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RESEARCH ARTICLE

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The genetic causal association between arthritis and low back pain

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Abstract

Background: Arthritis and low back pain (LBP) are prevalent musculoskeletal conditions with a perceived association. Previous observational studies have suggested a possible link between arthritis and LBP, but causality has not been firmly established.

Methods: The analysis involved data from a meta-analysis of genome-wide association studies sourced from the UK Biobank Genetics resources on rheumatoid arthritis (RA), osteoarthritis (OA) at any site, knee osteoarthritis (KOA), hip osteoarthritis (HOA), and LBP. Two-sample Mendelian randomization analysis was utilized to evaluate the causal link between arthritis and LBP. The primary method employed was inverse-variance weighting (IVW), with additional techniques such as MR-Egger, weighted median, Cochran *Q* statistic, and leave-one-out analysis used to identify heterogeneity and pleiotropy.

Results: Genetically determined RA exhibited a causal impact on LBP (Weighted median: odds ratio [OR] = 1.094, 95% confidence interval [CI] 1.002–1.195, $p = 0.043$). Furthermore, OA at any site and KOA showed causal associations with LBP (Inverse variance weighted: OR = 1.089, 95% CI 1.011–1.173, $p = 0.026$) and (OR = 1.0004, 95% CI 1.000–1.008, $p = 0.019$), respectively. Additionally, HOA was also linked causally with an elevated risk of developing LBP (Weighted median: OR = 1.002, 95% CI 1.000–1.004, $p = 0.049$; Inverse variance weighted: OR = 1.002, 95% CI 1.001–1.004, $p = 0.003$).

Conclusions: This study offers genetic evidence supporting the causal relationship between RA, OA at any site, KOA, HOA and the increased risk of LBP, especially highlighting the significant impact of HOA.

KEYWORDS
arthritis, genetic, low back pain, Mendelian randomization

1 | INTRODUCTION

Osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common forms of arthritis. In 2021, more than 22% of adults over 40 had knee OA, with an estimated global impact affecting over 500 million individuals.[1] On the other hand, between 1980 and 2019, the global prevalence of RA was 460 per 100 000 population.[2] Arthritis is characterized by inflammation and sensitivity in one or multiple joints.[3] The primary indications of arthritis are discomfort and rigidity in the joints, which generally increase as individuals get older. This condition

is characterized by multiple joint involvement and the potential to affect organs outside the joints. Arthritis is commonly linked to extra-articular manifestations in various organs, with frequent involvement of the lower back. One study indicated that approximately 33% of individuals with RA may encounter lower back pain (LBP).[4] Other estimates propose that over 80% of those with RA may experience spinal issues, with some occurring as early as 2 years after diagnosis.[5]

The research findings on this topic may present conflicting information. A recent review indicated that the prevalence of back pain, in general, is approximately 34%, but found limited evidence supporting RA as a common cause.[6] In a study involving 1369 women aged ≥40 years in the general population, KOA and LBP were significantly linked to a decline in quality of life,[7] though a direct association between the two symptoms was not established, nor was the predictive value of LBP analyzed. Conversely, another study showed a significant association between KOA and LBP/disability, as well as other risk factors.[8] In individuals with end-stage hip osteoarthritis (HOA), the incidence of concomitant LBP ranged from 21.2% to 49.4% in large cohort studies[9–11] and reaching 100% in a smaller study.[12] However, these studies[9,12–14] did not differentiate between disorders of the lumbar spine, leaving uncertainty regarding whether the remaining LBP was attributable to hip or spinal issues. It is crucial to note that conclusions on causality cannot be definitively drawn solely from retrospective or cross-sectional studies due to their limited sample sizes and potential confounding factors. Thus, while acknowledging the potential association between arthritis and LBP, it remains challenging to establish a clear causal relationship between the two conditions.

The effectiveness of Mendelian randomization (MR) as a robust method for overcoming the limitations of observational studies and assessing causality has been well-established.[15] The random allocation of alleles during conception effectively controls common confounding factors, resulting in a balanced distribution of these factors across different genotypes. Additionally, MR eliminates the possibility of reverse causation, as it is biologically implausible for a disease to alter an individual's genotype.[15] Two-sample MR analysis can leverage SNP-exposure and SNP-outcome associations from independent genome-wide association studies (GWASs) and combine them into a single causal estimate.[16]

Therefore, we conducted a two-sample MR analysis to investigate the causal relationship between various forms of arthritis (i.e., RA, OA at any site, KOA, and HOA) and LBP.

2 | METHODS

2.1 | Study design

We utilized publicly available data from published studies or GWAS summaries to inform our research. Since the study did not utilize primary data, there was no need to obtain ethical approval. All the studies that were incorporated have been approved by their respective academic ethics committees, and each participant has provided informed consent. Figure 1 depicts the flow of this study.

2.2 | Data sources

A two-sample MR analysis was conducted to estimate the causal relationship between arthritis and LBP. The analysis involved exploring genome-wide associations between exposures and outcomes through

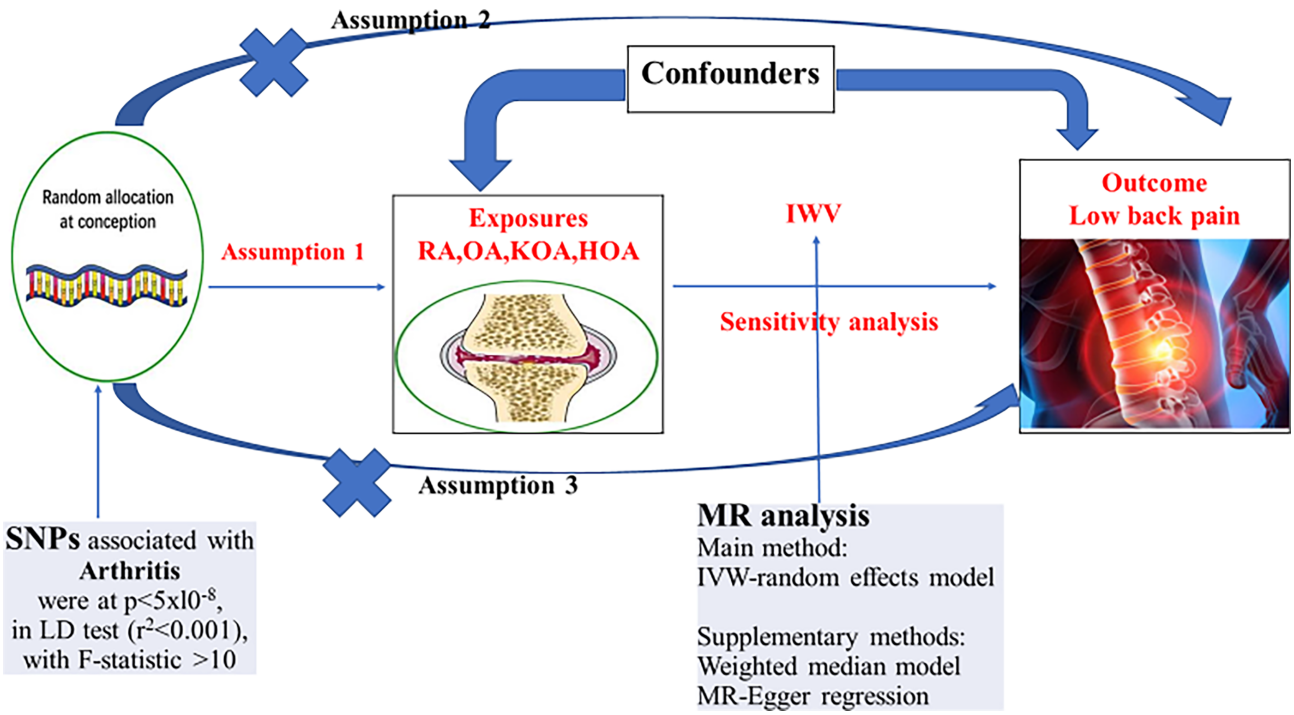

FIGURE 1 Flowchart of a Mendelian randomization study.

the online database MRBASE (http://app.mrbase.org/).[17] All data utilized in the analysis were sourced from publicly available GWAS. Instrumental single-nucleotide polymorphisms (SNPs) utilized in the analysis were chosen based on findings from GWAS studies.

2.3 | Exposure and outcome

A MR analysis was conducted using multi-database data. The exposure variables encompassed four types of arthritis: RA ($n = 484\,598$), OA at any site ($n = 484\,598$), knee osteoarthritis (KOA, $n = 403\,124$), and HOA ($n = 393\,873$). The outcome variable was defined as LBP ($n = 361\,194$) (ukb-d-M13_LOWBACKPAIN). All databases utilized in this study focused on the European population. Details of the sample sizes for each database are provided in Table 1.

The instrumental variants used in the analysis were derived from the GWAS studies mentioned previously. To ensure the robustness of the instrumental variables, a filtering process was implemented to remove SNPs that might introduce bias.[18,19] This filtering process included identifying genetic variants associated with the exposure factors at genome-wide significance ($p < 5 \times 10^{-8}$), ensuring no linkage disequilibrium ($R^2 < 0.01$).[20] And setting a minor allele frequency (MAF) threshold of ≥0.05, and excluding SNPs with an MAF <0.01.[21]

2.4 | Statistical analysis

Sensitivity analysis was conducted to eliminate nonspecific SNPs, and SNPs with inconsistent information in allele and frequency data between the exposure and outcome groups were excluded. The "Two-Sample-MR" R package, utilized in previous research,[22] was employed for selecting appropriate variants. The analysis included MR Egger, weighted median, inverse variance weighted (IVW), and heterogeneity tests using IVW and MR-Egger methods. Sensitivity analysis was performed using the weighted median method and leave-one-out analysis.[23] Additional information on each MR approach utilized can be found in a previous publication.[17] Significance was defined as a p-value <0.05.

2.5 | Heterogeneity

A test for heterogeneity was conducted using Cochran's Q statistics or the MR-Egger intercept through the two-sample MR package between instruments. Heterogeneity was indicated by a Q statistic larger than the number of instruments minus one, suggesting potential issues with instrument validity. Alternatively, significant Q statistics with a p-value <0.05 also pointed toward the presence of heterogeneity.[24,25]

3 | RESULTS

3.1 | SNPs selection

Characteristics of study participants are presented in Table 2. First, the key details of several large-scale genetic association studies on arthritic and LBP. Second, the population studied providing the numbers of cases and controls, which were primarily of European ancestry. Finally, we identified SNPs associated with RA ($n = 9$), OA at any site ($n = 7$), KOA ($n = 8$), HOA ($n = 24$) on LBP, respectively.

3.2 | Estimates of the causal effect

The casual relationships between RA, OA at any site, KOA, HOA, and LBP are summarized in Table 2. The analysis revealed a statistically significant association between RA and an elevated risk of LBP (Weighted median: odds ratio [OR] = 1.094, 95% CI: 1.002–1.195, $p = 0.043$). This association did not remain consistent across both the MR-Egger and inverse variance weighted methods. We observed the causally OA at any site and KOA are associated with an increased

TABLE 1 Summary of GWAS data.

	Group ID	Sample size	SNP size	First author	Year	Population studied	Sample sources
Exposure							
Rheumatoid arthritis	ebi-a-GCST90038685	484 598	9 587 836	Dnerta HM	2021	Case: 5427 Control: 479 171	European
Osteoarthritis at any site	ebi-a-GCST90038686	484 598	9 587 836	Dnerta HM	2021	Case: 39 515 Control: 445 083	European
Knee osteoarthritis	ebi-a-GCST007090	403 124	29 999 696	Tachmazidou I	2019	Case: 24 955 Control: 378 169	European
Hip osteoarthritis	ebi-a-GCST007091	393 873	29 771 219	Tachmazidou I	2019	Case: 15 704 Control: 378 169	European
Outcome							
Low back pain	ukb-d-M13_LOWBACKPAIN	361 194	12 184 069	Neale lab	2018	Case: 5423 Control: 355 771	European

TABLE 2 Estimates of the causal effect.

Exposure	Outcome	MR methods	Number of SNPs	Beta	SE	*p*-Value	OR (95% CI)
RA	Low back pain	MR-Egger	9	0.045	0.094	0.644	1.046 (0.870–1.258)
		Weighted median		0.090	0.045	0.043	1.094 (1.002–1.195)
		Inverse variance weighted		0.078	0.056	0.167	1.081 (0.969–1.207)
OA at any site		MR-Egger	7	0.161	0.101	0.173	1.175 (0.964–1.431)
		Weighted median		0.045	0.046	0.328	1.046 (0.956–1.144)
		Inverse variance weighted		0.085	0.038	0.026	1.089 (1.011–1.173)
KOA		MR-Egger	8	−0.014	0.009	0.191	0.986 (0.969–1.004)
		Weighted median		0.002	0.002	0.361	1.002 (0.998–1.006)
		Inverse variance weighted		0.004	0.002	0.019	1.004 (1.000–1.008)
HOA		MR-Egger	24	0.005	0.003	0.079	1.005 (0.999–1.011)
		Weighted median		0.002	0.001	0.049	1.002 (1.000–1.004)
		Inverse variance weighted		0.002	0.001	0.003	1.002 (1.001–1.004)

TABLE 3 Pleiotropy and heterogeneity test for RA, OA, KOA, and HOA on LBP.

Outcomes	MR methods	Cochran *Q* statistic	Q_df	Heterogeneity *p*-value	I^2	MR-Egger intercept-derived *p*-value
RA	MR Egger	15.45	7	0.031	0.550	0.672
	Inverse variance weighted	15.88	8	0.044	0.496	
OA at any site	MR Egger	7.722	5	0.172	0.352	0.454
	Inverse variance weighted	8.738	6	0.189	0.313	
Knee OA	MR Egger	3.136	6	0.792	0.913	0.104
	Inverse variance weighted	6.813	7	0.449	0.027	
Hip OA	MR Egger	24.28	22	0.333	0.094	0.302
	Inverse variance weighted	25.52	23	0.324	0.099	

risk of LBP (Inverse variance weighted: OR = 1.089, 95% CI: 1.011–1.173, $p = 0.026$) and (OR = 1.004, 95% CI: 1.000–1.008, $p = 0.019$), respectively. This association does not remain consistent across both the MR-Egger and weighted median methods. In addition, just as we expected, HOA was also found to be causally associated with an increased risk of LBP (Weighted median: OR = 1.002, 95% CI: 1.000–1.004, $p = 0.049$) and (Inverse variance weighted: OR = 1.002, 95% CI: 1.001–1.004, $p = 0.003$). However, MR-Egger ($p = 0.079$) does not demonstrate a causal effect on LBP.

3.3 | Sensitivity analyses

The test of heterogeneity results for significant and nominally significant estimates is detailed in Table 3. The MR-Egger and inverse variance weighted methods exhibited consistent causal estimates in terms of magnitude and direction. No evidence of horizontal pleiotropy for RA ($p = 0.672$), OA at any site ($p = 0.454$), KOA ($p = 0.104$), HOA ($p = 0.302$) in LBP with $p > 0.05$ when using the MR-Egger regression intercept approach. In addition, the results of the Cochrane Q statistics showed no significant heterogeneity ($p > 0.05$), except for KOA ($p_{IVW} = 0.027$). While MR-Egger intercept derived ($p = 0.104 > 0.05$), indicating that no pleiotropy was detected. The "leave-one-out" analysis and scatter plot confirmed that no single SNP was driving the IVW point estimate (Supporting Information S1).

4 | DISCUSSION

In this study, the results revealed significant causal associations between arthritis (RA, OA at any site, KOA, and HOA) and LBP. Notably, HOA was found to significantly increase the risk of LBP.

The findings of our study indicated a causal relationship between RA and LBP, which aligned with the conclusions drawn in multiple published researches.[26–28] Although various factors may contribute to this association, the patient's immunologic status seems to be a key determinant. The inflammation associated with RA may contribute to the deterioration of bone and soft tissue at the interface between vertebrae and intervertebral discs (endplates). Additionally, RA has been shown to increase the risk of osteoporosis and low bone mineral density, which in turn can elevate the chances of bone erosion and vertebral fractures.[29] A Japanese cross-sectional study of RA patients

found that the factor most strongly associated with severe LBP was a high disease activity score.[26] The researchers hypothesized that the inflammatory response in the lumbar spine, secondary to high RA disease activity, may contribute to the development of severe LBP in this population.[26] The existing literature indicates that increased radiographic damage and progression are associated with a higher level of disability in RA patients.[30] The available research suggests that late-onset RA is linked to impaired LBP management. A study that analyzed 1206 RA patients found that individuals with elderly-onset RA experienced a greater number of RA-related comorbidities and poorer functional status compared to their younger counterparts.[31] The factors associated with problematic LBP in RA patients include increased vertebral fractures, longer disease duration, greater pelvic tilt (PT), older age of RA onset, greater sagittal vertical axis (SVA), and less methotrexate (MTX) usage.[4] Additionally, our study has provided evidence through MR analysis that RA causally increases the risk of developing LBP.

Our findings indicate that OA at any site, as well as KOA specifically, can causally increase the risk of LBP, consistent with previous studies.[32,33] When managing KOA, any structural or functional factors that could contribute to concurrent LBP, such as increased body mass index (BMI) or repetitive postures, should be carefully considered.[34] One study suggested that the biomechanical relationship between LBP and KOA may be attributed to an altered compensation mechanism in the lower limb joints and musculature.[34] The normal upright standing posture is maintained by the correct alignment of the spine, pelvis, lower extremities, and associated musculature.[35] In the sagittal view, spinal flexion promotes further pelvic posterior tilt, hip extension, knee flexion, and ankle plantar flexion as compensatory mechanisms. These compensatory changes can induce increased loading on the knee joint, leading to the progression of KOA. Severe KOA can also influence the sagittal alignment of the spine-pelvis and lower extremity axis.[36] Conversely, degenerative changes in the lumbar spine and loss of lumbar lordosis may be associated with degenerative changes in the knee, and the limitation of knee extension significantly increases with a reduction in lumbar lordosis.[37] The precise mechanism, nature, and common factors leading to the concurrent occurrence of LBP and KOA remain unclear.

Notably, HOA greatly increases the risk of LBP, which is consistent with the findings of several previous studies.[38–41] One proposed mechanism is that the fixed flexion deformity in hip OA leads to a forward pelvic tilt and exaggerated lumbar lordosis,[42] which subsequently results in further subluxation of the posterior facets and may trigger LBP. Additionally, regional abnormalities in sagittal pelvis alignment have been reported in various studies.[43,44] The reduced range of motion (ROM) in hip OA was also found to be involved in the mechanism of LBP. Furthermore, the limited hip flexion, reduced hip abduction, total rotation, and asymmetric hip rotation were also identified in patients with LBP. Previous studies have suggested that the reduced ROM in the hip joint may contribute to the pathogenesis of LBP. The proposed mechanism is that the diminished hip ROM leads to greater compensatory lumbopelvic rotation, which subsequently induces increased mechanical stress in the lumbopelvic region.[45,46] These findings have clinical implications for the management of patients with hip OA. The observed association between LBP and hip OA may be related to the shared anatomical structures and biomechanics between the hip and the lumbar spine/sacroiliac joints.

Due to the prevalence of cross-sectional or retrospective studies, it has been challenging to establish the temporal link between arthritis and LBP. While subsequent cohort studies emerged, effectively addressing the impact of confounding variables remains an ongoing issue. To overcome these limitations, we turned to MR analysis, which provides a more robust approach to examine this intricate relationship. By integrating various statistical methods, we have enhanced the strength and dependability of our conclusions. Additionally, the GWAS data summary used in our research was exclusively focused on individuals of European descent, thus reducing the potential for inherent bias. Importantly, our findings support the advancement of scientific research and clinical management of the association between arthritis and LBP. However, our MR analyses have some limitations. First, the use of different methods in the analyses may lead to inconsistent outcomes due to the unique advantages and disadvantages of each method. Second, we are unable to control for potential horizontal pleiotropy. Third, the study population consisted solely of individuals of European ancestry.[47] Further research is required to evaluate the generalizability of these findings to diverse ethnic populations.

5 | CONCLUSION

This MR study provides genetic evidence supporting causal links between RA, OA at any site, KOA, and HOA with an increased risk of LBP, particularly emphasizing the significant impact of HOA. Future research should investigate the underlying mechanisms of these associations. These findings may offer new insights into the mechanisms connecting arthritis and LBP.

AUTHOR CONTRIBUTIONS

AG and MZ designed the study, conducted data analyses, drafted and reviewed the manuscript, MZ and DY conducted statistical analysis, and AG obtained funding. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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