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RESEARCH

Revealing the mediating mechanisms between BMI and osteoarthritis: a Mendelian randomization and mediation analysis

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Abstract

Background Despite well-documented associations between Body mass index (BMI) and Osteoarthritis (OA), the specific biological pathways and mediators involved remain poorly understood. This study aims to explore mediators through which BMI influences OA risk, particularly knee osteoarthritis (KOA), using Mendelian Randomization (MR) and mediation analysis.

Methods We used a two-step MR approach with data from the IEU OpenGWAS and FinnGen version 7 databases. BMI (N=322,154) was the primary exposure, with knee disorders (KD), total bone mineral density (TBMD), metabolic disorders (MD), and anxiety disorders (AD) as potential mediators. Outcomes included KOA (N=22,347), hip OA (HOA) (N=11,989), and all OA (AllOA) (N=50,508). Univariate MR evaluated causal relationships, followed by multivariate MR to quantify mediation effects. Multiple sensitivity analyses were conducted to validate robustness, while horizontal pleiotropy and heterogeneity were assessed using MR-Egger intercept and Cochran's Q statistic.

Results BMI significantly increased the risk of KOA (odds ratio [OR]: 2.00, 95% confidence interval [CI]: 1.56–2.56), HOA (OR: 2.05, 95% CI: 1.40–2.98), and AllOA (OR: 1.66, 95% CI: 1.41–1.95). KD and TBMD significantly mediated the effect on KOA, with mediation proportions of 20.89% and 3.59%, respectively. MD and AD showed no significant effects. Sensitivity analyses supported the robustness of these findings. Horizontal pleiotropy and heterogeneity tests indicated minimal evidence of bias, supporting the reliability of our results.

Conclusions BMI increases OA risk, with KD and TBMD partially mediating the effect, particularly for KOA. The direct impact of BMI remains predominant, emphasizing the importance of weight reduction, joint protection, and physical activity as preventive measures.

Keywords Osteoarthritis · Body mass index · Mendelian randomization · Mediator analysis · Knee disorders · Bone mineral density

Introduction

Osteoarthritis (OA) is a multifactorial and chronic degenerative joint disease that impacts not only the cartilage but also the entire joint structure, including synovium, ligaments, and surrounding muscles [1]. With over 500 million people worldwide affected by OA, it is a leading cause of disability, particularly among middle-aged and older adults, significantly impacting quality of life and functional independence [2]. The economic burden of OA is substantial, with treatment costs estimated to be around 1–2.5% of the gross domestic product in some countries [3]. Given the societal and economic consequences, identifying the underlying etiological mechanisms of OA remains a critical task for both researchers and healthcare professionals.

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Body mass index (BMI) has been widely recognized as a major risk factor for OA, especially in weight-bearing joints such as the knees and hips [1]. However, the exact mechanisms by which increased BMI contributes to OA are not fully understood. Traditionally, the role of BMI in OA pathogenesis has been attributed to biomechanical factors—excess weight leading to increased joint load, thereby accelerating joint degeneration [4]. Beyond the mechanical strain, metabolic factors are also thought to contribute, with adipose tissue acting as an endocrine organ that secretes pro-inflammatory cytokines, exacerbating joint inflammation and cartilage degradation [5]. Recent studies have also pointed towards additional contributors such as bone mineral density (BMD) and mental health factors, including anxiety and depression, which may influence the relationship between BMI and OA through complex and interconnected pathways [6, 7]. Previous researchers have explored potential influences between BMI and OA, including leptin, lipocalin, and lower extremity muscle as a percentage of body weight [8–10]. However, due to the limitations of observational studies, these findings of BMI on OA remain at the correlation finding stage, and there is currently no favorable evidence to provide proof of causation.

Observational studies investigating the relationship between BMI and OA are often constrained by several limitations, including confounding factors, reverse causation, and susceptibility to environmental influences. These limitations can obscure true causal relationships, making it difficult to derive definitive conclusions regarding the impact of BMI on OA. To address these challenges, alternative methodologies that can mitigate such biases are necessary. Mendelian Randomization (MR) offers a promising solution by utilizing genetic variants as instrumental variables (IVs) to infer causal relationships between an exposure and an outcome, thereby reducing the influence of confounding factors and reverse causality [11]. MR is based on Mendel's principles of inheritance, where genetic alleles are randomly assigned, providing a framework similar to randomized controlled trials. By using single nucleotide polymorphisms (SNPs) strongly associated with BMI as IVs, MR allows for a more accurate assessment of the causal impact of BMI on OA while minimizing the biases inherent in traditional observational studies [12]. The mediated MR analysis achieved through the two-step approach became a reliable method for exploring the mediating mechanisms, providing deeper insights into the pathways by which the exposure affects the outcome [13]. Traditional mediation analysis is limited by the potential impact of exposure, mediator and outcome interactions, which makes it difficult to establish causally related mediators, while mediation analysis based on Mendelian randomization allows for the selection of instrumental variables independently correlated with each factor, which effectively compensates for the shortcomings of traditional mediation analysis [14].

In this study, we employed both standard MR and two-step MR methods to evaluate whether specific mediating factors, including biomechanical, metabolic, and psychiatric contributors, play a role in the causal pathway from BMI to OA. Specifically, we included knee disorders (KD), metabolic disorders (MD), and anxiety disorders (AD) as representative factors for biomechanical, metabolic, and psychiatric influences, respectively, while also considering the role of BMD. The aim of this study was to elucidate whether these factors mediate the effect of BMI on OA and to quantify the extent of this mediation. By leveraging the power of MR and mediation analysis, our research seeks to provide a clearer understanding of the causal pathways involved, ultimately informing better-targeted interventions for the prevention and management of OA in individuals with high BMI.

Materials and methods

Experimental design

This study employed a MR approach coupled with mediation analysis to investigate the mediating mechanisms linking BMI and OA. The experimental design is depicted in Fig. 1, outlining BMI as the primary exposure, potential mediators including KD, total bone mineral density (TBMD), MD, and AD, and outcomes comprising knee osteoarthritis (KOA), hip osteoarthritis (HOA), and all osteoarthritis (AllOA). To perform univariate MR, three key assumptions must be satisfied: (i) the instrumental variable (IV) must be strongly associated with the exposure of interest; (ii) the IV must be independent of other confounders that could bias the exposure-outcome relationship; and (iii) the IV should influence the outcome only through the exposure, not via alternative pathways. Multivariate MR requires that IVs are strongly associated with at least one risk factor under investigation.

Data sources

All exposure and outcome summary data were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) and the FinnGen version 7 database (https://finngen.gitbook.io/documentation/v/r7/). A summary of these datasets is provided in Table 1.

FinnGen database

Data for KD, MD, and AD were derived from a genome-wide association study (GWAS) conducted using the FinnGen

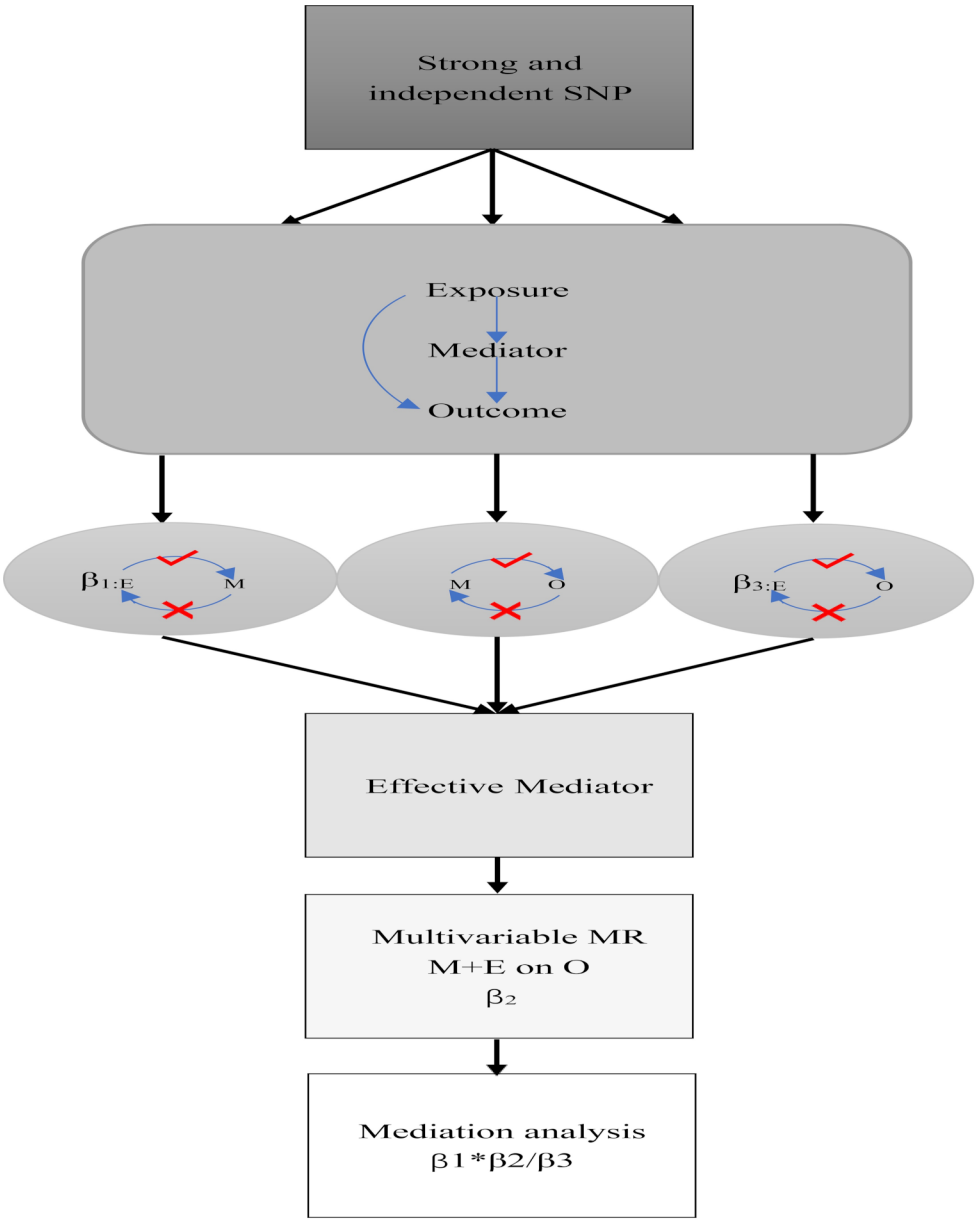

Fig. 1 Experimental design. In the first step, we used univariate bivariate MR to estimate exposure on mediator, mediator on outcome, and exposure on outcome effects, and to screen for effective mediators that possess only unidirectional causal associations with exposure and outcome. In the second step, to avoid bias due to interactions between exposure and mediators, we used multi-variate MR to estimate the direct effects of all effective mediators on OA. Finally, we calculated the mediating effects and their proportions. E = exposure, M = mediator, O = outcome, β1 = effect of exposure to mediator, β2 = effect of medi-ator to outcome, β3 = total effect of exposure to outcome

Table 1 GWAS for MR analysis

Exposure/Mediators	GWASID	PMID	Database	No. of cases	Sample size	Year
BMI	ieu-a-835	25,673,413	GIANT	322,154	322,154	2015
KD	M13_KNEEDERANGEMENTS	NA	FinnGen	28,554	202,617	2022
TBMD	ebi-a-GCST005348	29,304,378	GEFOS	56,284	56,284	2018
MD	E4_METABOLIA	NA	FinnGen	39,582	269,572	2022
AD	finngen_R7_KRA_PSY_ANXIETY	NA	FinnGen	39,582	269,572	2022
KOA	ebi-a-GCST005813	29,559,693	UK Biobank	4462	22,347	2018
HOA	ebi-a-GCST005810	29,559,693	UK Biobank	2396	11,989	2018
ALLOA	ebi-a-GCST005814	29,559,693	UK Biobank	10,083	50,508	2018

GWASID = GWAS summary data id; PMID = PubMed ID; BMI = body mass index; KD = knee disorders; TBMD = total bone mineral density; MD = metabolic disorders; AD = anxiety disorders; KOA = knee Osteoarthritis; HOA = hip Osteoarthritis; AllOA = all Osteo-arthritis

Biobank, which aims to gather genetic and health data from a prospective cohort of 500,000 Finnish participants as of June 2022. A total of 309,154 individuals were involved, consisting of 173,746 females and 135,408 males [15]. KD

were diagnosed according to ICD-10 (M23), ICD-9 (717), and ICD-8 (72410) codes, which include meniscal, ligament, and other knee joint disorders resulting from injury or degeneration. The KD-related GWAS comprised 14,608 women and 13,946 men, with an average age of 46 years. MD were characterized by ICD-10 (E70-E90) codes, covering a wide range of endocrine and metabolic abnormalities including amino acid, lipid, sugar, mineral, and hormonal metabolism. The MD GWAS involved 19,061 women and 20,521 men, with an average age of 62 years. AD were defined by ICD-10 (F40-F48), ICD-9 (300–303, 306–309, 3078 A, 309), and ICD-8 (300–302, 30030, 305–309, 305, 30680, 30799) codes, including psychiatric symptoms like anxiety, obsessive-compulsive behaviors, and depressive symptoms. The AD-related GWAS involved 20,729 women and 10,002 men, with an average age of 39 years. The detailed information for these GWAS datasets is accessible via https://r7.risteys.finngen.fi/.

IEU OpenGWAS database

The data for OA, BMI, and TBMD were obtained from the IEU OpenGWAS database, which is a comprehensive resource for MR studies and currently contains over 42,000 GWAS datasets [16]. Data for OA were derived from a genome-wide meta-analysis conducted by the UK Biobank, which included 30,727 cases and 297,191 controls [17]. The UK Biobank is a population-based cohort comprising approximately 500,000 individuals aged 40–73 years. We selected hospital-diagnosed KOA, HOA, and AllOA cases based on ICD-10 codes captured from the Hospital Episode Statistics (HES) database, ensuring high diagnostic accuracy [17]. BMI-related GWAS data were sourced from the Genetic Investigation of Anthropometric Traits (GIANT) consortium, which conducted a meta-analysis across 125 studies, involving 339,224 individuals, where BMI was measured as weight (kg) divided by height squared (m^2) [18]. TBMD data were obtained from the Genetic Factors for Osteoporosis (GEFOS) consortium, which included participants from the United States, Europe, and Australia, with BMD measured via dual-energy X-ray absorptiometry (DXA) [19].

In order to minimize sample overlap, we took steps to ensure that the datasets used represented independent populations as much as possible. Although complete elimination of overlap in large-scale meta-analyses is challenging, it has been shown that sample overlap introduces minimal bias, particularly when overlap remains below 30% and IV strength remains sufficiently high [20, 21]. Thus, potential bias in this study was limited.

All data used in this study were obtained from publicly available sources, and appropriate ethical approvals were obtained by the original study teams [15, 17–19]. Consequently, no additional ethical approval was required for this analysis.

Instrumental variable selection

IVs were selected from the IEU OpenGWAS and FinnGen version 7 databases. We filtered SNPs that exhibited a strong correlation with the exposure, using a stringent significance threshold of $P < 5 \times 10^{-8}$. If insufficient SNPs were available for the analysis, the threshold was relaxed to $P < 5 \times 10^{-7}$, and for reverse MR analyses of OA, the threshold was set to $P < 5 \times 10^{-6}$ [22]. Specific steps for selection included: (1) using the TwoSampleMR package in R to extract SNPs strongly correlated with exposure; (2) clumping these SNPs (using $r^2 = 0.001$ and a distance of 10,000 kb) to ensure that only independent SNPs were selected; (3) correcting for palindromic SNPs and verifying the presence of SNPs in the outcome GWAS data, excluding those that violated MR assumption (iii); and (4) querying all SNPs in PhenoScanner to exclude those associated with known confounders, thus satisfying MR assumption (ii). All selected IVs had F-statistics greater than 10, indicating robust strength, as shown in Supplementary Table 1.

Statistical analysis

For univariate MR analysis, the inverse variance weighting (IVW) method was employed as the primary analysis method. Additionally, the weighted median and MR-Egger regression methods were used to account for potential violations of MR assumptions. We conducted horizontal pleiotropy assessments using the MR-Egger intercept test and MR-PRESSO global and outlier tests, while heterogeneity was evaluated using Cochran's Q statistic. In instances where significant MR results were obtained, reverse MR was also performed to assess the potential for bidirectional causality between exposure or mediator and outcome.

The IVW method calculates the inverse variance-weighted average of effect estimates from each SNP, assuming that all SNPs are valid instruments. We used a random-effects model to allow for potential heterogeneity, and rigorous pleiotropy assessments were conducted to ensure robustness [23]. The weighted median method provides a reliable causal estimate even if up to 50% of the SNPs are invalid, making it particularly robust against pleiotropic effects [24]. MR-Egger analysis allows for the detection of directional pleiotropy. The MR-Egger intercept test compares the intercept value to zero, with any significant deviation suggesting horizontal pleiotropy [25]. The MR-PRESSO global test and outlier test were used to assess and correct for horizontal pleiotropy. Any significant

outliers ($P<0.05$) were removed, and the MR analysis was repeated to verify results [26]. Heterogeneity was assessed using Cochran's Q statistic, and a leave-one-out analysis was conducted to evaluate the robustness of the findings by iteratively removing individual SNPs.

Multivariate MR analysis was performed to quantify the direct effects of mediators and exposures on OA outcomes [27]. This approach incorporated effective mediators (KD, MD, AD, and TBMD) alongside BMI into a single model to determine their individual effects on OA (denoted as β_2). Exposure-related SNPs were queried in the full GWAS datasets for mediators to extract corresponding genetic effect data (β and SE), which were subsequently used as instrumental variables for mediation. Although this operation results in a lower F-statistic for the instrumental variables, their mean value is still greater than 30 (Supplementary Tables 2–4). Both the IVW and MR-Egger regression methods were applied, with heterogeneity and pleiotropy assessed as described for univariate MR.

For estimating indirect effects of mediators on binary outcomes, we used the product of coefficients method due to its minimal bias in calculating mediation effects [28]. The total effect (β_3) was derived from univariate MR (exposure-to-outcome effect), while the indirect (mediated) effect was calculated as the product of the univariate MR-estimated exposure-to-mediator effect (β_1) and the multivariate MR-estimated mediator-to-outcome effect (β_2). The proportion mediated was calculated as $(\beta_1 \times \beta_2) / \beta_3$, with confidence intervals determined to evaluate significance. If the confidence interval crossed zero, the mediating effect was considered non-significant [29].

All statistical analyses were conducted using R version 4.2.1 with the TwoSampleMR and MR-PRESSO packages.

Results

The detailed results of the MR analysis are presented in Supplementary Tables 2–5, with corresponding visualizations provided throughout the main text. The statistical significance of the findings was determined using *p*-values in combination with confidence intervals and sensitivity analyses, as outlined in prior studies [30]. The statistical power of the univariate MR results was estimated with a type I error rate of 0.05% using an online tool (https://shiny.cnsgenomics.com/mRnd/), and the specific details are reported in Supplementary Table 6. All statistical analyses were conducted using RStudio version 4.2.1. For univariate MR, the R packages used included TwoSampleMR version 0.5.6 and MR-PRESSO version 1.0, while the R package used for multivariate analysis was MendelianRandomization version 0.6.0. The implementation of all statistical analyses occurred in September 2022.

Univariate MR analysis

As shown in Fig. 2A and B, and 2C, univariate MR analyses using IVW as the primary analysis method suggested a significant causal effect of BMI on each OA subtype. Specifically, BMI demonstrated a robust causal relationship with KOA (OR = 2.00[1.56–2.56]), HOA (OR = 2.05[1.40–2.98], and AllOA (OR = 1.66[1.41–1.95]).

KD also exzibited a strong causal effect on KOA (OR = 1.47[1.13–1.90]) and AllOA (OR = 1.27[1.08–1.51]), though no significant causal effect on HOA was observed (OR = 1.21[0.41–3.56]). TBMD was found to have a weaker causal effect on each OA subtype, with notable associations for KOA (OR = 1.19[1.06–1.35]), HOA (OR = 1.19[1.02–1.39]), and AllOA (OR = 1.10[1.01–1.19]). Neither MD nor AD showed significant causal effects on any OA subtype; therefore, KD and TBMD were prioritized for further MR analysis.

As depicted in Fig. 2D, in the mediation-focused univariate MR analysis, the IVW method indicated a strong causal relationship between BMI and KD (OR = 1.35[1.21–1.52]) and a comparatively weaker effect of BMI on TBMD (OR = 1.12[1.04–1.20]). For BMI, MD, and AD for each OA type, both MR-Egger and weighted median methods were consistent with IVW findings, supporting the robustness of these results. While the findings for KD and TBMD were less consistent across methods, larger confidence intervals in MR-Egger and weighted median approaches suggested higher uncertainty, underscoring IVW as the most reliable estimate when significant pleiotropy and heterogeneity were not evident.

Heterogeneity assessments revealed possible evidence of heterogeneity for BMI on HOA (PIVW = 0.049, PEgger = 0.51) and BMI on KD (PIVW = 0.036, PEgger = 0.040). Additionally, the MR-PRESSO Global Test indicated a borderline level of horizontal pleiotropy for both analyses (BMI on HOA: $P = 0.059$, BMI on KD: $P = 0.051$). However, the Egger intercept test suggested a lower likelihood of horizontal pleiotropy in these relationships (BMI on HOA: $P = 0.300$, BMI on KD: $P = 0.245$). For all other MR analyses, the likelihood of heterogeneity and horizontal pleiotropy was minimal (Supplementary Table 5). We employed a random-effects IVW model and closely controlled for horizontal multiplicity using both manual search and statistical screening, followed by multivariate MR to further mitigate the effects of horizontal pleiotropy. Consequently, these marginal findings did not compromise the robustness of our overall results.

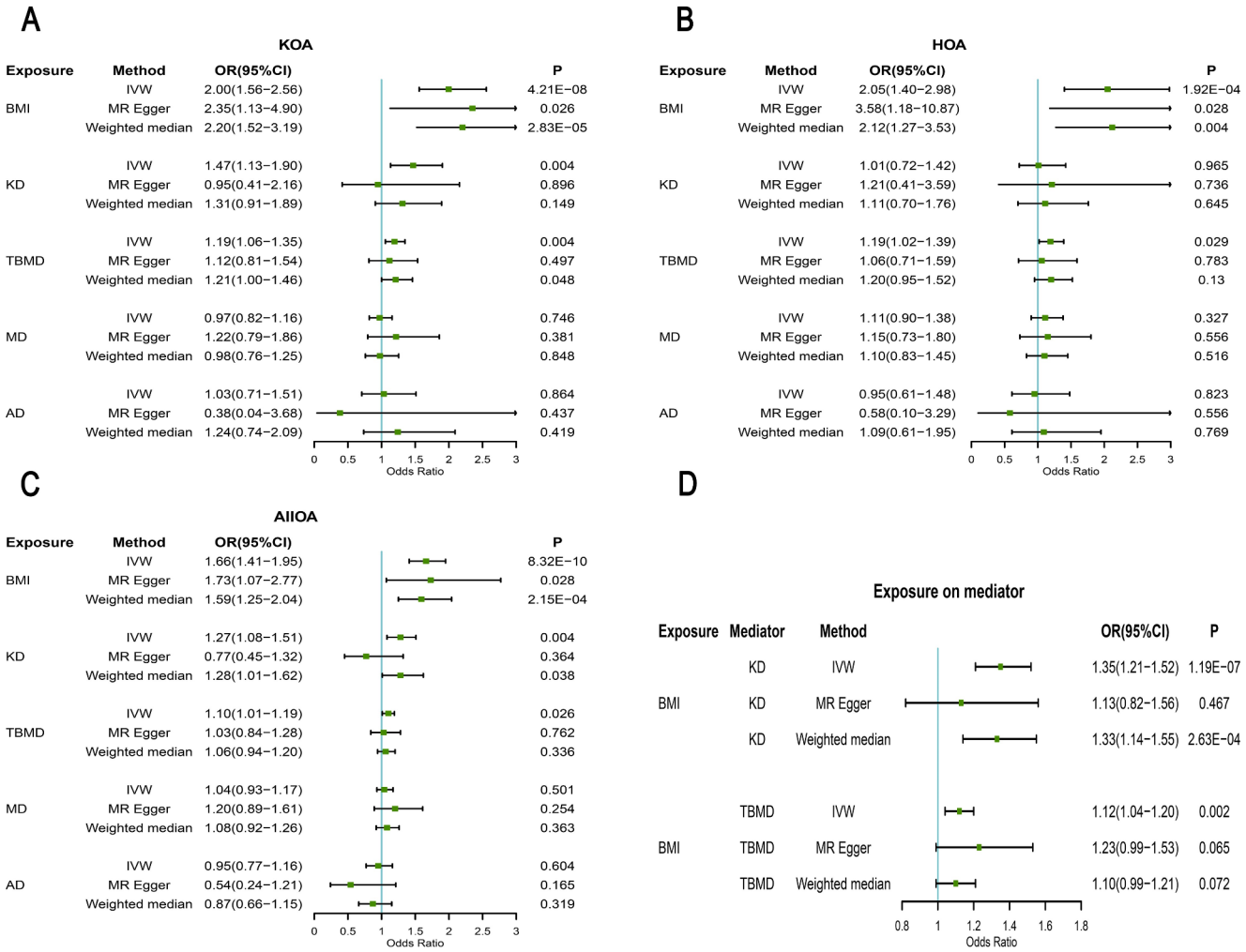

Fig. 2 Forest plots of univariate MR results for exposure and mediator on outcome. **A** = exposure and mediator on KOA; **B** = exposure and mediator on HOA; **C** = exposure and mediator on AllOA; **D** = exposure on effective mediator; OR = Odds ratio; *P* = significance *P*-value

The leave-one-out sensitivity analysis indicated that TBMD on HOA and TBMD on AllOA had two SNPs touching the invalid line, although they were not eliminated since subsequent multivariate MR was conducted, and those results were considered final. For all other outcomes, no outliers were detected. Reverse MR analysis of the significant results yielded negative findings, further supporting the causal direction. The related visualizations and detailed information can be found in Supplementary Tables 5 and Supplementary Figs. 1–6.

Multivariate MR analysis

Figure 3A displays the results of multivariate MR analyses, where IVW showed that BMI continued to exert a strong causal effect on each OA subtype, albeit with reduced effect sizes compared to univariate MR. Specifically, the causal effect of BMI on KOA was weaker in the multivariate context (OR = 1.76[1.35–2.29]), as was its effect on AllOA (OR = 1.51[1.27–1.80]). However, the causal effect on HOA remained consistent (OR = 2.05[1.39-3.00]). Multivariate MR findings for KD were consistent with the univariate MR results across all OA subtypes. For TBMD, multivariate MR findings diverged significantly from those in univariate analyses. TBMD maintained a significant causal relationship with KOA (OR = 1.24[1.04–1.47]), but the causal effects on HOA (OR = 1.22[0.95–1.56]) and AllOA (OR = 1.09[0.97–1.21]) were no longer statistically significant.

As depicted in Fig. 3B, MR-Egger results were consistent with IVW findings, and subsequent MR-Egger intercept tests, MR-PRESSO global tests, and Cochran's Q statistics indicated minimal likelihood of pleiotropy or heterogeneity (see details in Supplementary Table 5).

Mediation analysis

Table 2 presents the results of the mediation analysis. In the initial step, univariate MR was used to identify effective

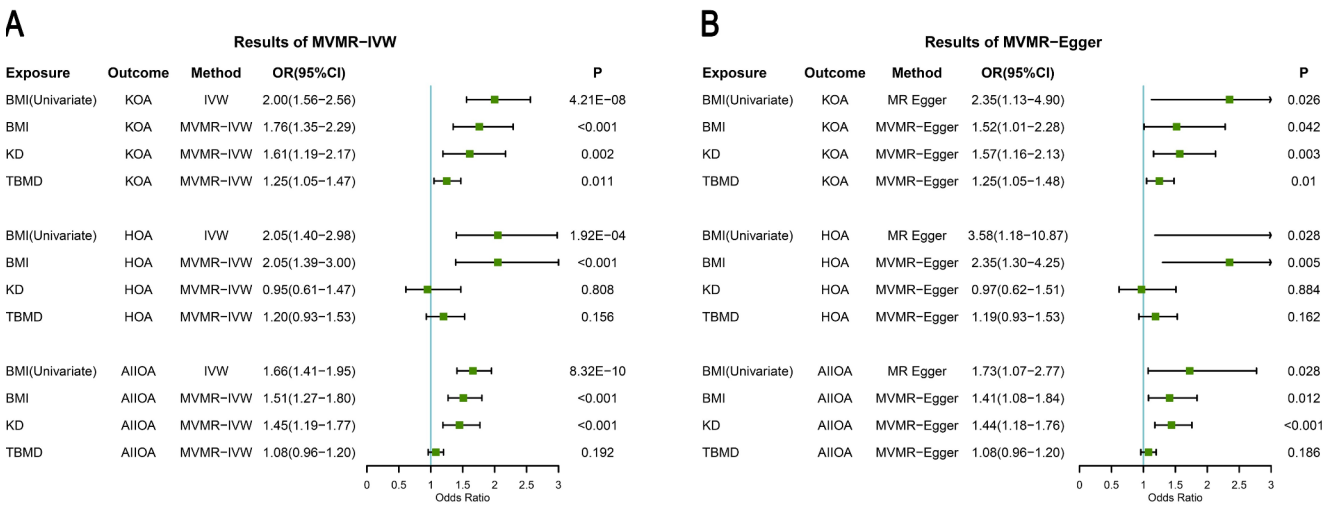

Fig. 3 Forest plots of multivariate MR results for exposure and effective mediator on outcome. **A** = results of IVW method; **B** = results of MR-Egger method; OR = Odds ratio; *P* = significance *P*-value

Table 2 Results of the mediation analysis

Mediator	β_1(95% CI)	β_2(95% CI)	β_3(95% CI)	Mediation effect (95% CI)	Mediated proportion (%) (95% CI)
KD	0.303(0.191–0.416)	0.476(0.176–0.776)	0.691(0.444–0.939)	0.144(0.039–0.250)	20.89(5.62–36.15)
TBMD	0.113(0.043–0.184)	0.219(0.050–0.388)	0.691(0.444–0.939)	0.025(2.55*$^{e-4}$-0.049)	3.59(0.04–7.14)

β1 = effect of exposure to mediator; β2 = effect of mediator to outcome; β3 = total effect of exposure to outcome; Mediation effect is derived from the delta method; Mediated proportion = β1*β2/β3*100%

mediators (KD and TBMD), and estimates for the effect of exposure (BMI) on these mediators (β1) as well as the total effect of exposure on outcome (β3) were obtained. The second step involved multivariate MR analysis, where KD retained a consistent causal relationship with each OA subtype, while TBMD maintained a causal effect solely with KOA. Consequently, the mediation effect sizes and their respective proportions were calculated for KD and TBMD as mediators in the relationship between BMI and KOA. Specifically, the proportion of the genetically predicted effect of BMI on KOA mediated by KD was 20.89% (95% CI: 5.62–36.15%), while the proportion mediated by TBMD was 3.59% (95% CI: 0.04–7.14%). These findings suggest that KD plays a more substantial role in mediating the impact of BMI on KOA compared to TBMD.

Discussion

In this study, we utilized MR and mediation analyses to explore the effect of BMI on OA and identify potential mediators. Previous research consistently supports a deleterious effect of elevated BMI on OA, particularly in the knee joint [31, 32]. However, specific causal mechanisms underlying this relationship have remained unclear. Our findings confirmed a strong causal effect of BMI on all OA subtypes, with KOA being notably influenced through mediating pathways involving KD and TBMD. No strong causal relationship was identified between MD, AD, and any OA subtype. By combining MR with mediation analysis, we successfully avoided limitations common to non-genetic mediation studies, while rigorously testing for horizontal pleiotropy and heterogeneity to ensure the robustness of our results.

The role of KD as a mediator in the development of KOA is consistent with findings from prior studies, which highlighted that various structural and tissue injuries in the knee joint could contribute to OA progression. Genetic alterations in mice leading to abnormal knee joint morphology have been linked to increased OA susceptibility, indicating that even mild structural abnormalities can predispose joints to degeneration over time [33]. Our findings that KD was strongly correlated with KOA (OR = 1.57[1.16–2.11]) support these experimental observations. Furthermore, studies have demonstrated that abnormalities in ACL significantly increase cartilage degeneration [34], and acute KD involving joint effusion or hematoma is a risk factor for KOA [35]. However, our MR results indicate that KD does not have a significant association with HOA, consistent across both univariate and multivariate analyses. Although some biomechanical studies have suggested that changes induced by KD may be linked to both KOA and HOA, these findings need to be considered in the context of genetic differences over a

full life cycle, which could result in compensatory mechanisms that attenuate genetic risks [36, 37]. Notably, BMI's strong influence on KD, as observed in our MR analysis (OR = 1.35[1.21–1.52]), highlights the increased mechanical stress and risk of joint injuries posed by obesity [38].

The large-scale GWAS data from Yang et al. [39] have identified SNPs associated with KD that also reach genome-wide significance for traits related to height development and monocyte count. For instance, rs11734412 and rs73991578 are closely associated with height development. Additionally, the correlation between rs4954405 and monocyte levels reaches a significance level of 7×10^{-14} [39]. This finding can be interpreted from two perspectives to elucidate KD as the strongest mediator between BMI and OA. On one hand, elevated BMI may exert excessive mechanical stress that affects chondrocyte growth and development, thereby contributing to OA [40, 41]. On the other hand, high BMI may induce chronic systemic low-grade inflammation [42], which manifests in OA as high levels of mononuclear or macrophage infiltration in the joints [43], this infiltration is closely related to OA joint pain and swelling. Elevated levels of mononuclear or macrophages further secrete a large amount of inflammatory factors such as IL-1, IL-6, and TNF-α, exacerbating cartilage damage and degeneration [43]. Therefore, it is essential to focus not only on how high BMI mechanically impacts knee joint stability and accelerates OA but also on its potential to induce local immune and inflammatory disturbances in the joints, thereby promoting OA.

The relationship between BMD and OA has long been controversial. Higher bone mass may increase susceptibility to microfractures, subsequently exacerbating OA [44]. A longitudinal study found that elevated femoral neck BMD was associated with an increased risk of both KOA and HOA [45]. Our multivariate MR results showed that TBMD retained a significant association with KOA after adjusting for BMI and KD, but its association with HOA and AllOA became non-significant. This discrepancy from prior findings, which focused on site-specific BMD, may be attributable to our use of TBMD as an aggregate measure encompassing multiple anatomical sites (e.g., lumbar spine, femoral neck, total hip) [46, 47]. High BMD could indeed have an independent effect on KOA, as suggested by a study involving patients with high bone mass, which found that these individuals were at increased risk of OA even after adjusting for BMI and other systemic factors [48]. The shared biological pathways between BMD and OA, such as those involving SMAD3, a gene implicated in both bone remodeling and cartilage maintenance, highlight the complexity of their relationship [49]. However, the absence of a bidirectional causal link between BMD and OA suggests that the association may not be entirely driven by common genetic mechanisms [6]. Mechanistically, higher BMI aggravates the pressure load on the tibial plateau of the joint, and these pathological changes in OA can lead to the occurrence of subchondral bone remodeling, especially in advanced OA manifested by an abnormally high bone density phenomenon [50, 51]. This suggests that the effect of high BMI on the process of OA may not be limited to cartilage damage, but may be related to abnormal subchondral bone remodeling, which is an all-round damage to the whole joint.

The lack of significant associations between MD or AD and OA in our univariate MR analysis was consistent with previous studies showing no direct link between metabolic or anxiety-related biomarkers and OA after controlling for BMI [52]. Different biomarkers, such as low-density lipoprotein and adipokines, have opposing effects on OA development, potentially canceling each other out and leading to insignificant overall effects [53, 54]. Furthermore, the observed association between AD and OA is likely confounded by pain and symptom burden, resulting in reverse causation rather than true causality [55]. Therefore, our findings that do not support a causal relationship between MD or AD and OA are reasonable.

The established link between BMI and OA underscores the importance of weight reduction for the prevention and management of OA. Physical activity has been found to reduce BMI effectively without increasing OA risk, irrespective of exercise intensity or duration [56, 57]. Our results further elucidate that KD plays a significant mediating role (mediating effect size: 20.89%) in the relationship between BMI and KOA. However, caution should be exercised in interpreting these results due to inaccuracies in estimating mediating effect sizes in binary outcomes [28]. The weaker mediating effect of TBMD indicates that, although bone mass contributes to OA, the direct impact of BMI remains the predominant factor. Ensuring a stable, healthy knee joint through reasonable exercise, weight control, and prevention of joint injuries is crucial for mitigating OA risk.

Our study has several limitations: (1) The population sample was derived from individuals of European ancestry, which may limit the generalizability of the findings to other populations. (2) Genetically predicted traits reflect lifetime exposure and may be influenced by developmental compensatory mechanisms or environmental factors, which could bias the results. (3) Stringent methods to exclude pleiotropic SNPs might have reduced statistical power, potentially leading to conservative effect estimates. (4) We relaxed the significance thresholds for SNP inclusion to ensure sufficient IVs for analysis; nonetheless, the mean F-statistic was above 10, minimizing the likelihood of weak IV bias. (5) The binary nature of the outcome variables in the mediation analysis could limit the accuracy of quantitative effect

estimates. (6) Overlap between KOA and AllOA could have introduced confounding; thus, mediation analysis was performed only for KOA.

Conclusions

Our study demonstrates that BMI is a significant risk factor for multiple OA subtypes, with its impact on KOA partially mediated through KD and total TBMD. The mediating role of KD is more substantial compared to TBMD, yet the direct effect of BMI remains the dominant contributor to OA development. Individuals at high risk for OA should aim to reduce weight, avoid joint injuries, and engage in appropriate physical activity to maintain joint health. Further research is needed to elucidate the unknown mechanisms linking BMI and OA to develop targeted interventions for high-risk populations.

Abbreviations

AD	Anxiety disorders
AllOA	All osteoarthritis
BMD	Bone mineral density
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
GEFOS	Genetic Factors for Osteoporosis
GIANT	Genetic Investigation of Anthropometric Traits
GWAS	Genome-wide association study
HOA	Hip osteoarthritis
IV	Instrumental variable
IVs	Instrumental variables
IVW	Inverse variance weighting
KD	Knee disorders
KOA	Knee osteoarthritis
MD	Metabolic disorders
MR	Mendelian randomization
OA	Osteoarthritis
SNPs	Single nucleotide polymorphisms
TBMD	Total bone mineral density

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate Ethical review, approval, and patient consent were waived for this study due to only publicly available summary-level data were used.

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