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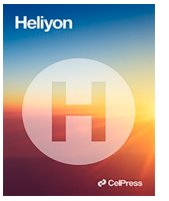

Research article

A clinical study based on bidirectional Mendelian randomization: Correlation between generalized anxiety disorder and weight-bearing joints osteoarthritis

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ABSTRACT

Objectives: Bidirectional Mendelian randomization (MR) combined with clinical case analysis was used to elucidate the relationship between generalized anxiety disorder (GAD) caused by mental overload and the risk of weight-bearing joint (hip/knee) osteoarthritis (OA).
Methods: We performed MR analyses using publicly released genome-wide association study summary statistics to measure the causal effects between mental overload and weight-bearing joint OA risk. The primary MR analysis utilized the inverse-variance weighted (IVW) method, complemented by additional methods, including simple mode, weighted mode, MR-Egger regression, and weighted median. The leave-one-out method was used for sensitivity analysis. Concurrently, data from patients with OA (Kellgren–Lawrence grades III–IV) who needed total knee/hip arthroplasty were collected. Patient assessments were conducted utilizing the Western Ontario and McMaster Universities arthritis index, Penn State worry questionnaire, and visual analogue scale.
Results: Genetically predisposed GAD did not correlate with the risk of weight-bearing joint OA (IVW odds ratio [OR] = 0.840, 95 % confidence interval = 0.128, 5.50, P = 0.855). In reverse MR analyses, we detected no causal effect of weight-bearing OA on GAD (IVW OR = 1.00, 95 % CI = 0.985, 1.03, P = 0.687). In the clinical case evaluation, weight overload joint OA and GAD were highly correlated.
Conclusion: MR analysis indicated no bidirectional causal effect of GAD caused by mental overload on weight-bearing joint (hip or knee) OA. Clinical studies support the finding that GAD is highly correlated with weight-bearing joint OA. However, whether there is a causal relationship between GAD caused by mental overload and weight-overloading joint OA requires further investigation.

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1. Introduction

Osteoarthritis (OA), a principal cause of joint discomfort and disability among older individuals, impacts the life satisfaction of over 595 million people worldwide and aggravates their health burden [2,3]. Its occurrence is related to age, weight, inflammation, trauma, and heredity, and it creates significant implications for healthcare systems and substantial socioeconomic strain [4–6]. Therefore, further exploration of the etiology of OA to prevent its occurrence and development is an urgent global issue.

The effect of OA on joints is different from the effect of aging alone [4,7]. Aside from cartilage degeneration, the disease also affects the entire joint, including sub-chondral sclerosis, osteophyte formation, synovitis, and various other pathological changes [8,9]. Each cause of OA influences different molecular pathways, leading to diverse pathogenesis [10,11]. For instance, genome mutations in the vitamin D receptor (VDR) gene located on (12q13.11) and the estrogen receptor (ESR1) gene located on (6q25.1) can increase the susceptibility to cartilage damage [10,12]. Thus, genetic susceptibility, as a significant independent risk contributor, promotes the occurrence and progression of OA [10,13]. Mechanical overloading can excessively stimulate nuclear factor (NF)-κB signal transduction, speeding up the senescence of chondrocytes [9,11]. Moreover, inflammatory cytokines, including interleukin-1β, also play a pivotal role in OA, instigating articular tissue cells to massively synthesize matrix metalloproteinases, cyclooxygenase-2, and inducible nitric oxide synthase; this cascade results in inflammatory damage [14,15]. Therefore, as a heterogeneous disease encompassing a broad spectrum of potential pathways, the pathogenesis of OA is complex [16,17]. However, the influence of psychological changes caused by mental overload (such as anxiety disorders and depression) on OA has not been completely elucidated. The prevalence of individuals experiencing mental status changes due to mental overload is becoming increasingly obvious in today's fast-paced society.

Generalized anxiety disorder (GAD) is a relatively recent diagnosis and common psychological disorder in primary care [18–20]. It is now being adopted by epidemiologists and clinical psychopharmacologists [20]. With increasing mental overload in modern society,

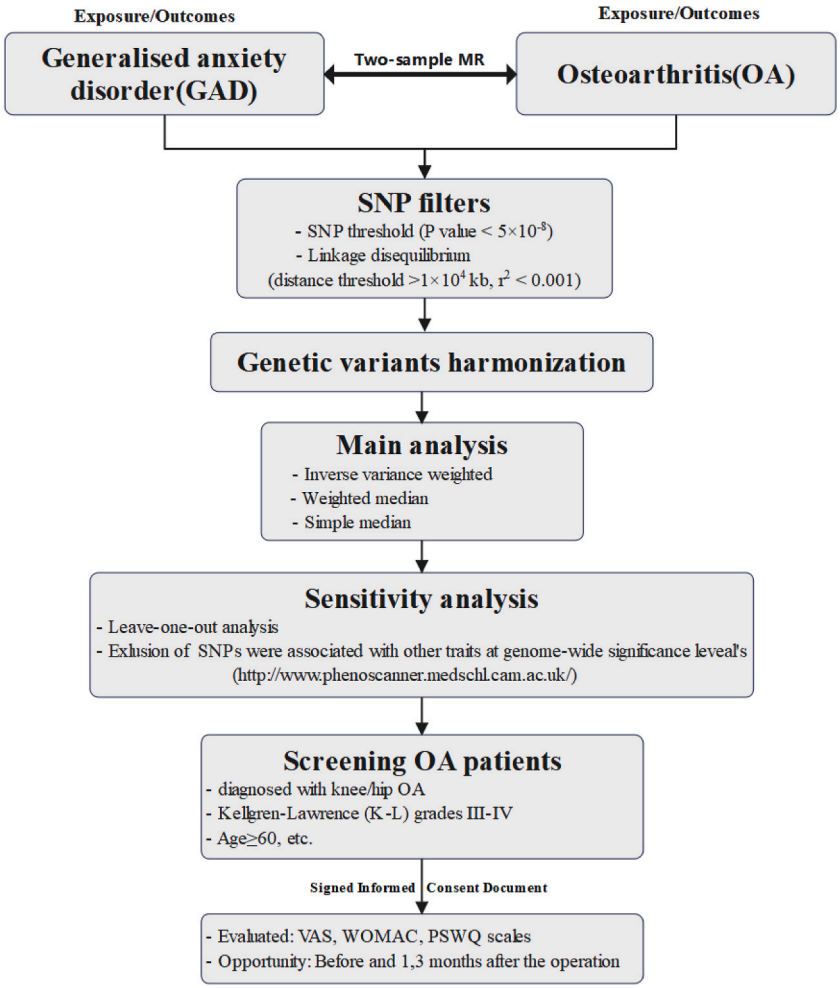

Fig. 1. Procedure for Bidirectional Mendelian Randomization Analysis and Clinical Case Studies.
The underlying principle of Mendelian Randomization analysis: 1) Correlation hypothesis: IVs exhibit a robust correlation with the exposure. 2) Independence hypothesis: IVs are not related to confounders (e.g., BMI and age). 3) Exclusive hypothesis: The chosen IVs are not directly engaged in the outcome except via the exposure route.

the prevalence of GAD continues to increase, making this disease a significant contributor to substantial morbidity and disability [21,22]. The etiology of GAD is related to congenital heredity and cerebral metabolism affected by the environment. Environment affects the genetics of GAD [23]. Although the criteria for diagnosing GAD have evolved, the symptoms invariably encompass pervasive and consistent excessive anxiety caused by genetics and the external environment; autonomic arousal (including palpitations, sweating, trembling, or dry mouth) is crucial for diagnosis [20]. Genetics suggests that GAD and major depressive disorder (MDD) have a common genetic basis [20,24]. Meanwhile, Ancha et al. suggested that there is a significant genetic correlation between MDD and OA, confirming that *ESR1*, as a new genome-wide risk gene shared by MDD and OA, contributes to the etiology of OA and MDD [24]. However, the relationship between GAD and OA has not yet been established.

Mendelian randomization (MR) study is a method used to infer causality between a risk factor and an outcome using genetic information. It is used to explore the etiology in epidemiology as an analytical method for evaluating causal effects [25,26]. Genetic variants serving as instrumental variables (IVs) for exposure and genetic variants randomly distributed during meiosis were used to assess the causal effect of exposure on the outcome [26]. As alleles are randomly assigned and their correlation with the disease is not influenced by typical confounders, MR analysis significantly reduces the influence of confounders, thereby generating a more reliable causal relationship between the exposure and outcome [26,27]. Moreover, MR analysis prevents bias from reverse causation because genetic variants are not modified by the progression of the disease [28].

This study aimed to ascertain whether there is a correlation between GAD caused by mental overload and the risk of weight-bearing joint (hip/knee) OA.

2. Materials and methods

2.1. Study design summary

The bidirectional MR analysis design is displayed in Fig. 1. Briefly, the causal effects of GAD caused by mental overload on weight-bearing joint OA were first evaluated, and the causal effects of weight-bearing joint OA on GAD caused by mental overload were evaluated. Finally, the correlation between GAD caused by mental overload and OA caused by mechanical overloading was analyzed using the collected clinical data. Genetic variants were only deemed as IVs when they adhered to the following three rigorous hypotheses [27]: 1) Correlation hypothesis: IVs exhibited a robust correlation with exposure. 2) Independence hypothesis: IVs were not related to confounders (including sex and age). 3) Exclusive hypothesis: The selected IVs were not directly involved in the outcome except via the exposure route [29,30].

2.2. Data source

Publicly available genome-wide association study (GWAS) databases for eligible exposures and outcomes include GWAS Summary data, nealelab, and IEU openGWAS. The GWAS database of weight-bearing joint (hip/knee) OA was obtained from the IEU OpenGWAS Project, comprising 117,677 participants (46,020 cases vs. 71,657 controls), with a total of 30,265,359 single-nucleotide polymorphisms (SNPs, variations at a single position in DNA among individuals, which can influence how diseases develop). The GWAS database of GAD was also obtained from the IEU OpenGWAS Project, which included 417,596 participants (39,427 cases vs. 378,169 controls), with a total of 13,571,561 SNPs. The characteristics of the investigated population are shown in Supplementary Table 1.

2.3. Filtration of SNPs associated with exposure and outcome

To meet the hypotheses of MR, we filtered SNPs strongly associated with OA and GAD in the GWAS database ($P < 5 \times 10^{-8}$). Subsequently, a linkage disequilibrium (LD) analysis was implemented on these nucleotide polymorphisms to clump SNPs ($r^2 < 0.001$), and the genetic variants for pairs in LD were pruned. To reduce bias due to sample overlap, we employed robust instruments (including an F-statistic >10 for the instrument-exposure association). Additionally, we searched for SNPs associated with exposure in the Phenoscanner database to determine if there were SNPs associated with confounding factors ($P < 1 \times 10^{-5}$). Finally, the filtered SNPs were utilized as IVs for MR analysis. The details of the instrumental SNPs are displayed in Supplementary Table 2. The F-statistic was calculated using the following equation: $F = R^2 (\text{Sample Size} - 2)/(1 - R^2)$. R^2 denotes the variance in exposure explained by each IV individually [25,31].

2.4. MR analysis

In this study, the TwoSampleMR package within the R software environment was utilized to conduct MR analyses [31], including inverse variance weighted (IVW), simple median, MR-Egger, weighted mode, and weighted median; IVW and MR-Egger are the major approaches for estimating the causal effects of a genetically forecasted exposure on an outcome [32]. The IVW method, which integrates findings from various genetic variants to provide an aggregate estimate, assesses the causal effects of a genetically forecasted exposure on outcomes via a weighted regression of SNP-specific Wald ratios (i.e., $\beta_{outcome}/\beta_{exposure}$) [25]. MR-Egger efficiently evaluates the null causal hypothesis and offers a robust assessment of causality, even if none of the genetic variants are valid IVs. If the P-value of the Egger intercept exceeds 0.05, no potential pleiotropic effects are suggested [33]. Because the result was a binary variable, the beta effect estimates were converted to odds ratios (OR), which were interpreted as odds for outcome per unit increase in exposure, and a 95 % confidence interval (CI) provides a range where the true effect size is expected to lie with 95 % certainty [34]. The

MR-pleiotropy residual sum and outlier methodology were utilized to assess the presence of horizontal pleiotropic outliers rigorously. Subsequently, we quantified the degree of heterogeneity utilizing Cochran Q statistics [35]. Finally, a "leave-one-out analysis" was conducted, involving the sequential exclusion of each SNP, to ensure the sensitivity and reliability of the outcomes [34]. Considering the issue of multiple testing, the main results were deemed statistically significant at P values < 0.025 (0.05/2), after applying a Bonferroni correction. The statistical power was calculated using the online tool available at https://shiny.cnsgenomics.com/mRnd/, and the results are displayed in Supplementary Table 3.

2.5. Screening patients

Patients with OA (n = 80) who required total knee/hip arthroplasty (TKA/THA) at the affiliated hospital of Qingdao University between January 2022 and June 2023 were included. The inclusion criteria were as follows: (1) diagnosis of knee/hip OA according to the guidelines for the diagnosis and treatment of OA in China [36]; (2) Kellgren–Lawrence (K-L) grades III–IV [37]; (3) age ≥60 years, and (4) knee or hip pain lasting at least 6 months. The exclusion criteria were as follows: (1) history of intra-articular injection within 6 months or arthroscopy within 1 year; (2) coagulation disorders; (3) pregnant or lactating women; (4) discomfort of the knee/hip caused by other reasons, including joint cavity effusion, infection, autoimmune disease, trauma, malignant tumor, and various other factors; (5) severe organic pathomorphological changes, mental abnormalities, and psychiatric or neurological disorders; (6) diagnosis with mental disorders, such as depression, schizophrenia, or obsessive-compulsive disorder; and (7) participation in other clinical studies in the past 6 months.

Participants signed an informed consent document. The visual analogue scale and the Western Ontario and McMaster Universities arthritis index (WOMAC) were used to evaluate the severity of OA before and at 1 and 3 months post-operation. Meanwhile, the Penn State worry questionnaire (PSWQ) was used to assess the mental overload of the participants [38,39]. In these three scales, a higher score indicated a more severe disease status of the patient.

2.6. Statistical analysis

The GWAS database was analyzed using R software 4.3.1, with the TwoSample MR Package. All measurable data were presented using SPSS 25.0 and plotted using GraphPad Prism 6.02. $P < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Results from MR analysis

3.1.1. Causal effect of GAD caused by mental overload on weight-bearing joint (hip/knee) OA

Three LD-independent genetic variants were filtered as IVs for GAD caused by mental overload utilizing the mentioned method (Supplementary Table 2). Significant heterogeneity (Q = 12.56, P = 0.018) was detected through the Cochran Q test (Table 1); therefore, a random-effects model was used for the IVW method. As shown in the results of MR analysis (Table 1, Fig. 2), the predisposition to genetic mutations causing GAD did not demonstrate a causal effect on weight-bearing joint OA in the IVW model [OR = 0.840, 95 % CI = 0.128, 5.50, P = 0.855]. The findings of the MR-Egger analysis were consistent with those of the IVW method [OR = 0.0439, 95 % CI = 7.70^{-09}, $2.50e^{+05}$, P = 0.761]. The MR-Egger analysis did not indicate the presence of horizontal pleiotropy in the IVs (P for intercept = 0.771). To further verify the sensitivity and reliability of the outcomes, a "leave-one-out" analysis was used to remove individual SNPs, and a secondary MR analysis was employed to verify the causal effects of each GAD-associated SNP on weight-bearing joint OA. The results revealed that no SNPs exerted a potential influence on the pooled results. Funnel plots are shown in Supplementary Fig. 1.

3.1.2. Causal effect of weight-bearing joint (hip/knee) OA on GAD caused by mental over-load

Twenty-six LD-independent genetic variants were used as IVs for weight-bearing joint (hip/knee) OA using the same analytical method. Three SNPs correlated with the confounding factors were excluded, and twenty-three genetically independent variants were selected as IVs for OA (Supplementary Table 2). By using the random-effects model in the IVW method as the primary approach, the results revealed that (Table 2, Fig. 3) hip/knee OA was not causally correlated with GAD [OR = 1.00, 95 % CI = 0.985, 1.03, P =

Table 1
Causal effect of GAD caused by mental pressure on hip/knee OA.

Exposure	Outcome	No. of SNPs	Methods	OR (95 % CI)	Pval	Heterogeneity test	Pleiotropy test
						Cochran's Q *Pval*	P Intercept
GAD	OA	3	IVW	0.840 (0.128, 5.50)	0.855	12.56 **0.018**	
			Weighted Median	1.09 (0.366, 3.21)	0.885		
			Simple Mode	1.05 (0.154, 7.18)	0.699		
			MR Egger	0.0439($7.70e^{-09}$, $2.50e^{+05}$)	0.761		0.771
			Weighted Mode	1.58 (0.353, 7.08)	0.623		

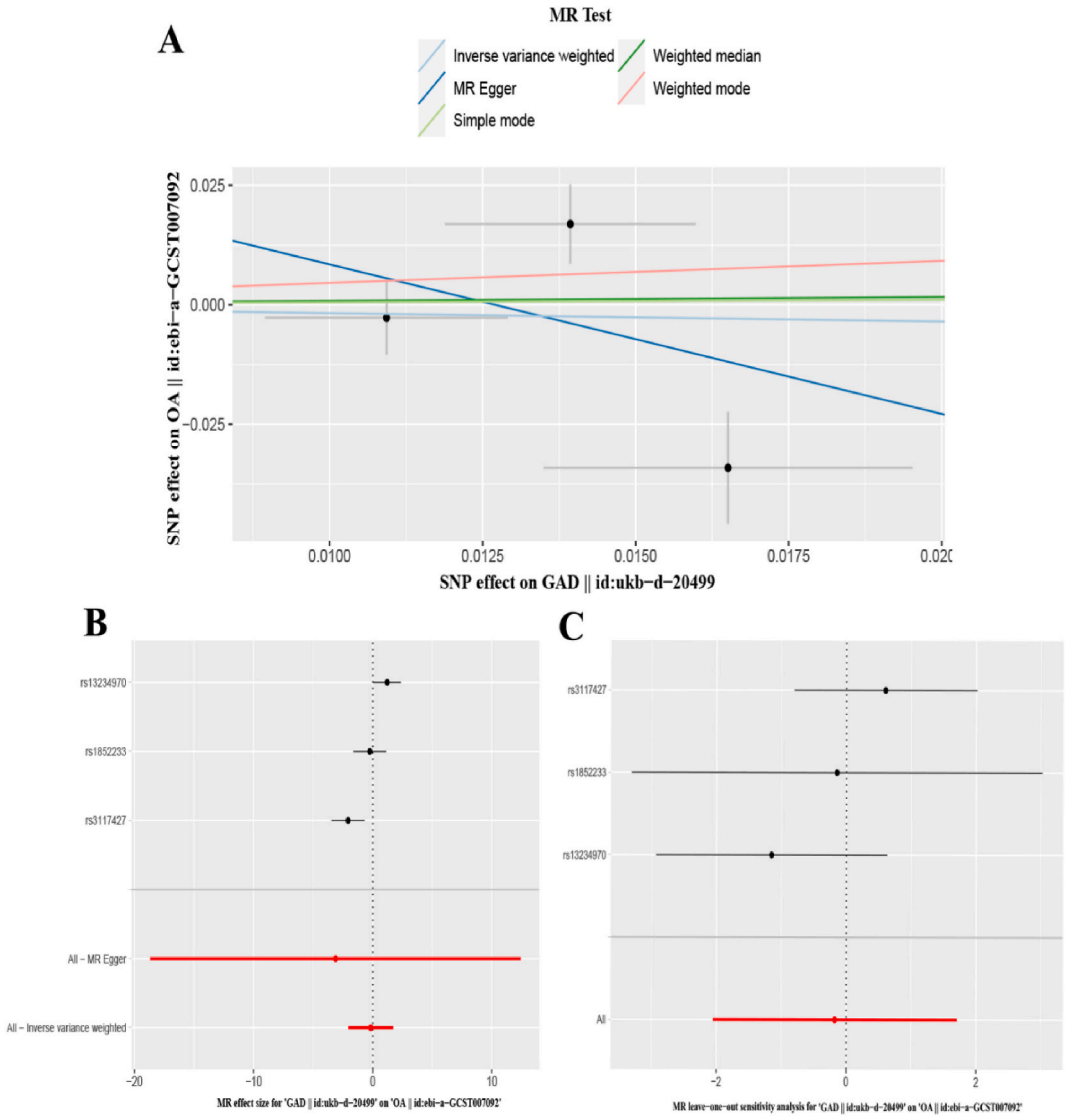

Fig. 2. (A) Scatter plots, (B) Forest plots, and (C) Leave-one-out sensitivity analysis for association of GAD caused by mental pressure with weight-bearing joint (hip/knee) OA.

0.687]. No heterogeneity was detected through the Cochran's Q test (Q = 27.66, P = 0.150). These findings were similar to those observed in other MR appraisals. The MR-Egger analysis did not indicate the presence of horizontal pleiotropy in the IVs (P for intercept = 0.545). The "leave-one-out" analysis revealed that certain SNPs had potential effects on the pooled outcomes, indicating the need for further explanation of the outcomes. Funnel plots are shown in Supplementary Fig. 1.

Table 2
Causal effect of hip/knee OA on GAD caused by mental pressure.

Exposure	Outcome	No. of SNPs	Methods	OR (95 % CI)	Pval	Heterogeneity test	Pleiotropy test
						Cochran's Q *Pval*	P Intercept
OA	GAD	26	IVW	1.00 (0.985, 1.03)	0.687	27.66 0.150	
			Weighted Median	1.01 (0.986, 1.02)	0.435		
			Simple Mode	1.02 (0.974, 1.06)	0.447		
			MR Egger	0.971 (0.874, 1.08)	0.600		0.545
			Weighted Mode	1.01 (0.967,1.05)	0.773		

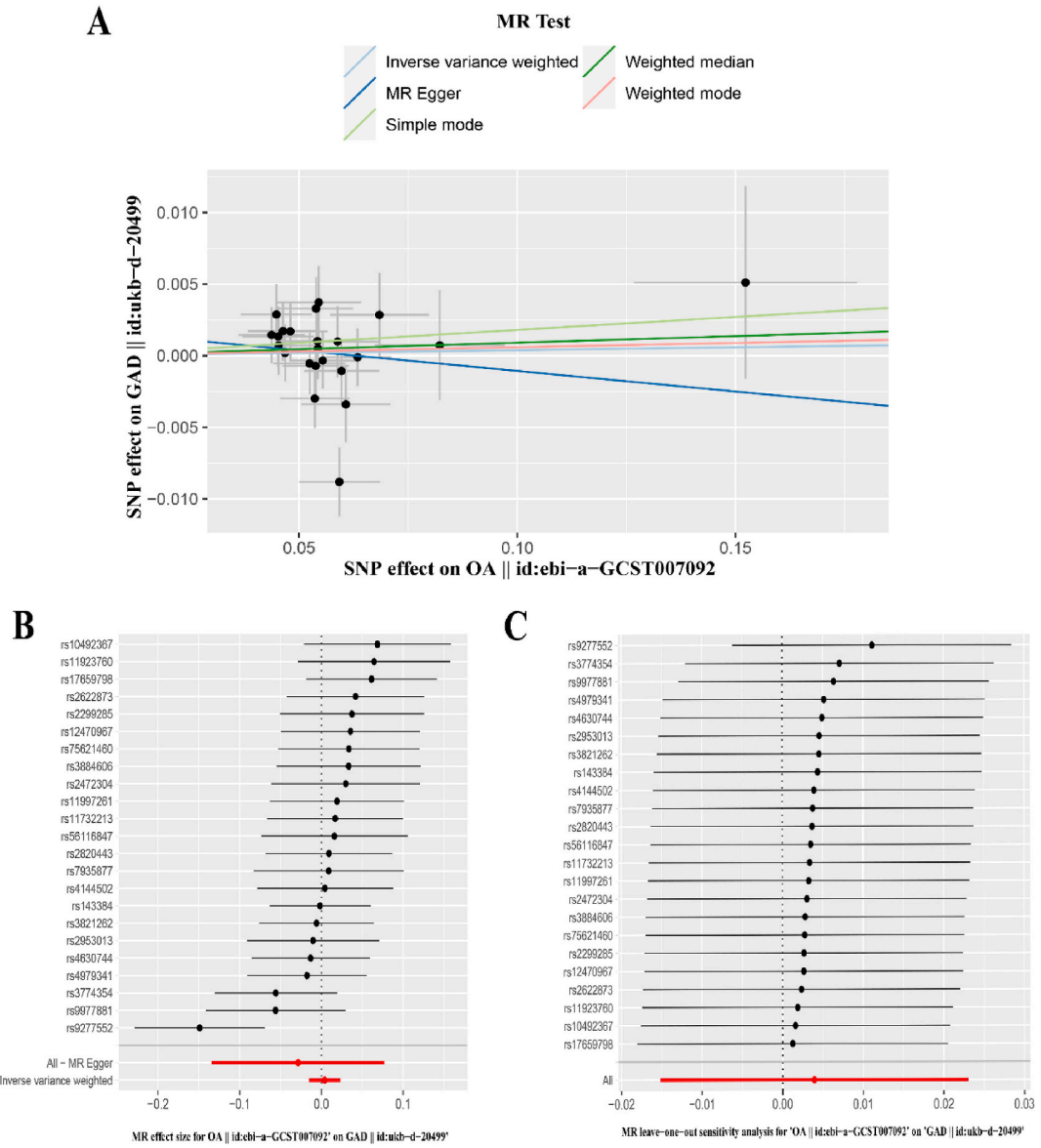

Fig. 3. (A) Scatter plots, (B) Forest plots, and (C) Leave-one-out sensitivity analysis for association of weight-bearing joint (hip/knee) OA with GAD caused by mental pressure.

3.2. Results from clinical case studies

3.2.1. Analysis of the correlation between hip/knee OA and GAD

To further explore the correlation between weight-bearing joint OA and GAD caused by mental overload, patients with OA who required TKA/THA were screened in a 3-month clinical trial (n = 80). This trial included 34 patients with K–L grade III and 46 with K–L

Table 3
The results of Canonical Correlations analysis.

Groups	Correlation	Wilks Statistic	F	Sig.
WOMAC(0)-PSWQ(0)	0.945	0.022	70.673	<0.05**
WOMAC(1)-PSWQ(1)	0.791	0.200	42.556	<0.05**
WOMAC(3)-PSWQ(3)	0.682	0.535	60.907	<0.05**

Set 1 Variables:WOMAC scores at 0,1 and 3 month after the TKA/THA surgery, that is WOMAC(0), WOMAC(1), WOMAC(3).
Set 2 Variables: PSWQ scores at 0, 1 and 3 month after the TKA/THA surgery, that is PSWQ(0), PSWQ(1), PSWQ(3).

grade IV, with 43 patients classified as overweight (BMI = 24.9–29.9 kg/m^2) and 37 classified as obese (BMI ≥27.9 kg/m^2) [40]. The average age of the participants was 66.7 ± 6.6 years. Eventually, 74 patients accepted return visits (92.5 %). The information regarding these clinical cases is provided in Supplementary Table 4. The D'Agostino-Pearson's test, used to determine the distribution of scores, indicated a distribution close to a Gaussian distribution (Table 4). Canonical and Pearson correlation analyses were used to examine the correlation between hip/knee OA (WOMAC) and GAD caused by mental overload (PSWQ). The results confirmed a significant correlation between hip/knee OA and GAD (average correlation = 0.823, $P < 0.05$) (Table 3, Fig. 4A). One-way analysis of variance followed by Tukey's post-hoc tests were applied to identify statistical differences between the groups. The results demonstrated a significant decrease in PSWQ scores of the patients with improved OA symptoms after TKA/THA, with a significant increase in postoperative time ($P < 0.01$) (Table 4, Fig. 4B–D). The results indicated a positive correlation between hip/knee OA and GAD, which did not align with the outcomes of the MR analysis.

4. Discussion

This study used bidirectional MR analysis combined with a clinical trial to reveal the association between GAD caused by mental overload and weight-bearing joint (hip/knee) OA. Current animal models have demonstrated that abnormalities in the hippocampus and reductions in the volume of the medial prefrontal cortex (mPFC) induced by chronic stress are among the most substantiated neural anomalies associated with MDD [41]. Given the notable correlation between MDD and OA, we were keenly interested in exploring the relationship between mental overload and weight-bearing joint OA. Therefore, we investigated the causality between GAD induced by mental overload and weight-bearing joint (hip/knee) OA using MR analysis. The result provided no evidence of the causal effect of GAD caused by mental overload on weight-bearing joint (hip/knee) OA. Conversely, there was no causal association between weight-bearing joint (hip/knee) OA and GAD caused by mental overload. However, few SNPs met the standard bioinformatic threshold of $P < 5 \times 10^{-8}$, suggesting that the selection of IVs might not have fully captured the genetic architecture of GAD, especially regarding its interaction with physiological pathways leading to OA. Hence, the interaction between genes and the environment still requires attention.

In our clinical trial incorporating real-world interactions and behaviors, unlike MR, which relies on genetic data, we observed a correlation between hip/knee OA and mental overload. This suggests that social and psychological mechanisms or environmental factors may influence the correlation, as well as potential areas of residual confounding in genetic studies. Therefore, further investigation is needed to understand the correlation between mental overload and weight-bearing joint (hip/knee) OA.

Mechanical overloading, such as gravity, weight, and other load on weight-bearing joints, is widely acknowledged as promoting the occurrence and development of OA [11,42]. Research has demonstrated that every 5 kg of weight gain confers a 36 % increase in the risk of weight-bearing joint OA for patients with obesity (BMI ≥30 kg/m^2). The increase in BMI is positively correlated with the risk of weight-bearing joint OA [43]. The elevated risk is attributed to the activation of mechanoreceptors on chondrocytes in the setting of obesity. These mechanoreceptors include stretch-activated channels, α5β1 integrin, and CD44. This activation induces an increased expression of mitogen-activated protein kinase, NF-κB, and second messengers, including adenosine monophosphate, inositol triphosphate, and calcium. These molecular changes lead to the generation of pro-inflammatory cytokines and the accumulation of senescence phenotypes, resulting in the inflammation and aging of chondrocytes [43,44]. However, the precise impact of mental overload (including anxiety and depression) on the occurrence and progression of weight-bearing joint OA remains unclear.

This study is the first to utilize an MR analysis to assess the bidirectional causal effect between GAD resulting from mental overload and OA in weight-bearing joints such as the hip and knee. We used five models to identify the causal relationship and the IVW method and MR-Egger random-effects models were selected as the main analysis methods for our work. The results indicated no bidirectional causal relationship between mental overload and weight-bearing joint (hip/knee) OA (Figs. 2 and 3; Tables 2 and 3). However, previous studies have confirmed that MDD, also caused by mental overload, leads to increased inflammation, exacerbating joint pain and progression of OA [1,24,41]. Clinical evaluations observing patients' lifestyles and stress management may detect this relationship; however, if the MR analysis fails to account for these factors, it may overlook crucial connections. Therefore, we screened patients with OA who required TKA/THA (n = 80) and used the PSWQ to assess their mental overload. The results demonstrated a marked remission in mental overload, which aligned with the alleviation of OA symptoms after TKA/THA (Fig. 4, Tables 3 and 4). Our analysis of clinical trials indicated that hip/knee OA was correlated with GAD caused by mental overload, which matched the findings of Baranova et al. [24]. Although our MR analysis did not find a genetic basis for a causal relationship between GAD and OA, clinical evaluations suggested that environmental factors, such as stress management and physical activity, which are not accounted for in MR, play a significant role [45]. Therefore, further investigation is still required to determine whether causality exists between OA and mental overload.

This study has some limitations. First, as few SNPs met the standard bioinformatic threshold of $P < 5 \times 10^{-8}$, a larger GWAS with

Table 4
VAS, WOMAC, and PSWQ scores at 0, 1 and 3 months after the TKA/THA.

Groups	VAS	WOMAC	PSWQ
	Scores Pval$_{(D\&P)}$	Scores Pval$_{(D\&P)}$	Scores Pval$_{(D\&P)}$
0 month	7.91 ± 1.14 0.42	184.03 ± 17.50 0.41	59.61 ± 10.87 0.04
1 month	5.78 ± 1.16 0.98	123.53 ± 22.65 0.80	42.23 ± 12.27 0.73
3 months	3.15 ± 1.25 0.41	68.51 ± 12.75 0.59	30.56 ± 6.36 0.80

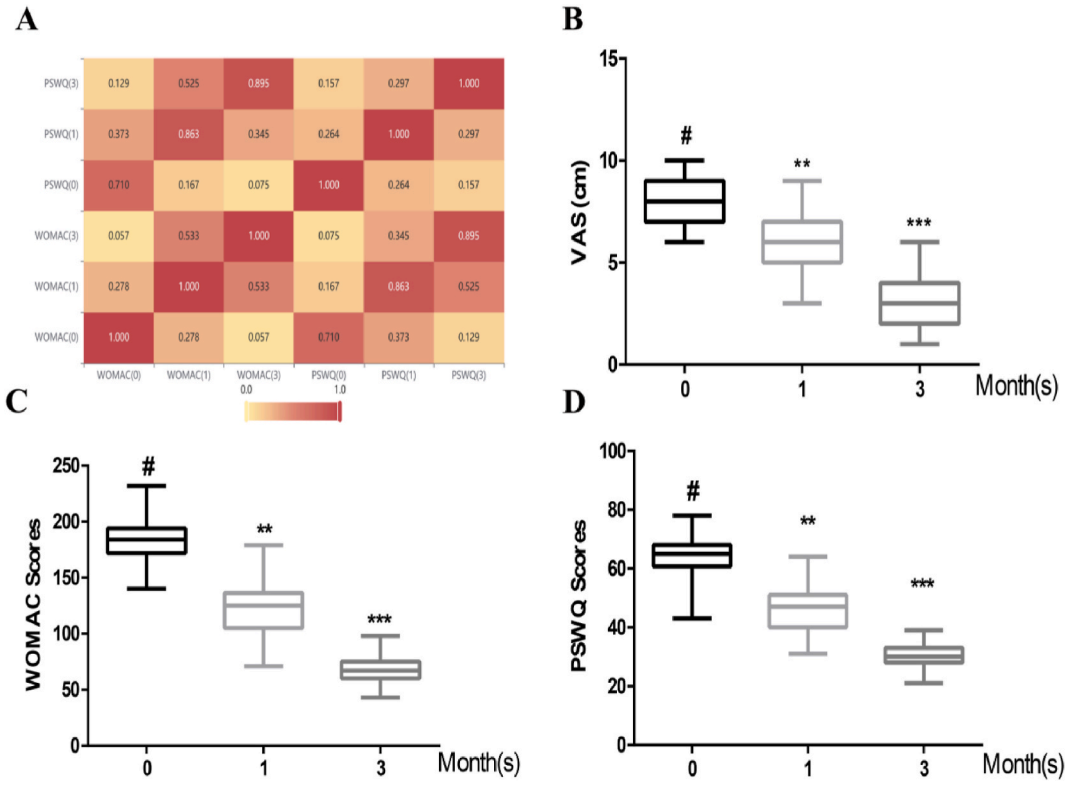

Fig. 4. (A) Pearson correlation analysis presents the correlation between every group. WOMAC scores at 0,1 and 3 months after the TKA/THA surgery, that is, WOMAC (0), WOMAC (1), and WOMAC (3). PSWQ scores are at 0, 1, and 3 months after the TKA/THA surgery, that is, PSWQ (0), PSWQ (1), and PSWQ (3). The deeper it is in red, the higher the correlation. (B) VAS, (C) WOMAC, and (D) PSWQ scores at 0, 1, and 3 months after the TKA/THA surgery, respectively. *P < 00.05, **P < 00.01 versus the group of #; n = 74. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

more SNPs as instruments is required to enhance the association capacity. Second, we restricted the genetic background of the population for the MR analysis to individuals of European descent and the genetic background of the population for the clinical trial to individuals of Asian descent. Because ethnic differences can lead to differences in the results, which may explain the inconsistency between the results from MR analysis and clinical trials in our study, MR studies on other races are needed to verify the reliability of the clinical study. Third, our clinical trial analyzed the correlation between hip/knee OA and GAD caused by mental overload; however, a reverse analysis was not performed, which requires further exploration. Additionally, the relatively small number of clinical case samples included in this study is another limitation.

However, this study still has some strengths. First, although previous studies have demonstrated that mechanical loading (including gravity and weight) affects weight-bearing joint OA, few studies have shown that mental overload affects the occurrence and progression of OA. This study used MR analysis to assess the causal effect between mental overload and weight-bearing joint OA, filling the gaps in previous OA research. Second, based on our current knowledge, this is the first study to combine MR analysis with a clinical trial. Although our MR findings did not show a genetic causal relationship between GAD and OA, aligning with those of Smith et al., who also found no genetic causal links between GAD and OA [3], our clinical observations differed from their findings. The discrepancy may be due to differences in the clinical assessment tools used or the demographic characteristics of the study populations. This also helps to confirm the complexity and multifactorial nature of OA, highlighting the complex interactions between genetics and environmental factors in disease development.

Overall, this study was devoted to investigating the relationship between GAD caused by mental overload and hip/knee OA, combining MR with clinical trials. The MR analysis did not provide enough evidence of a causal relationship between GAD caused by mental overload and weight-bearing joint OA. However, clinical trials showed a significant correlation between these factors. The study underscores the multifactorial nature of OA and suggests that psychological factors, such as mental overload, should be considered when assessing the risk of OA. Further research is necessary to understand the complex relationship between mental overload and weight-bearing joint OA and to investigate potential interventions that address mental well-being to reduce the risk of weight-bearing joint OA. Although our MR study did not establish a causal relationship, future studies should explore the underlying mechanisms through which environmental and lifestyle factors contribute to the correlation between GAD and OA observed in clinical settings. Additionally, longitudinal studies could help determine whether changes in mental health status precede or follow the development of OA symptoms.

5. Conclusions

Our MR analysis did not reveal a genetic causation between GAD and OA; however, the strong correlation between the two observed in clinical evaluations suggests that non-genetic factors, potentially environmental or lifestyle-related, play a significant role. This dichotomy highlights the complexity of the etiology of OA and suggests that both genetic predispositions and environmental factors should be considered in OA management strategies.

Ethics statement

This retrospective study was approved by the Medical Research Ethics Committee of the Affiliated Hospital of Qingdao University (No. QYFY WALL 28102, Sep/22/2023) and conducted in compliance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All participants in this work have consented to the use of their information for publication.

Data availability statement

The authors declare that all the data supporting the findings of this study are available within the article and its Supplemental information files.

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CRediT authorship contribution statement

Xiao Ma: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Software, Supervision, Validation, Writing – original draft. **Han Zhang:** Formal analysis, Methodology. **Guangyu Li:** Formal analysis. **Jingjing Ma:** Data curation, Methodology. **Wendan Cheng:** Conceptualization, Funding acquisition, Writing – review & editing. **Tianrui Wang:** Conceptualization, Data curation, Writing – review & editing. **Yingze Zhang:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32988.

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