (Kurilshikov et al. 2021; Xia et al. 2023). Besides, while our Mendelian randomization design minimizes confounding, residual pleiotropy or weak instrument bias (despite F-statistics > 10) may persist. Additionally, the restriction to European populations limits generalizability to other ethnic groups. Finally, numerous studies have shown that gut microbiota is closely related to diet, health habits, and environmental factors (Chen et al. 2022a; Castro-Mejía et al. 2020; Fan and Pedersen 2021). In the future, discovering musculoskeletal-related biomarkers, as well as specific bacterial species and corresponding signaling pathways involved in pathogenesis, through more in-depth studies will make it possible to target the gut microbiome for the treatment of MSDs and open new avenues for therapeutic interventions and diagnostic tools (Lewis et al. 2019). For example, longitudinal studies tracking microbiome dynamics in RA patients initiating biologic therapies could clarify microbial contributions to treatment response. RCTs testing Bifidobacterium longum supplementation in osteoporosis or FMT in calcific tendonitis are warranted. Integrating multi-omics (metagenomics, metabolomics) with deep phenotyping will elucidate mechanistic pathways for precision interventions (McCabe et al. 2015; Sun et al. 2023; Chen et al. 2022c; Price et al. 2024).

Clinical translation and future directions

Our findings highlight specific gut microbiota taxa (e.g., *Prevotella* for rheumatoid arthritis, Bifidobacterium for osteoporosis) as potential therapeutic targets. To operationalize these discoveries, future studies should prioritize metagenomic sequencing of microbial communities in MSD patients to identify strain-specific functional pathways (e.g., short-chain fatty acid synthesis, vitamin D metabolism) (Lucas et al. 2018). Mechanistic studies should prioritize gnotobiotic mouse models (e.g., fecal microbiota transplantation into RA-prone SKG mice) to validate causality and identify effector metabolites (e.g., bile acids). For instance, *Ligilactobacillus salivarius*, previously shown to mitigate osteoporosis in murine models (Yuan et al. 2022), could be evaluated in human trials. Clinical translation could involve stratified interventions: (1) dietary modulation (e.g., prebiotic fiber to enrich protective taxa) (Makki et al. 2018), (2) probiotic supplementation targeting taxa with causal associations (e.g., *Bacteroides* for rotator cuff syndrome) (Price et al. 2024; Wu et al. 2016), and (3) fecal microbiota transplantation (FMT) for refractory cases (Chen et al. 2024). Functional validation via in vitro models (e.g., gut-on-a-chip systems) could mechanistically link microbial metabolites (e.g., butyrate) to osteoclast inhibition or anti-inflammatory cytokine upregulation (Lucas et al. 2018).

Conclusion

In our study, we constructed a library of causal relationships between gut microbiota and MSDs and validated it by constructing a context-specific Bayesian model. We found a more significant negative correlation between gut microbiota and osteoporosis, while gut microbiota had a significant protective effect on rheumatoid arthritis, calcific tendonitis of the shoulder, and rotator cuff syndrome, contributing to a better understanding of the pathogenesis of MSDS. Based on our analyses, we were unable to confirm any causal effect of gut microbes on the outcomes of the other 22 common MSDs investigated in this study. Therefore, changes in the microbiota associated with MSDs may be a response to the disease process rather than a direct genetic-level cause of these 22 outcomes. While our MR analysis provides genetic evidence for gut microbiota-MSDS associations, large-scale prospective cohorts and randomized controlled trials (RCTs) are critical to validate causality.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11274-025-04318-6.

Author contributions Y.H.W. (Yunhao Wang) contributed the majority of the manuscript content. Y.Z.S. (Yingze Sun) was responsible for drafting and revising the manuscript. H.X.L. (Hongxing Liao), as the corresponding author, was responsible for securing funding, data verification, and final approval of the manuscript. All authors reviewed the manuscript. All authors contributed to the study conception and design. Data collection, analysis, and interpretation were performed by Yunhao Wang and Yingze Sun. The first draft of the manuscript was written by Yunhao Wang, and all authors critically revised subsequent versions. Hongxing Liao supervised the study and provided methodological expertise. All authors read and approved the final manuscript.

Funding This work was supported by the Medical Research Foundation of Guangdong Province of China (Grant No. B2023192) and the Medical and Medicine Research Project of Meizhou City, Guangdong Province of China (Grant No. 2022B33).

Data availability No datasets were generated or analysed during the current study. The GWAS summary statistics for gut microbiota were obtained from the MiBioGen consortium (https://gwas.mrcieu.ac.uk/datasets/), and musculoskeletal disorder data were sourced from the FinnGen Public Data R9 database (https://www.finngen.fi/en). Processed datasets and analytical code are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests. The authors declare no financial or non-financial interests directly or indirectly related to the work submitted for publication.

Ethical approval This study utilized publicly available summary-level GWAS data. Ethical approval for the original studies was obtained by the respective consortia: MiBioGen: Approved by institutional review boards at all participating centers (see Kurilshikov et al. 2021). FinnGen: Approved by the Finnish Ethics Committee in the FinnGen Public Data R9 database (https://www.finngen.fi/en).

Consent to participate As this study relied on de-identified, aggregate genetic data, informed consent was obtained by the original GWAS cohorts. Detailed consent procedures are described in the primary publications (Kurilshikov et al. 2021; Kurki et al. 2023).

Consent to publish This manuscript does not contain individual-level data, images, or videos requiring participant consent for publication.

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