The Causal Association Between Gestational Diabetes Mellitus and Arthritis: A Bidirectional Two-Sample Mendelian Randomization Analysis

Yiwei Zhao  
The Second Affiliated Hospital of Xi’an Jiaotong University

Jiewen Zhang  
The Second Affiliated Hospital of Xi’an Jiaotong University

Xudong Duan  
The Second Affiliated Hospital of Xi’an Jiaotong University

Ruomu Cao  
The Second Affiliated Hospital of Xi’an Jiaotong University

Ning Kong  
The Second Affiliated Hospital of Xi’an Jiaotong University

Yiyang Li  
The Second Affiliated Hospital of Xi’an Jiaotong University

Fangze Xing  
The Second Affiliated Hospital of Xi’an Jiaotong University

Huanshuai Guan  
The Second Affiliated Hospital of Xi’an Jiaotong University

Heng Li  
The Second Affiliated Hospital of Xi’an Jiaotong University

Yutian Lei  
The Second Affiliated Hospital of Xi’an Jiaotong University

Run Tian  
The Second Affiliated Hospital of Xi’an Jiaotong University

Kunzheng Wang  
The Second Affiliated Hospital of Xi’an Jiaotong University

Pei Yang (yangpei@xjtu.edu.cn)  
The Second Affiliated Hospital of Xi’an Jiaotong University

Research Article

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Abstract

Background

The long-term complications of gestational diabetes mellitus (GDM) may be associated with the development of arthritis, particularly rheumatoid arthritis (RA) and osteoarthritis (OA). However, the possible relationship between these two conditions remains unclear, hindering our understanding of both diseases. We conducted a novel study using bidirectional two-sample Mendelian randomization to explore the potential causal bidirectional relationship between GDM and arthritis.

Methods

In this study, we extracted single nucleotide polymorphisms closely associated with GDM and arthritis (RA, OA) from published genome-wide association studies (GWAS) data in open databases as instrumental variables (IVs). We employed inverse variance-weighted as the main evaluation criterion, the weighted median method as a possible alternative criterion, and multiple methods as supplements to assess causal relationships. Results were presented as odds ratios (ORs). Additionally, leave-one-out sensitivity analysis, horizontal pleiotropy, and heterogeneity tests were used to verify the reliability and stability of the results.

Result

Our results indicate a causal association between GDM and an increased risk of arthritis (RA: OR = 4.34, 95% CI = 3.49–5.41, P = 1.96 × 10^{-39}, OA: OR = 1.05, 95% CI = 1.02–1.07, P = 5.27 × 10^{-05}). In reverse MR analysis, our findings supported the promoting effect of RA on the development of GDM (OR = 1.15, 95% CI = 1.11–1.20, P = 4.44 × 10^{-14}), while the evidence is insufficient to support the conclusion that OA affects the development of GDM (P = 0.757). The heterogeneity test, horizontal pleiotropy test, and leave-one-out sensitivity analysis demonstrated the reliability and stability of our study’s results.

Conclusion

Our study suggests that genetically predisposed GDM increases the risk of developing arthritis (OA, RA). Additionally, genetically predisposed RA is causally associated with an increased risk of GDM. However, we did not find evidence for a causal association between genetically predisposed OA and GDM. These results contribute to a better understanding of the underlying mechanisms of GDM and arthritis. Furthermore, our study has significant potential to guide clinical management and the prevention of complications in patients with GDM and arthritis.

Introduction
Gestational Diabetes Mellitus (GDM) is a condition characterized by varying degrees of carbohydrate intolerance that is first detected in the second or third trimester of pregnancy\(^1\). It is one of the most common complications during pregnancy, with incidence rates ranging from 9.5–26.6% across different regions\(^2\). The incidence of this condition is anticipated to persistently increase, attributed to factors such as escalating obesity rates, sedentary lifestyles, and advancing maternal age. This trend not only poses significant health risks to patients but also imposes substantial economic burdens on healthcare systems\(^3\). In addition to the risk of maternal and neonatal complications during pregnancy, GDM also increases the risk of long-term complications for females with a history of GDM, including type 2 diabetes mellitus (T2DM), chronic kidney disease, cardiovascular disease, and chronic inflammation\(^4,5\).

Arthritis is a significant contributor to the burden of musculoskeletal disease, with rheumatoid arthritis (RA) and osteoarthritis (OA) being the most prevalent forms\(^6\). RA is characterized by joint structural changes resulting from chronic autoimmune reactions and synovial inflammation, which affects approximately 0.5-1% of the population\(^7\). Conversely, OA is a total joint disease involving the articular cartilage, subchondral bone, ligaments, capsule, and synovium that eventually leads to joint destruction\(^8\). It is estimated that OA affects over 240 million people worldwide\(^9,10\). While the pathogenesis of RA and OA differs, they both demonstrate similar associations with female gender, obesity, T2DM, chronic inflammation, and cardiovascular disease, which also overlap with the long-term complications of GDM\(^11–14\). Previous research has revealed that genetic factors influence the development of both GDM and arthritis. Moreover, inflammation and oxidative stress are known to play a critical role in the pathological processes of both diseases\(^7,8,15\), which suggests a possible connection between GDM and arthritis.

Despite the potential associations between GDM and arthritis have been suggested, only a limited number of studies have investigated this link\(^16\). Given the complexity of the development and progression of both diseases, and the presence of confounding factors that could lead to reverse causation, the authenticity of this association remains uncertain. This knowledge gap significantly hinders our understanding of the underlying mechanisms of both diseases. Mendelian randomization (MR) is a promising epidemiological approach that can shed light on this potential association\(^17\). MR employs genetic variants as instrumental variables (IVs) to act as proxies for exposure factors, which have the advantage of being stable and long-term, reducing the impact of confounding factors and leading to reliable causal conclusions\(^17\). In cases where large-scale double-blinded randomized controlled trials (RCTs) are not feasible due to high costs or practical challenges, MR can serve as a reliable alternative research method.

In this study, bidirectional two-sample MR analysis was employed to examine the potential causal relationship between GDM and arthritis (primarily RA and OA). To the best of our knowledge, this is the first study to investigate the causal relationship between GDM and arthritis using MR analysis.

**Methods**
Study design

In this study, we utilized single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to satisfy the three key assumptions required for MR analysis: (i) the genetic variants used as IVs are strongly associated with the exposure of interest; (ii) the IVs are not associated with any known potential confounding factors; (iii) the IVs influenced the outcome solely through their effect on the exposure, without any other indirect pathways\textsuperscript{18}.

Data source

The study data for GDM were derived from a genome-wide association study (GWAS) dataset of European populations, which comprised 6033 cases and 110,330 normal controls. Genetic statistics for arthritis were extracted from two independent GWAS datasets. The statistics for RA were derived from a GWAS study on the RA risk locus analysis by Eli A Stahl et al, which included 5539 autoantibody-positive RA cases and 20169 control populations\textsuperscript{19}. The OA statistics included 12658 OA cases and 50898 controls\textsuperscript{20} (supplementary table1).

All genetic data used in this study were sourced from populations of European ancestry, which minimized the potential stratification bias from populations. Ethical approval as well as study participants informed consent has been obtained in studies with data sources. The GWAS datasets were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk).

Instrumental variable selection

In this study, we conducted a rigorous screening of SNPs to select IVs that satisfy the study design principles. We selected SNPs that were strongly associated with the outcome ($P < 5 \times 10^{-8}$). However, due to the unavailability of eligible SNPs in the analysis of OA causality to GDM, we moderately relaxed the criterion to $P < 5 \times 10^{-5}$ to obtain instrumental variables. In addition, linkage disequilibrium (LD) testing was performed, where $R^2 < 0.05$ was set to ensure a strong association of SNPs. For the analysis with GDM as an exposure factor, we modestly selected a screening criterion of $R^2 < 0.5$ to obtain appropriate SNPs. SNPs with minor allele frequency (MAF) threshold were set to 0.01. Additionally, we used the F statistic to measure the strength of IVs, where $F = R^2 (N - 2) / (1 - R^2)$, $R^2$ is the proportion of changes in exposure factors explained by each IV, and $N$ is the sample size of the exposure dataset. SNPs with F-value $> 10$ were considered strong IVs in this study and included in the analysis. At the same time, we performed the Steiger filtering test to exclude SNPs that were more associated with outcome rather than exposure. We also excluded palindromic SNPs with moderate allele frequencies. These rigorous measures were implemented to establish the certainty of the causal direction in the findings and to ensure the reliability of the association effect.

Statistical analysis

Several methods were incorporated into the assessment criteria for this study. The standard inverse variance-weighted (IVW) was used as the primary analysis method to evaluate the causal relationship
between GDM and arthritis. The IVW method evaluates and obtains the overall causal effect of exposure on the outcome by precisely calculating the Wald ratio for each SNP\textsuperscript{21}. MR Egger, weighted median, simple mode, and weighted mode were also utilized as evaluation criteria. The MR-Egger regression method allowed for pleiotropic effects of genetic variation and performed weighted linear regression of the resulting coefficients on exposure coefficients\textsuperscript{22}. Furthermore, when at least 50% of variables met the validity criterion, the weighted median method was employed to accurately assess the association, thus compensating for potential imprecision in the MR-Egger regression resulting from the inclusion of external gene variables\textsuperscript{21}. If heterogeneity between IVW is evident, the weighted median approach can often serve as an alternative criterion to evaluate the results\textsuperscript{22}. Simple mode and weighted mode were used as complementary analysis methods to ensure the validity of the results. Heterogeneity among individual SNPs was assessed using Cochran’s Q test. The level of pleiotropy of IVs was assessed by the intercept values from the MR-Egger intercept. Sensitivity analysis was performed using the leave-one-out test to assess the consistency and stability of MR analysis results by removing SNPs one by one and combining the remaining effect values.

All statistical analyses were conducted using the R package (TwosampleMR) and R version 4.2.1, with a significance level of \( P < 0.05 \) was considered statistically different.

**Results**

**Causal effects of GDM on arthritis**

**Screening of SNPs**

In this study, GDM was used as an exposure factor, while OA and RA were the outcome variables. Following Steiger filtering test screening and removal of palindromic sequences with moderate allele frequencies, a total of 30 SNPs for RA and 76 SNPs for OA were obtained as IVs. The significance threshold was set at \( P < 5 \times 10^{-8} \) and the maximum R\(^2\) threshold was set at 0.5. All F-statistics were greater than 10. Further details on the SNPs can be found in Supplementary Table 2.

**Two-sample Mendelian randomization analysis**

The results from the IVW analysis showed that GDM was associated with an increased risk of both RA (OR = 13.54, 95% CI = 8.15–22.49, \( P = 7.81 \times 10^{-24} \)) and OA (OR = 1.05, 95% CI = 1.02–1.07, \( P = 5.27 \times 10^{-5} \)). The weighted median analysis also indicated a positive association between GDM and RA (OR = 4.34, 95% CI = 3.49–5.41, \( P = 1.96 \times 10^{-39} \)), OA (OR = 1.05, 95% CI = 1.01–1.08, \( P = 0.006 \)). Moreover, MR Egger, simple mode, and weighted mode approaches yielded similar results in the analysis with RA as the outcome, which were statistically significant \( (P < 0.05) \). However, for the analysis with OA as the outcome, the results from these three methods were not statistically significant \( (P > 0.05) \). Given the persuasiveness of IVW and weighted median analysis in causality assessment, we consider these results as the main evidence for the causal association between GDM and arthritis. Thus, we believe that the MR findings
support a causal association between the prevalence of GDM and an increased risk of arthritis. All statistical results above are presented in Table 1, while the forest plots and scatter plots for the causal association of GDM with RA and OA are shown in Fig. 1.

Table 1
Bidirectional Mendelian randomization analysis results of causal association between GDM and arthritis.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Methods</th>
<th>N.SNPs</th>
<th>P-value</th>
<th>OR</th>
<th>95%CI</th>
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<tr>
<td>GDM</td>
<td>RA</td>
<td>MR Egger</td>
<td>30</td>
<td>0.016</td>
<td>7.94</td>
<td>1.62–38.86</td>
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<td></td>
<td></td>
<td>Weighted median</td>
<td>30</td>
<td>1.96E-39</td>
<td>4.34</td>
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<tr>
<td></td>
<td></td>
<td>Inverse variance weighted</td>
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<td>7.81E-24</td>
<td>13.54</td>
<td>8.15–22.49</td>
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<tr>
<td></td>
<td></td>
<td>Simple mode</td>
<td>30</td>
<td>2.90E-05</td>
<td>5.58</td>
<td>2.82–11.01</td>
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<td></td>
<td></td>
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<td>3.83E-12</td>
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<td>3.32–5.49</td>
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<td></td>
<td></td>
<td>MR Egger</td>
<td>76</td>
<td>0.068</td>
<td>1.07</td>
<td>1.00-1.15</td>
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<tr>
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<td>Weighted median</td>
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<td>0.006</td>
<td>1.05</td>
<td>1.01–1.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inverse variance weighted</td>
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<td>5.27E-05</td>
<td>1.05</td>
<td>1.02–1.07</td>
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<tr>
<td></td>
<td></td>
<td>Simple mode</td>
<td>76</td>
<td>0.139</td>
<td>1.06</td>
<td>0.98–1.14</td>
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<tr>
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<td>Weighted mode</td>
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<td>0.155</td>
<td>1.05</td>
<td>0.98–1.12</td>
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<tr>
<td>RA</td>
<td>GDM</td>
<td>MR Egger</td>
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<td>2.92E-05</td>
<td>1.20</td>
<td>1.11–1.29</td>
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<td>Weighted median</td>
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<td>4.44E-14</td>
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<td>1.17</td>
<td>1.07–1.28</td>
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<td>2.24E-09</td>
<td>1.17</td>
<td>1.13–1.23</td>
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<tr>
<td>OA</td>
<td></td>
<td>MR Egger</td>
<td>119</td>
<td>0.871</td>
<td>0.99</td>
<td>0.88–1.11</td>
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<tr>
<td></td>
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<td>Weighted median</td>
<td>119</td>
<td>0.972</td>
<td>1.00</td>
<td>0.91–1.10</td>
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<td>Inverse variance weighted</td>
<td>119</td>
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<td>0.94–1.05</td>
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<td></td>
<td>Simple mode</td>
<td>119</td>
<td>0.661</td>
<td>1.04</td>
<td>0.86–1.27</td>
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<tr>
<td></td>
<td></td>
<td>Weighted mode</td>
<td>119</td>
<td>0.890</td>
<td>1.01</td>
<td>0.88–1.15</td>
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</tbody>
</table>

Sensitivity analysis

The Cochran's Q test was used to quantify the heterogeneity between SNPs in the MR analysis with RA as the outcome, which showed significant heterogeneity (Q = 2568.95, P< 0.05) (Fig. 2A). Therefore, the weighted median method was considered more appropriate for RA outcome criteria, which was more
consistent with the results of other methods. No heterogeneity was detected in analyses with OA as the outcome ($P>0.05$) (Fig. 2B). The MR-Egger intercept showed no horizontal pleiotropy in the results of this study ($P>0.05$). To assess the sensitivity of the results, a leave-one-out test was performed, which indicated that the causal effect of GDM on arthritis did not significantly fluctuate with the absence of any single SNP (Fig. 2C.2D). These results validate the reliability and stability of the MR analysis results. Specific statistical information is provided in supplementary table 4.

**Reverse two-sample MR analysis**

We screened 48 independent SNPs for RA and 119 for OA as IVs respectively, with GDM as the outcome variable, using the criteria of $P<5\times10^{-8}$, $R^2<0.05$, and F statistics greater than 10. As there were no suitable SNPs for OA as an exposure factor, we modestly relaxed the P-value criterion to $<5\times10^{-5}$. Detailed information on SNPs is provided in supplementary table 3. Similarly, SNPs were detected to be heterogeneous in studies of RA (supplementary Fig. 1A.1B), so the weighted median method was used as the analysis criterion. As shown in Fig. 3, our study supports a causal relationship between RA and increased risk of GDM (OR = 1.15, 95% CI = 1.11–1.20, $P = 4.44 \times 10^{-14}$). However, our study was not powered to support a causal association between OA and an increased risk of GDM based on the results of the IVW method ($P = 0.757$). The results obtained by each analytical method were generally similar in value, trend, and statistical significance (Table 1). These results were tested for sensitivity (supplementary Fig. 1C.1D) and pleiotropy, which both demonstrated to have no impact on the study results. Specific statistical information is provided in supplementary table 4.

**Discussion**

This study presents a bidirectional two-sample Mendelian randomization analysis and is the first to investigate the potential bidirectional causal relationship between GDM and arthritis, utilizing a comprehensive MR system with multiple complementary evaluation methods. Our results indicate a causal association between GDM and an increased risk of arthritis (RA: OR = 4.34, 95% CI = 3.49–5.41, $P = 1.96 \times 10^{-39}$, OA: OR = 1.05, 95% CI = 1.02–1.07, $P = 5.27 \times 10^{-05}$). In reverse MR analysis, our findings supported the promoting effect of RA on the development of GDM (OR = 1.15, 95% CI = 1.11–1.20, $P = 4.44 \times 10^{-14}$), while the evidence is insufficient to support the conclusion that OA affects the development of GDM ($P = 0.757$). The heterogeneity test, horizontal pleiotropy test, and leave-one-out sensitivity analysis demonstrated the reliability and stability of our study’s results.

Unlike previous studies focused on the association between diabetes and bone disease, the relationship between GDM and bone health has gained increasing attention among investigators$^{23,24}$. A recent epidemiological study found that GDM was associated with increased odds of OA (OR: 1.47, 95% CI: 1.05–2.06). This association was independent of T2DM and metabolic syndrome$^{16}$, which is consistent with our study’s conclusion. Our study provides further evidence for a potential causal relationship between GDM and rheumatoid arthritis, which is statistically significant and differs from the previous cross-
sectional study. The discrepancy in findings may be attributed to differences in study design and analytical methods employed.

The association between GDM and arthritis may be explained by several factors, as shown by previous observational studies. First, a large meta-analysis study showed that women with a history of GDM had a 9.51-fold higher risk of developing T2DM compared to normal women (95% CI: 7.14–12.67, \( P < 0.001 \))\(^{25} \). T2DM has already been identified in studies as a contributor to female OA (OR: 5.06, 95% CI: 1.66–15.56, \( P < 0.05 \))\(^{26} \) and RA (OR: 1.46, 95% CI: 1.24–1.72, \( P < 0.001 \))\(^{27} \). In a cohort study of 196 RA patients, Takeuchi et al. reported that rheumatoid factor (RF) and cyclic citrullinated peptide antibodies (ACPA) were significantly positively correlated with insulin resistance\(^{28} \). Furthermore, high glucose levels may mediate autoimmune processes by affecting reactive oxygen species (ROS)\(^{29} \), which is also important in the development of RA\(^{30} \). Second, obesity tends to accompany the development of GDM and is a significant risk factor for GDM\(^{31} \). Cohort studies have shown that obesity increases the risk of OA (OR: 1.51, 95% CI: 1.14–1.98)\(^{32} \) and RA (OR: 1.4, 95% CI: 1.0–2.0)\(^{33} \), similar to other current findings\(^{32,34,35} \), suggesting that obesity may partially explain the impact of GDM on OA and RA. Third, hypertension, as a common complication of GDM, is often associated with arthritis\(^{23,36} \). A meta-analysis demonstrated that the overall odds of having OA significantly increased in people with hypertension compared to the normotensive ones (OR: 1.60, 95% CI: 1.33–1.94)\(^{37} \), suggesting that hypertension may be involved in the causal relationship between GDM and arthritis. In addition, disturbances in the gut microbiome are often accompanied by the development and progression of both GDM and arthritis\(^{38} \). Wang et al. found an enrichment of spirochetes and lactobacilli in the GDM group compared to the healthy pregnancy group\(^{39} \). Similar results were also found in the RA-related mouse model established by Bergot et al.\(^{40} \), suggesting that microbial composition may be involved in the association between these diseases. Although the above studies support the conclusion that GDM is associated with arthritis, the limitations of observational studies make it difficult to rule out confounding factors. Furthermore, some studies still yield different results\(^{41,42} \), which poses a challenge in determining the causal association between GDM and arthritis.

Compared with previous studies, this study innovatively uses bidirectional two-sample Mendelian randomization to perform bidirectional causal inference for GDM and arthritis. This method utilizes genetic variants that are not affected by extrinsic conditions as instrumental variables, thus minimizing the impact of reverse causality and potential confounding factors. To reduce sample bias caused by sample size, the study screened for strong tool SNPs with an F-value greater than 10\(^{43} \). At the same time, multiple complementary analytical methods were used in this study, leading to consistent results. Moreover, this study focused on individuals of the same European ancestry to avoid bias caused by population stratification. The study was also subjected to leave-one-out sensitivity tests, heterogeneity, and pleiotropy tests, which affirm the validity and reliability of the study's conclusions.

However, this study has several limitations. First, our investigation only explored the causal association between GDM and arthritis without conducting a more detailed subgroup analysis of the population data.
to hierarchically confirm the possible association between each factor and the outcome. Subsequent studies will focus on advancing this approach to better understand the association and mechanism between GDM and arthritis. Second, our study only examined the two most predominant types of arthritis, RA and OA, and did not include other types. Third, our study is based on European population data. The feasibility of extrapolating our conclusions should be verified by a larger sample size in other regions.

**Conclusion**

In summary, our study findings suggest that genetically predisposed GDM increases the risk of developing arthritis (OA, RA). Additionally, genetically predisposed RA is causally associated with an increased risk of GDM. However, we did not find evidence for a causal association between genetically predisposed OA and GDM. These results contribute to a better understanding of the underlying mechanisms of GDM and arthritis. Furthermore, our results have significant potential to guide clinical management and the prevention of complications in patients.

**Declarations**

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the [GWAS] repository, [https://gwas.mrcieu.ac.uk/datasets]

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Yiwei Zhao made significant contributions in research conceptualization and design, data collection, and analysis. Jiewen Zhang made significant contributions in data collection, analysis, and manuscript writing. Xudong Duan made significant contributions in research conceptualization, design, and manuscript writing. Ruomu Cao made significant contributions in data collection. Huanshuai Guan made
significant contributions in research conceptualization and design. Ning Kong made significant contributions in data collection. Yiyang Li made important contributions in data analysis and interpretation. Fangze Xing and Yutian Lei made important contributions in data analysis and interpretation. Heng Li made significant contributions in data analysis and interpretation. Run Tian made significant contributions in manuscript writing. Kunzheng Wang critically revised important content. Pei Yang made significant contributions in research conceptualization, design, and critically revising important content. All authors read and approved the final manuscript.

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23. INVALID CITATION {}.


**Figures**
Figure 1

Legend not included with this version
Figure 2

Legend not included with this version

Figure 3

Legend not included with this version

**Supplementary Files**

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- SupplementaryTable3.csv
- SupplementaryTable4.csv
- supplementaryfigure1.docx