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Causal Effects of Rheumatoid Arthritis, Ankylosing Spondylitis, Juvenile Idiopathic Arthritis on Psoriasis: A Mendelian Randomization Study

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Background: It is well-documented that rheumatoid arthritis (RA), ankylosing spondylitis (AS), and juvenile idiopathic arthritis (JIA) often exhibit skin manifestations, with psoriasis typically occurring around the time of diagnosis. Thus, it is essential to investigate the potential causal relationship between these forms of arthritis and psoriasis.

Methods: The OpenGWAS provided traitIDs for exposure factors (RA (bbj-A-74), AS (ebi-A-GCST005529), and JIA (finn-b-JUVEN-ARTHR)) and outcome (psoriasis, finn-b-L12-PSORIASIS). bbj-A-74 had 19,190 samples (9,739,303 SNPs), ebi-A-GCST005529 had 22,647 samples (99,962 SNPs), finn-b-JUVEN-ARTHR had 173,622 samples (16,380,296 SNPs), and psoriasis had 216,752 samples (16,380,464 SNPs). Initially, 57 RA SNPs, 25 AS SNPs, and 5 JIA SNPs were acquired. Causal links were explored via univariate Mendelian Randomization (UVMR) analysis, with sensitivity analyses ensuring reliability. Additionally, multivariate MR (MVMR) analysis was conducted to further estimate the effect of each exposure factor on psoriasis.

Results: Significant causal links ($P < 0.05$, $OR > 1$) were found between bbj-A-74, ebi-A-GCST005529, finn-b-JUVEN-ARTHR, and finn-b-L12-PSORIASIS, indicating associations of RA, AS, and JIA with psoriasis. Sensitivity analyses ensured the reliability of these finding, showing no heterogeneity, horizontal pleiotropy, or SNP locus oversensitivity in UVMR results. Furthermore, MVMR analysis revealed AS and JIA as psoriasis risk factors, while RA showed non-significant protective effects. This suggests AS and JIA may contribute to psoriasis onset or exacerbation when coexisting.

Conclusion: MR analyses were conducted to investigate the causal links between RA, AS, JIA, and psoriasis, enhancing our grasp of the underlying mechanisms of psoriasis.

Keywords: causal links, openGWAS, sensitivity analyses, risk factors

Introduction

Psoriasis is a chronic immune-mediated inflammatory characterized by skin erythema, desquamation and with or without joint pain, which is related to many factors such as heredity, environment and auto-immunity.[1,2] In recent years, studies have also found that psoriasis is related to the cutaneous and intestinal microbiome, host immunity and other diseases.[3,4] Psoriasis occurs equally in men and women equally, and the mean age of onset was 33 years. The overall incidence ranges from 0.1% in east Asia to 1.5% in western Europe, and is higher in high-income countries.[5] Moreover, psoriasis patients experience a higher prevalence of anxiety and depressive symptoms.[6]

Rheumatoid arthritis (RA) is chronic inflammatory diseases which primarily affects the joints and may result in extra-articular manifestations.[7] Although the exact etiology of RA is unclear, it is linked to genetic and environmental factors.[8] Ankylosing spondylitis (AS) is inflammatory arthritis predominantly affecting the spine. The pathogenesis of AS is not completely clear,[9] the main clinical features are back pain and progressive spinal stiffness. Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of unknown etiology in childhood, characterized primarily by peripheral arthritis.[10] It is known that RA, AS and JIA are associated with psoriasis, and psoriasis usually occurs before

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and after the diagnosis of these diseases.[11–13] Inflammatory cytokines such as interleukin (IL-17), IL-23, and tumor necrosis factor (TNF-α) have been found to play a central driving role in the pathogenesis of AS, JIA, and psoriasis, suggesting that these diseases may share a common pathologic pathway[14–16] In addition, the levels of acylcarnitine and free fatty acids in peripheral blood of patients with RA and psoriasis showed a downward trend.[17–19] Of note, cross-sectional and cohort studies have reported that patients with AS are more likely to develop psoriasis than healthy controls[20,21]. Currently, the diagnosis of psoriasis mainly relies on skin examination, but when psoriasis patients are complicated by arthritis, interdisciplinary collaboration is required to comprehensively monitor the comorbidities of patients[22] This evidence further highlights the close association between psoriasis and arthritis, and the need to explore the complex relationship between the two.

Mendelian randomization (MR), which uses genetic variants as instrumental variables (IVs), is a method for assessing the causal association between risk factors and disease.[23] In order for the causal effect to be estimated in a consistent manner, each variant used in an MR analysis must fulfill three assumptions: 1) it is linked to the risk factor, 2) it is unrelated to any confounder of the risk factor-outcome association, and 3) it is conditionally independent of the outcome given the risk factor and confounders.[24] In recent years, MR has been increasingly used in observational studies. Previous MR studies have tended to be carried out in small sample populations and using low levels of genetic variation, reducing the power of MR studies. But the discovery of many genetic variants strongly associated to traits, and the publication of many large genome-wide association studies (GWASs), pooling data on hundreds of thousands of exposures and genetic variants associate whit disease, has revolutionised the field. These aggregated data facilitate the development of MR studies by allowing researchers to estimate genetic associations in large data samples. MR reduces reverse causality and confounding bias, providing us with a more accurate and reliable way to explore the causal relationships behind these complex diseases. Univariate Mendelian Randomization (UVMR) and Multivariate Mendelian Randomization (MVMR) are two commonly used statistical methods for MR, UVMR is often used to initially explore the causal relationship between a single risk factor and a specific outcome, and its results are generally easier to understand and explain, while MVMR can more comprehensively explain the pathogenesis of diseases and improve the accuracy of causal inference when exploring the causal relationship between multiple factors and multiple outcomes. These methods contribute to a deeper understanding of the role of genetic variation in complex diseases and provide scientific basis for precision medicine and disease prevention, both addressing the complexity of clinical manifestations and improving the reliability of research. Therefore, by using MR technology to explore the association between different types of rheumatoid arthritis (RA, AS, JIA) with psoriasis, new references have been provided to understand the causal relationship between these diseases.

Based on MR method, this paper took RA, AS and JIA as exposure factors and psoriasis as the outcome to explore the causal relationship between them, providing new theoretical support for further understanding of the occurrence and development of psoriasis.

Materials and Methods

Sources of GWAS Data

From the OpenGWAS database (https://gwas.mrcieu.ac.uk/), the traitID of RA, AS, and JIA were downloaded as exposure factors, respectively, and traitID for psoriasis was download as an outcome. The datasets were screened based on key elements such as disease type, sample size, number of Single Nucleotide Polymorphisms (SNPs), and temporal conditions. The bbj-A-74 of RA consisted of 19,190 samples and 9,739,303 SNPs, ebi-A-GCST005529 of AS included 22,647 samples and 99,962 SNPs, and finn-b-JUVEN-ARTHR of JIA contained 173,622 samples and 16,380,296 SNPs, and finn-b-L12-PSORIASIS for psoriasis had 216,752 samples and 163,80464 SNPs (Table 1).

Acquisition of IVs

When using SNPs as a IV to estimate the causal effect of exposure factors on outcome, selecting the appropriate SNPs was crucial. In the current study, based on the three crucial assumptions of MR, SNPs that sensibly associated with exposure factors were founded by extract instruments function of the R package TwoSampleMR (version 0.5.6) by

Table 1 Sample Information on Exposure Factors and Outcome

Year	Trait	Population	Ncase	Ncontrol	Sample size
2021	Psoriasis	European	4510	212,242	216,752
2019	Rheumatoid Arthritis	Mixed	3636	15,554	19,190
2021	Ankylosing spondylitis	European	9069	1550	10,619
2021	Juvenile arthritis	European	788	172,834	173,622

setting $P < 5\times10^{-8}$. SNPs that were significantly associated with exposure factors were selected under the condition of clump = TRUE. And SNPs with linkage disequilibrium (LD) were removed via r^2=0.001 and kb=10,000. Based on the GWAS data of outcome and the SNPs screened out from the previous steps, the SNPs that notably associated with the outcome were removed. Finally, totally 57 SNPs for RA, 25 SNPs for AS, and 5 SNPs for JIA were separately acquired after matching exposure factors, instrumental variables, and outcome.

Analysis of the Causal Relationship of RA, as and JIA on Psoriasis Through UVMR Analysis

In order to investigate the causal relationship between RA, AS and JIA with psoriasis respectively, we used UVMR method for the study. Firstly, the MR function was combined with five algorithms for UVMR analysis (MR Egger[25], Weighted median,[26] Inverse variance weighted (IVW)[27], Simple mode[28], Weighted mode[29], and the causal relationship of RA, AS and JIA on psoriasis was mainly analyzed via IVW method. The IVW method could significantly improve the accuracy of estimation and had revealed causality more precisely, while demonstrating a high degree of flexibility and wide application versatility. According to the IVW method, exposure factors with p-values below 0.05 and odds ratios (ORs) exceeding 1 were considered as risk factors for psoriasis, whereas ORs below 1 suggested protective factors for psoriasis. Exposure factors with p-values above 0.05 indicate no significant causal link to psoriasis. Scatter plots were created to assess the SNP effects of exposure factors on psoriasis, a positive slope of the line indicates a risk factor and a negative slope of the line indicates a safety factor. Forest plot was plotted to judge the efficacy of SNP Loci for predicting the MR effect size for exposure factors on psoriasis. Moreover, funnel plot was applied to determine whether the SNPs locus randomized distribution.

Sensitivity Analyses

To assess the reliability of the UVMR analysis findings, sensitivity analyses encompassing heterogeneity, horizontal pleiotropy, and leave-one-out (LOO) tests were conducted. The “mr_heterogeneity” and “mr_pleiotropy_test” functions facilitated the detection of heterogeneity and horizontal pleiotropy, respectively. Heterogeneity testing and horizontal pleiotropy testing helped to assess the reliability and robustness of study results, and could also guide researchers to optimise the study design and make decisions accordingly. The Q_p value was an indicator of significance, Q_p-value above 0.05 indicated no significant heterogeneity or horizontal pleiotropy. The LOO analysis, supported by the “mr_leaveoneout” function, evaluated the impact of eliminating each SNP on the outcome variable, thereby assessing the robustness of the results.

MVMR Analysis

To further explore the total and direct causal relationships of RA, AS, JIA on the risk of psoriasis, the MVMR analysis was carried out. First, SNPs that sensibly associated with exposure factors were searched, and SNPs with LD were removed based on clump TRUE. Ultimately, SNPs not associated with psoriasis were screened. After that, the causal relationships of RA, AS, JIA and psoriasis was analyzed. The forest plot showing the MVMR analyses findings was plotted to further recognize the causal relationship between RA, AS, JIA and psoriasis.

Results

RA, as, and JIA Had Notable Causal Relationship with Psoriasis and They Were the Risk Factors for Psoriasis

Based on the IVW results, the relationship between bbj-A-74 and finn-b-L12-PSORIASIS, between ebi-A-GCST005529 and finn-b-L12-PSORIASIS, and between finn-b-JUVEN-ARTHR and finn-b-L12-PSORIASIS all satisfied $P < 0.05$, suggesting that RA, AS, and JIA all had notable causal relationships with psoriasis, and the OR values of these three exposure factors were greater than 1, further indicating that RA, AS, and JIA were risk factors for psoriasis. Subsequently, referring to the IVW method, scatter plots revealed that the slopes of RA, AS, and JIA were positive, demonstrating that RA, AS, and JIA all had positive causal relationships with psoriasis, and the results had good robustness and the overall trends were consistent (Figure 1a). Obviously, the MR effect size in forest plots all exceeded 0, further reflecting that the RA, AS, and JIA were risk factors for psoriasis (Figure 1b). The funnel plot showed symmetrical points, demonstrating that the results of MR conformed to Mendel's second law (Figure 1c).

UVMR Results Were Reliability

Subsequently, sensitivity analyses were implemented to guarantee the dependability of the UVMR results. Heterogeneity test found that the Q_p-values of RA, AS, and JIA were all less than 0.05, while the p-values of IVW method were less than 0.05, indicating that the heterogeneity of RA, AS, and JIA and psoriasis datasets did not significantly affect the analysis results. The analysis results are valid. Horizontal pleiotropy showed that the P values of RA, AS, and JIA all greater than 0.05, unveiling that there was no horizontal pleiotropy between the exposure factor and outcome datasets. Meanwhile, LOO test demonstrated that the points of exposure factors and outcome SNPs were on the right side of 0, and which were not excessive deviated, indicating that the overall results were consistent and there were no SNPs with extremely high sensitivity, the oversensitivity to individual SNP locus of MR results was not exhibited (Figure 2). In a word, sensitivity analyses confirmed the reliability and robustness of the UVMR results.

MVMR Analysis Revealed That as and JIA Were Risk Factors for Psoriasis

Based on the results of UVMR, in order to explore the intricate associations between RA, AS and JIA and psoriasis in more depth, and to enhance the precision of inferring the causal relationship between these diseases, we adopted the MVMR method for a systematic study. MVMR analysis certified that the causal relationships between ebi-A-GCST005529 and finn-b-L12-PSORIASIS, and between finn-b-JUVEN-ARTHR and finn-b-L12-PSORIASIS were notable ($P < 0.05$), and the OR values of them were greater than 1, further reflecting that the AS and JIA were risk factors for psoriasis. Besides, the forest plot showed that RA, AS and JIA were all risk factors for psoriasis in the UVMR analysis, and further analysis by MVMR revealed that AS and JIA remained risk factors for psoriasis. However, there was no significant causal relationship between RA and psoriasis, which could be due to the complexity of the disease or differences in the methods used for this analysis. The above results suggested that in the case of concomitant presence of the above three diseases, AS and JIA could cause psoriasis or exacerbate the development of psoriasis (Figure 3).

Discussion

Approximately one-third of individuals with psoriasis will either develop or eventually develop psoriatic arthritis (PsA)[30]. PsA manifests with a variety of features, such as nail and skin alterations, peripheral arthritis, enthesitis, dactylitis, and axial spondyloarthritis (SpA), reflecting its heterogeneous nature.[31] AS and PsA are both classified under the umbrella term SpA, which encompasses various inflammatory conditions. The hallmark feature of SpA is inflammation affecting the sacroiliac joints and the spinal apophyseal joints, distinguishing it as primarily a disease of the axial skeleton.[32] RA and PsA are chronic inflammatory joint diseases characterised by bone destruction.[33,34] JIA serves as a comprehensive term encapsulating all chronic arthropathies that occur in childhood,[35] psoriatic arthritis (pJIA) is one of the subtypes.[36] In UVMR analysis, RA, AS and JIA were all risk factors for psoriasis. In a further MVMR analysis, AS and JIA remained risk factors for psoriasis, while RA became a non-significant protective factor for psoriasis, suggesting that in the presence of all three diseases, AS and JIA may contribute to or exacerbate the development of psoriasis.

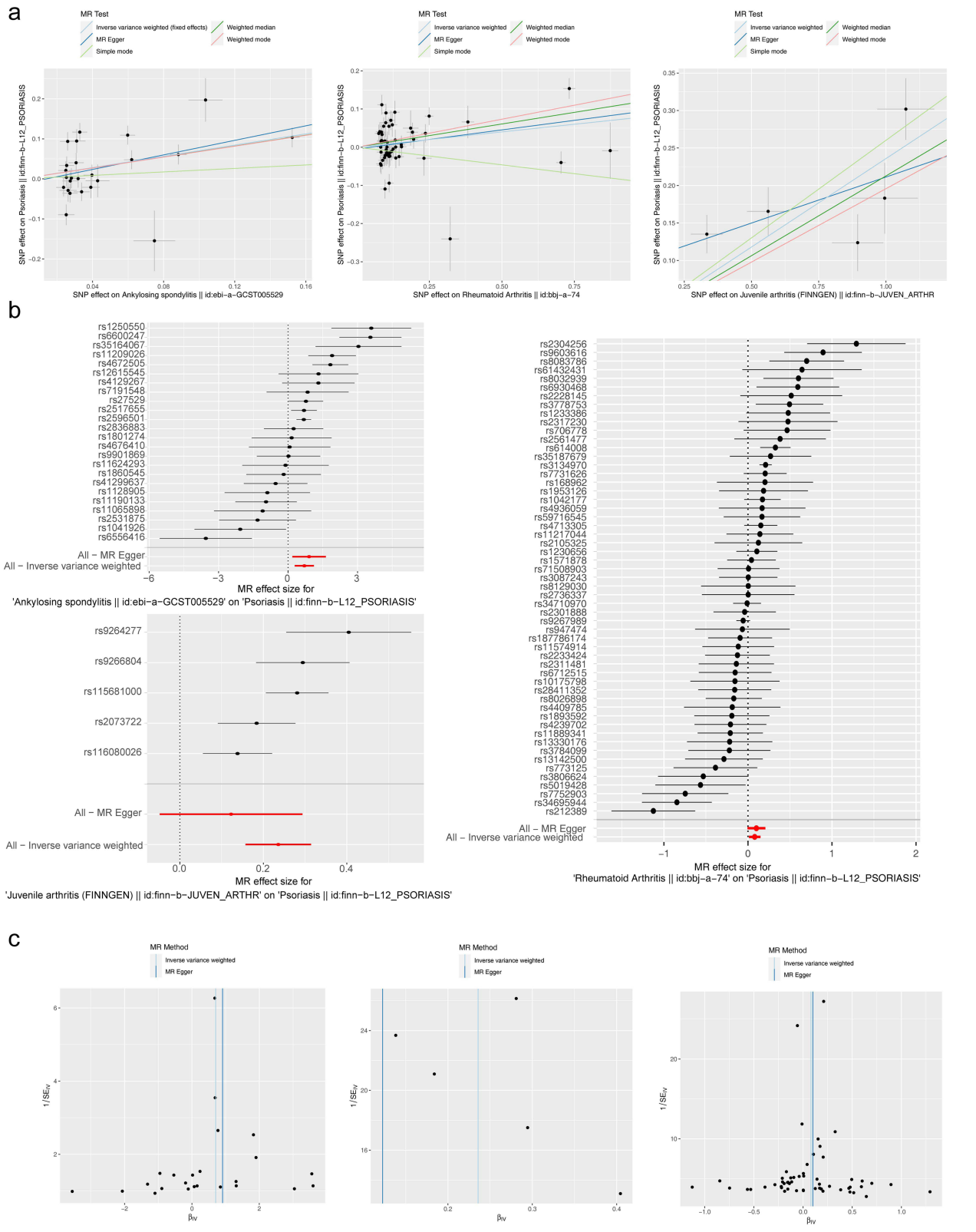

Figure 1 UVMR analysis of AS, RA, JIA and psoriasis: scatter plot and forest plot. (**a**) The scatter plot for UVMR analysis of AS, RA, JIA and psoriasis. A positive slope of the line indicates a risk factor and a negative slope of the line indicates a safety factor. (**b**) The forest plot for UVMR analysis of AS, RA, JIA and psoriasis. SNP points on the left side of the dotted line indicated a decrease in safety factors; SNP points on the right side of the dotted line indicated an increase in risk factors. The two bottom rows of data showed the overall efficacy assessment of the different models. (**c**) The funnel plot for UVMR analysis of AS, JIA, RA and psoriasis. SNP points were distributed roughly symmetrically from left to right, and MR was randomly grouped in accordance with Mendel's second law.

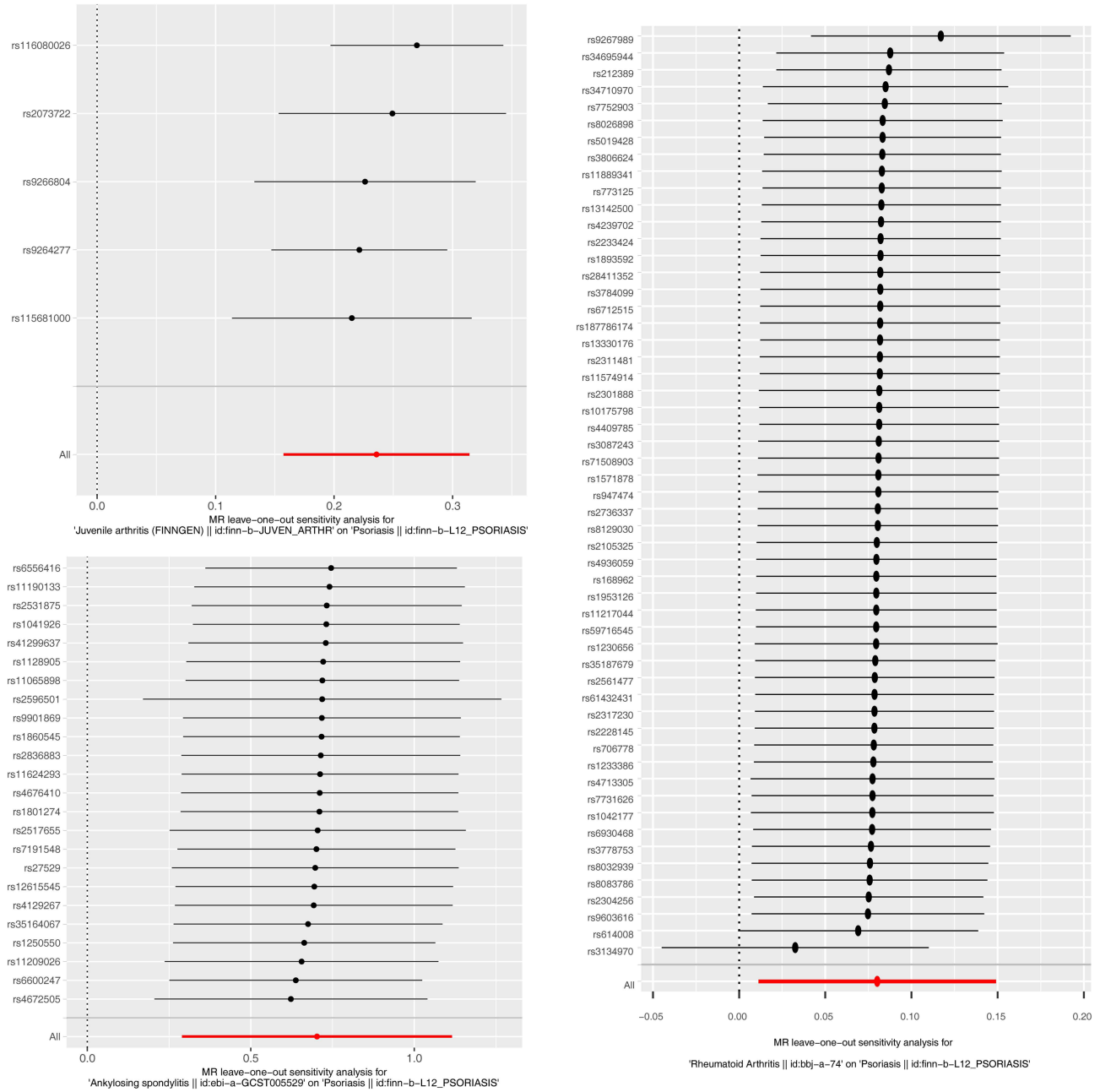

Figure 2 The forest plot presents the results of the leave-one-out analysis conducted for AS, RA, JIA and psoriasis. When all SNP points were on the same left or right side of 0, it indicates that the MR results were not significantly different from a single SNP, and therefore the MR results are robust.

In RA, a prominent clinical feature is joint swelling, indicative of inflammation within the synovial membrane.[7,33] The inflammatory process in RA is regulated by various pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-7, IL-15, IL-17, IL-18, IL-23, and interferon (IFN)-γ. These cytokines play pivotal roles in the pathogenesis of RA.[8] Increased concentrations of IL-17A have been observed in both the serum and synovial fluid of individuals with RA. Additionally, there is evidence of a synergistic effect between IL-17A and TNF in cells relevant to RA pathogenesis, such as synovial fibroblasts and chondrocytes, this suggests a cooperative role of these cytokines in promoting inflammation and joint damage in RA.[37] The TNF-α, IFN-γ and T helper type 17 (Th17) are also associated with the pathogenesis of psoriasis.[38] The IL23/IL17 axis plays an important role in the development of psoriasis.[39] Two studies have shown that the incidence of RA in patients with psoriasis has increased. It can be seen that the two diseases may be related in terms

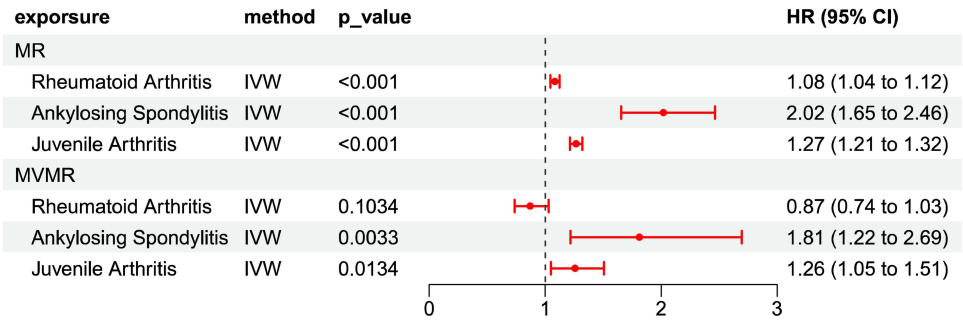

Figure 3 The forest plot for univariate and multivariate analysis results. HR greater than 1 is a risk factor and less than 1 is a safety factor.
Abbreviations: HR, hazard ratio; CI, confidence interval.

of pathogenesis.[40,41] Our study indicated that there was a causal relationship between this two diseases and RA was risk factors for psoriasis through UVMR Analysis. There was no significant causal relationship between RA and psoriasis in multivariate analysis, either because of the complexity of the disease or because of certain mediating variables, the presence of which may cause the association between RA and psoriasis observed in the UVMR analysis to become insignificant in the MVMR analysis. This study sheds light on a possible relationship between the two diseases from a genetic perspective, however, further research is needed in the future in order to fully understand the mechanisms behind it.

AS and psoriasis share a common feature: dysregulation of the immune system's regulatory pathways, leading to unchecked inflammation either systemically or in specific organs.[42] AS primarily involves inflammation of the axial joints, particularly the spine, and is frequently accompanied by additional symptoms outside of the joints, such as psoriasis.[43] Studies have shown that STAT3 and SPI1 play a crucial role in the pathogenesis of ankylosing spondylitis (AS) and have been identified as pivotal genes in the disease. In patients with AS, these two genes are upregulated and may be key factors in causing immune system disorders and triggering the pathogenesis of AS.[44] In addition, other studies have shown that the abnormal activity of STAT3 is not limited to AS, and it is also closely related to the occurrence and development of psoriasis.[45] Approximately 10% of individuals diagnosed with ankylosing spondylitis also experience symptoms of psoriasis, which can manifest as SpA.[46] In a retrospective analysis, 91 of 766 adult patients with AS had psoriasis.[47] Another study indicated that 4.86% of patients with AS have isolated axial disease with psoriasis.[32] The pathogenesis of both diseases is related to human leukocyte antigen-B27 (HLA-B27), to some extent HLA-B27 was more prevalent among patients with AS than those with axial psoriatic arthritis.[47,48] The precise connections between AS and psoriasis remain somewhat elusive. However, it's suggested that the overactivity of the IL-17/IL-23 cytokine axis may play a significant role in the pathogenic relationship between these conditions,[49,50] these phenomena may be linked to abnormal immune processes regulated by the mRNA surveillance pathway.[51] A two-sample MR analysis suggested that AS could potentially contribute to an elevated risk of psoriasis, however, the analysis did not find evidence to support the notion that psoriasis causally increases the risk of AS in individuals of European descent. Therefore, it is suggested that experiencing AS may be the causal factor behind the heightened risk of developing psoriasis.[52] Our study has a large sample size and adopts single-factor and multi-factor MR Analysis, which has higher reliability.

Oligoarticular and pJIA are characterized by the presence of autoreactive antigen-specific T-cells and elevated levels of autoantibodies. These conditions often exhibit significant correlations with major histocompatibility complex (MHC) class II alleles. The breakdown of immunological self-tolerance, particularly involving MHC class II alleles, highlights the crucial involvement of $CD4^+$ Th cells. Inflammation is believed to arise from an imbalance between pro-inflammatory Th1/Th17 cells and anti-inflammatory regulatory T-cells.[11] JIA patients exhibit elevated levels of TNF-α in both their bloodstream and synovial fluid.[53] TNF-α not only stimulates the accelerated proliferation of keratinocytes, but also induces the release of other inflammatory interleukins. In addition, TNF-α also upregulates the expression levels of adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1), P, and I-selectins. These adhesion molecules in turn promote the migration and aggregation of inflammatory cells to psoriatic lesions[54,55] In a retrospective review, 9 out of 166 JIA patients (5.4%) treated with tumor necrosis factor-α inhibitor (TNFi) developed psoriasis after starting

TNFi therapy.[56] However, a year-long safety evaluation of adalimumab usage revealed no serious occurrences of new-onset or worsening psoriasis in JIA studies.[57] Zimmer et al found that JIA patients treated with monoclonal antibodies targeting TNFi or non-TNFi biologic therapies had a greater likelihood of developing new cases of psoriasis.[58] The above three studies reflected the incidence of psoriasis after TNFi treatment of JIA, and cannot accurately describe whether JIA is a risk factor or a protective factor for psoriasis. During an 8-year observation period involving 440 JIA patients in Europe, it was observed that children with psoriasis or psoriasis-like rashes had a notably higher cumulative count of active joints. Additionally, they exhibited increased occurrences of dactylitis, nail pitting, enthesitis, and a familial history of psoriasis in comparison to children without psoriasis or psoriasis-like rashes.[59] A nationwide population-based retrospective cohort study in Taiwan showed that Children with JIA were at an increased risk of developing psoriatic disease in adulthood.[60] This study lacks experimental data and has geographical limitations. We identified JIA as a risk factor for psoriasis through both univariate and multifactorial MR Analysis, JIA may cause or aggravate the development of psoriasis.

Our study using MR offers several notable strengths. Firstly, it pioneers the investigation of genetic links between psoriasis and RA, AS, and JIA through a two-sample MR analysis using GWAS data. This method, unlike traditional observational studies, helps minimize biases like confounding and reverse causation, thereby bolstering the reliability of causal inferences. Secondly, the GWAS datasets used predominantly consist of individuals of European descent, reducing the impact of population differences. Additionally, we rigorously screened for and excluded IVs associated with potential confounding factors, mitigating the risk of horizontal pleiotropy. Moreover, by employing MR-Egger analysis, we thoroughly assessed the influence of pleiotropy and ensured the robustness of our findings.

However, this study also has some limitations. First, when exploring the causal relationship between JIA and psoriasis, this study failed to fully consider pJIA, a key factor that is both a subtype of JIA and a manifestation of psoriasis. Therefore, there are certain limitations in explaining the causal relationship between JIA and psoriasis. In the future, it is necessary to eliminate the data of this subtype and conduct further exploration to verify the reliability of our results. In addition, this study preliminarily explored the complex relationship between RA, AS and JIA and psoriasis, but the specific mechanism of action between these diseases is still not well understood. Future studies need to conduct experimental studies to explore the mechanism, such as protein interaction analysis, animal model experiments, etc. In order to more fully reveal how these diseases become risk factors for the development of psoriasis. Finally, the study needs to be validated in different ethnic groups based on large-scale GWAS aggregate data, and further validation is needed with Mendelian randomization (MR) analysis using other genetic tools.

Conclusion

In summary, our study has successfully identified a genetic link between psoriasis and RA, AS, and JIA. This discovery serves as a crucial foundation for understanding the underlying mechanisms and developing innovative treatments for psoriasis. In terms of clinical treatment, doctors can identify potential complications or comorbidity earlier, so as to take more timely intervention measures, but also by monitoring the genetic variation of patients, dynamically grasp the progress of patients, and ensure the flexible adjustment of treatment plans, thus significantly improving the treatment effect. In addition, doctors can also personalize treatment plans based on patients' genetic background information. In the future, we will continue to focus on studying the interrelationship and internal mechanism between RA, AS, JIA and psoriasis, with a view to contributing more valuable information to the research in this field.

Abbreviations

RA, Rheumatoid arthritis; AS, Ankylosing spondylitis; JIA, Juvenile idiopathic arthritis; SNP, Single Nucleotide Polymorphism; MR, Mendelian Randomization; UVMR, univariate Mendelian Randomization; MVMR, multivariate Mendelian Randomization; IV, Instrumental variable; GWAS, Genome-wide association study; LD, Linkage disequilibrium; IVW, Inverse variance weighted; OR, Odds ratio; PsA, Psoriatic arthritis; SpA, Spondyloarthritis; JIA, Juvenile idiopathic arthritis; pJIA, Psoriatic arthritis; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin-1β; IFN, Interferon; Th17, T helper type 17; MHC, Major histocompatibility complex; ERA, Enthesitis-related arthritis; TNFi, Tumor necrosis factor-α inhibitor.

Data Sharing Statement

The datasets supporting the conclusions of this article are available in the OpenGWAS database (https://gwas.mrcieu.ac.uk/). The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted based on public databases where the data information is publicly available and unrestricted reuse is permitted through open licences. The study was granted an exemption from ethical review by the Hangzhou Third People's Hospital Ethics Committee (NO.KY-2024293, Date: November 1, 2014).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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