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ORIGINAL RESEARCH

Causal Effects of Inflammatory Arthritis Subtypes on Fibromyalgia: A Comprehensive Mendelian Randomization Study

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Purpose: Fibromyalgia (FM) is a chronic pain disorder characterized by widespread musculoskeletal pain and central sensitization, often co-occurring with inflammatory arthritis (IA) in clinical presentation. While observational studies suggest a higher prevalence of FM among IA patients, the causal relationship between IA and FM remains uncertain due to potential confounding factors and the possibility of reverse causation.

Patients and Methods: We employed a two-sample Mendelian randomization (TSMR) approach to evaluate the causal effect of nine IA subtypes on FM, utilizing genetic summary data from large-scale genome-wide association studies (GWAS) encompassing up to 201,581 participants (exposure: IA phenotypes) and 168,378 participants (outcome: FM). The primary analysis was conducted using the Inverse-Variance Weighted (IVW) method, with sensitivity analyses assessing robustness and pleiotropy.

Results: MR analysis revealed significant causal links between several IA subtypes and FM. Rheumatoid arthritis (OR 1.105, 95% CI 1.020–1.198), enteropathic arthritis (OR 1.207, 95% CI 1.123–1.299), Juvenile Idiopathic Arthritis (OR 1.307, 95% CI 1.183–1.445), and other IA subtypes showed an increased risk of FM (all $p<0.0001$). Psoriatic arthritis demonstrated no significant association with FM (OR 1.006, 95% CI 0.909–1.112, $p=0.911$). Sensitivity analyses confirmed no significant heterogeneity and consistent results, despite minor horizontal pleiotropy observed in MR-Egger regression.

Conclusion: This study provides genetic evidence supporting a causal relationship between IA subtypes and an increased risk of FM. However, no significant causal link was found between psoriatic arthritis and FM. These findings emphasize the role of immune-mediated inflammation in FM pathogenesis and highlight the differential impact of various IA subtypes on FM risk.

Keywords: fibromyalgia, inflammatory arthritis, Mendelian randomization, genetic association, rheumatoid arthritis, psoriatic arthritis

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain, fatigue, cognitive dysfunction (often referred to as "fibro fog"), and sleep disturbances. It is regarded as a central sensitivity syndrome, where the central nervous system processes pain abnormally, leading to an exaggerated response to stimuli.[1,2] The prevalence of FM is notable, affecting approximately 2–4% of the global population, with women being disproportionately affected.[3,4] Owing to its heterogeneous presentation and overlap with other conditions, FM remains underdiagnosed or misdiagnosed, resulting in considerable morbidity, reduced quality of life, and increased healthcare costs.

Inflammatory arthritis (IA) refers to a group of chronic joint disorders, including rheumatoid arthritis (RA), enteropathic arthritis (EA), psoriatic arthritis (PsA), and Juvenile Idiopathic Arthritis (JIA). These conditions are characterized by persistent joint inflammation that leads to structural damage and functional impairment.[5] While RA is classically autoimmune, emerging evidence classifies PsA, EA, and JIA within the autoinflammatory spectrum, driven by dysregulated innate immunity (eg, *IL-23/Th17* axis activation in PsA) and genetic factors. Similar to FM, IA imposes significant systemic burden, including increased risks of cardiovascular disease, osteoporosis, and extra-articular manifestations.[6]

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Growing evidence also suggests an increased prevalence of FM among IA patients, particularly in subtypes such as RA. This overlap strongly implies shared or interconnected pathophysiological mechanisms between the two conditions.

However, determining the causal nature of this relationship—whether influenced by shared risk factors, concurrent disease progression, or other confounders—remains a significant challenge. Observational studies have shown a higher prevalence of FM in individuals with IA. For instance, patients with Ankylosing Spondylitis (AS) have a higher incidence of FM (0.52 per 1000 person-months) compared with the general population (0.39 per 1000 person-months).[7] Similarly, patients with RA had an FM odds ratio (OR) of up to 25 (95% CI, 13–34) compared to controls, with older patients with AS (>65 years of age) exhibiting particular vulnerability.[8] Despite these associations, the exact temporal sequence between exposure (IA) and outcome (FM) remains unclear. Observational studies struggle with confounding factors, such as comorbidities and reverse causation, making it difficult to infer causal relationships from simple correlations.

To address the limitations in previous research, this study employs Mendelian randomization (MR) to investigate the causal relationship between IA and FM. MR leverages genetic variants that are randomly allocated at conception, thereby approximating the randomization of controlled trials. This method enables robust causal inference by minimizing biases from confounding factors and reverse causation.[9,10] Recognized for its strength in causal assessment, MR provides evidence surpassed only by randomized controlled trials (RCTs).[11] This study is among the most comprehensive in the field, incorporating all available data on IA which includes RA, seronegative rheumatoid arthritis (SERA), spondyloarthritis (SpA), spinal arthritis (SP), PsA, EA, reactive arthritis (ReA), sacroiliitis (SI), and JIA.[5] By applying the robust two-sample MR (TSMR) methodology, this study aims to elucidate the temporal and causal relationships between IA and FM. This broad framework allows for a detailed examination of the causal effects between exposure and outcome, potentially unveiling shared pathophysiological mechanisms. The findings may optimize risk stratification, identify IA patients at elevated risk of FM, and inform the development of targeted, personalized interventions. Ultimately, this research seeks to advance the understanding and management of these interrelated chronic diseases.

Methods

Study Design

This study employed a TSMR approach to investigate the causal relationship between IA as the exposure and FM as the outcome. The study adhered strictly to the STROBE-MR reporting guidelines to ensure transparency and reproducibility.[12] Publicly available, anonymized summary-level genetic data were exclusively sourced from IEU Open GWAS (https://gwas.mrcieu.ac.uk/). Original GWAS included in this repository received ethical approval with participant consent for anonymized secondary use. Per China's Ethical Review Measures for Life Sciences and Medical Research Involving Humans (Article 32(1–2), 2023), research using legally acquired public non-identifiable data is exempt from ethical review. As this study repurposed such pre-approved data, institutional review boards (IRBs) approval was not required. The flowchart of the MR study design is shown in Figure 1 below.

Data Sources

For the exposure, data pertaining to IA were obtained from the FinnGen biobank, the EBI database, and the IEU database between 2020 and 2022. The exposure included nine phenotypes: RA, SERA, SpA, SP, PsA, EA, ReA, SI, and JIA. It is important to note that the FinnGen-derived phenotypes "SP" (FinnGen code: finn-b-SPONDYLOARTHRITIS) and "SI" (FinnGen code: finn-b-M13_SACROILIITIS) represent technical classifications within the database. These terms denote specific manifestations within broader arthritic syndromes (eg, SP indicates spinal inflammation, typically associated with axial spondyloarthritis; SI indicates inflammatory involvement of the sacroiliac joints, commonly observed in spondyloarthritis or other inflammatory conditions). They are not considered distinct disease entities. Each phenotype's dataset included a total number of single nucleotide polymorphisms (SNPs) ranging from 13,108,512 to 16,380,342. All participants in these datasets were of European ancestry, ensuring homogeneity in genetic backgrounds for the analysis.

The outcome data were sourced from the FinnGen biobank, specifically from ID finn-b-M13_FIBROMYALGIA. This dataset comprised a total of 168,378 participants, with 737 cases and 167,641 controls, all of European ancestry. The

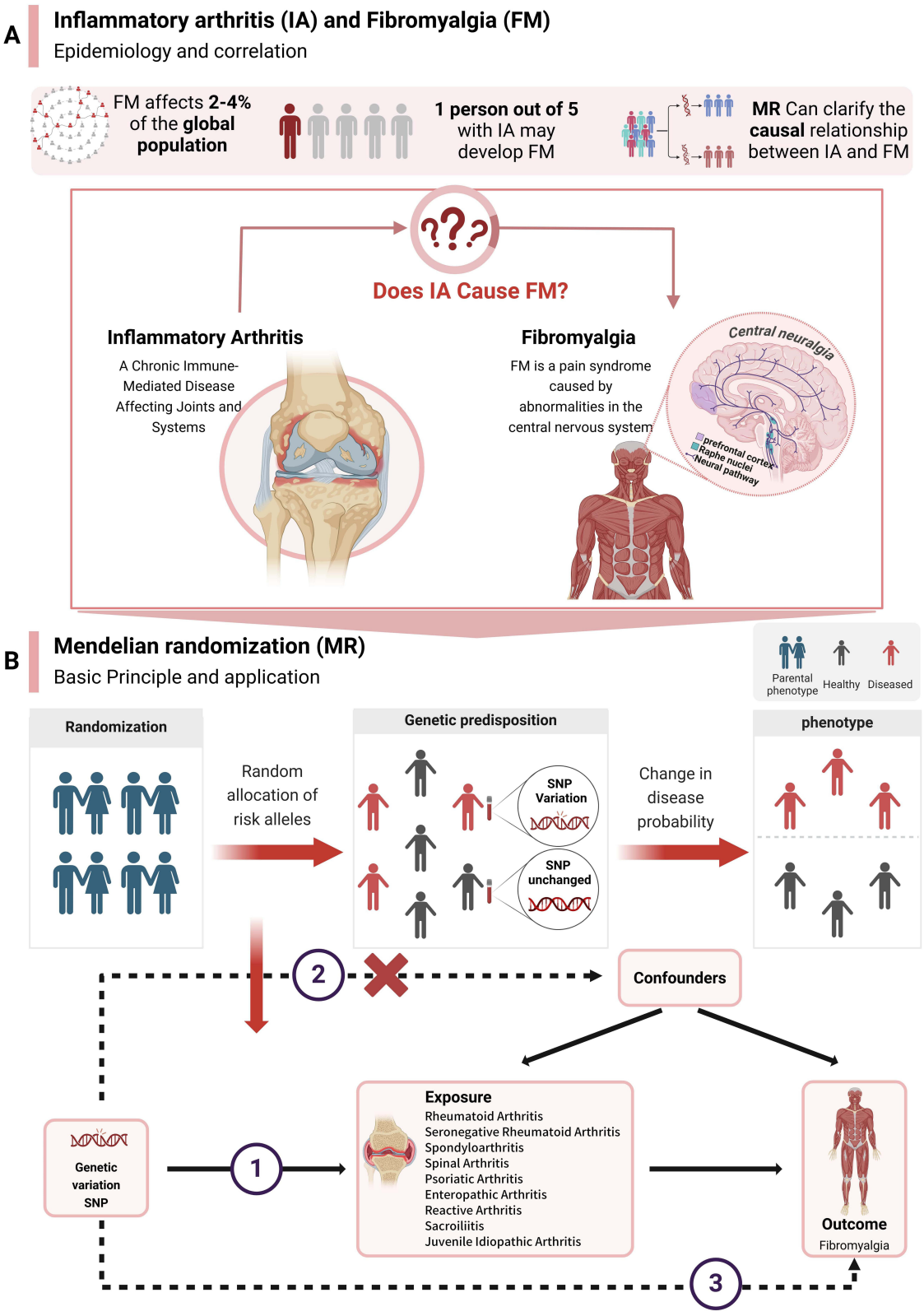

Figure 1 The Relationship Between IA and FM and the Application of MR Analysis. (**A**) Epidemiological data show that 1 in 5 IA patients develops FM, suggesting a potential causal link. The key question addressed is: Does IA cause FM? To clarify the causal relationship between IA and FM, MR can be applied as a powerful epidemiological method that leverages genetic data. (**B**) MR utilizes genetic variants (SNPs) as instrumental variables to infer causality. By minimizing confounding through random allocation of genetic risk alleles, MR evaluates whether genetically predicted IA (exposure) increases the risk of FM (outcome).

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total number of SNPs included in this dataset was 16,380,308, ensuring compatibility with the exposure datasets. The specific details and characteristics of all the above data are shown in Table 1.

The SNP-related information is provided in Supplementary Table 1.

Screening of IVs

Instrumental variables (IVs) were selected based on the following criteria to meet the three core assumptions of MR analysis: (1) IVs must be strongly associated with the exposure ($p < 5 \times 10^{-8}$); (2) IVs must be independent of confounding factors; and (3) IVs must influence the outcome only through the exposure. To minimize linkage disequilibrium (LD), an r^2 threshold of <0.001 and a genetic distance of >10,000 kb were applied. The datasets for exposure and outcome were harmonized, and strand-ambiguous SNPs with intermediate allele frequencies (AF ≥ 10%) were excluded. The F-statistics were calculated for each SNP, and SNPs with an F > 10 were retained as strong instrumental variables for inclusion in the analysis.

Statistical Analysis

Genetic associations were quantified as odds ratios (OR) scaled per 1-standard deviation (SD) increase in genetically predicted exposure risk. For binary exposures (all IA subtypes) and binary outcome (FM), the Inverse-Variance Weighted (IVW) model combined Wald ratio estimates (β_{GY}/β_{GX}) using fixed-effect meta-analysis weighted by inverse-variance ($1/SE^2$). Sensitivity analyses (MR-Egger, weighted median) maintained identical scaling. The primary statistical method employed for this analysis was the IVW approach. The IVW method was chosen because it yields the most reliable results under the assumption that there is no horizontal pleiotropy among the IVs, as supported by Burgess et al.[13] This method combined the Wald ratio estimates of the causal effects from individual SNPs to provide a consistent and precise estimation of the causal effect of exposure on the outcome.

To complement the IVW analysis, supplementary methods were also implemented. The weighted median approach was utilized to improve the robustness of causal estimates, as it can provide valid results even when up to 50% of the instruments are invalid.[14] Additionally, the MR-Egger regression method was applied to detect and adjust for potential horizontal pleiotropy. MR-Egger offers unbiased estimates when the instrument strength is independent of pleiotropic effects, albeit with reduced efficiency due to wider confidence interval.[15,16] These methods were used collectively to ensure robustness and validity in the estimation of causal effects.

The statistical analyses were conducted using R software (version 4.4.1), utilizing the TwoSampleMR package for MR analysis. The power of the MR analysis was assessed using the F-statistics to ensure sufficient instrument strength.

Table 1 Details of Data Included in TSMR

Phenotype	GWAS ID	Year	Sample Size	Number of SNPs	Ethnicity
FM	finn-b-M13_FIBROMYALGIA	2021	168,378	16,380,308	European
RA	ebi-a-GCST90013534	2020	58,284	13,108,512	European
SERA	finn-b-RHEUMA_SERONEG	2021	174,771	16,380,301	European
SpA	finn-b-M13_SPONDYLOPATHY	2021	183,232	16,380,334	European
SP	finn-b-SPONDYLOARTHRITIS	2021	201,581	16,380,342	European
PsA	ieu-b-5116	2022	26,351	Null	European
EA	finn-b-M13_ENTEROARTHR	2021	147,516	16,380,134	European
ReA	finn-b-M13_REACTARTH	2021	148,745	16,380,159	European
SI	finn-b-M13_SACROILIITIS	2021	165,276	16,380,217	European
JIA	finn-b-JUVEN_ARTHR	2021	173,622	16,380,296	European

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis (FinnGen technical phenotype; reflects spinal inflammation, eg, in axial spondyloarthritis); PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis (FinnGen technical phenotype; indicates inflammatory sacroiliac involvement, eg, in spondyloarthritis); JIA, Juvenile Idiopathic Arthritis.

Sensitivity Analysis

Sensitivity analyses were performed to evaluate the stability and reliability of the instrumental variable effects. The MR-Egger intercept was used to confirm the presence of horizontal pleiotropy among the IVs, where a significant intercept ($p < 0.05$) would indicate directional pleiotropy.[17] The Q-statistic was employed to assess heterogeneity, and leave-one-out analysis was conducted to evaluate the impact of individual SNPs on the overall causal estimates.[18]

Results

Selection of Instrumental Variables

This study conducted the MR analysis to explore the casual relationships between IA as exposure and FM as outcome, with IA including nine phenotypes. This TSMR analysis, employing a total of 147 effective SNPs (85 for RA, 6 SNPs for SERA, 6 SNPs for SpA, 11 SNPs for SP, 18 SNPs for PsA, 4 SNPs for EA, 6 SNPs for ReA, 4 SNPs for SI, 5 SNPs for JIA, and 2 SNPs for FM), all with F-values >10, provided robust instrumental strength.

Results of the Causal Relationship Between IA Subtypes and FM

Given the robustness of the IVW method, which is generally considered the primary approach in MR analysis, we focus on the IVW results in this study, while also presenting the MR-Egger results for comparison.[19]

The IVW method indicated strong evidence of a causal association between several IA subtypes and FM. Specifically, both the IVW and MR-Egger methods indicated a significant causal relationship for RA, SERA, SpA, SP, EA and ReA. Using the IVW method, the ORs for these associations were as follows: RA and FM (OR 1.105, 95% CI 1.019–1.198, p=0.015), SERA and FM (OR 1.354, 95% CI 1.190–1.540, p<0.001), SpA and FM (OR 2.099, 95% CI 1.608–2.739, p<0.001), SP and FM (OR 1.127, 95% CI 1.058–1.202, p<0.001), EA and FM (OR 1.207, 95% CI 1.123–1.299, p<0.001), and ReA and FM (OR 1.175, 95% CI 1.085–1.254, p<0.001).

In contrast, the MR-Egger method provided little evidence for a causal effect, while the IVW method showed a significant causal relationship for SI and JIA. The ORs for these associations were: SI and FM (OR 1.141, 95% CI 1.085–1.200, p<0.001) and JIA and FM (OR 1.307, 95% CI 1.183–1.445, p<0.001). However, the MR-Egger method showed non-significant results for SI and FM (OR 1.108, 95% CI 0.981–1.251, p=0.239) and JIA and FM (OR 1.267, 95% CI 0.993–1.616, p=0.153).

Finally, no significant causal relationship was observed between PsA and FM, as both MR-Egger and IVW methods yielded non-significant results (PsA and FM: IVW OR 1.006, 95% CI 0.909–1.112, p=0.911; MR-Egger OR 0.926, 95% CI 0.744–1.152, p=0.499). The detailed results of the MR analysis are shown in Table 2. The Mendelian randomization results for the causality between IA subtypes and FM are presented, with the corresponding forest plot shown in Figure 2 and the scatter plot in Figure 3.

Table 2 Results of TSMR Analysis

Exposure	Outcome	N. SNPs	IVW		MR-Egger	
			OR (95% CI)	*p*	OR (95% CI)	*p*
RA	FM	85	1.105 (1.019, 1.198)	0.015	1.117 (0.988, 1.264)	**0.081**
SERA		6	1.354 (1.190, 1.540)	<0.001	1.608 (1.153, 2.242)	0.049
SpA		6	2.099 (1.608, 2.739)	<0.001	1.898 (1.276, 2.823)	0.034
SP		11	1.127 (1.058, 1.202)	<0.001	1.137 (1.033, 1.251)	0.027
PsA		18	1.006 (0.909, 1.112)	**0.911**	0.926 (0.744, 1.152)	**0.499**
EA		4	1.207 (1.123, 1.299)	<0.001	1.283 (1.098, 1.499)	**0.089**
ReA		6	1.175 (1.085, 1.200)	<0.001	1.139 (1.037, 1.252)	**0.053**
SI		4	1.141 (1.085, 1.200)	<0.001	1.108 (0.981, 1.251)	**0.239**
JIA		5	1.307 (1.183, 1.445)	<0.001	1.267 (0.993, 1.616)	**0.153**

Notes: Bold-formatted *p*-values denote statistically non-significant associations (≥0.05). The causal relationships presented are primarily based on the IVW estimates.

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis; PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis; JIA, Juvenile Idiopathic Arthritis; OR, Odds ratios.

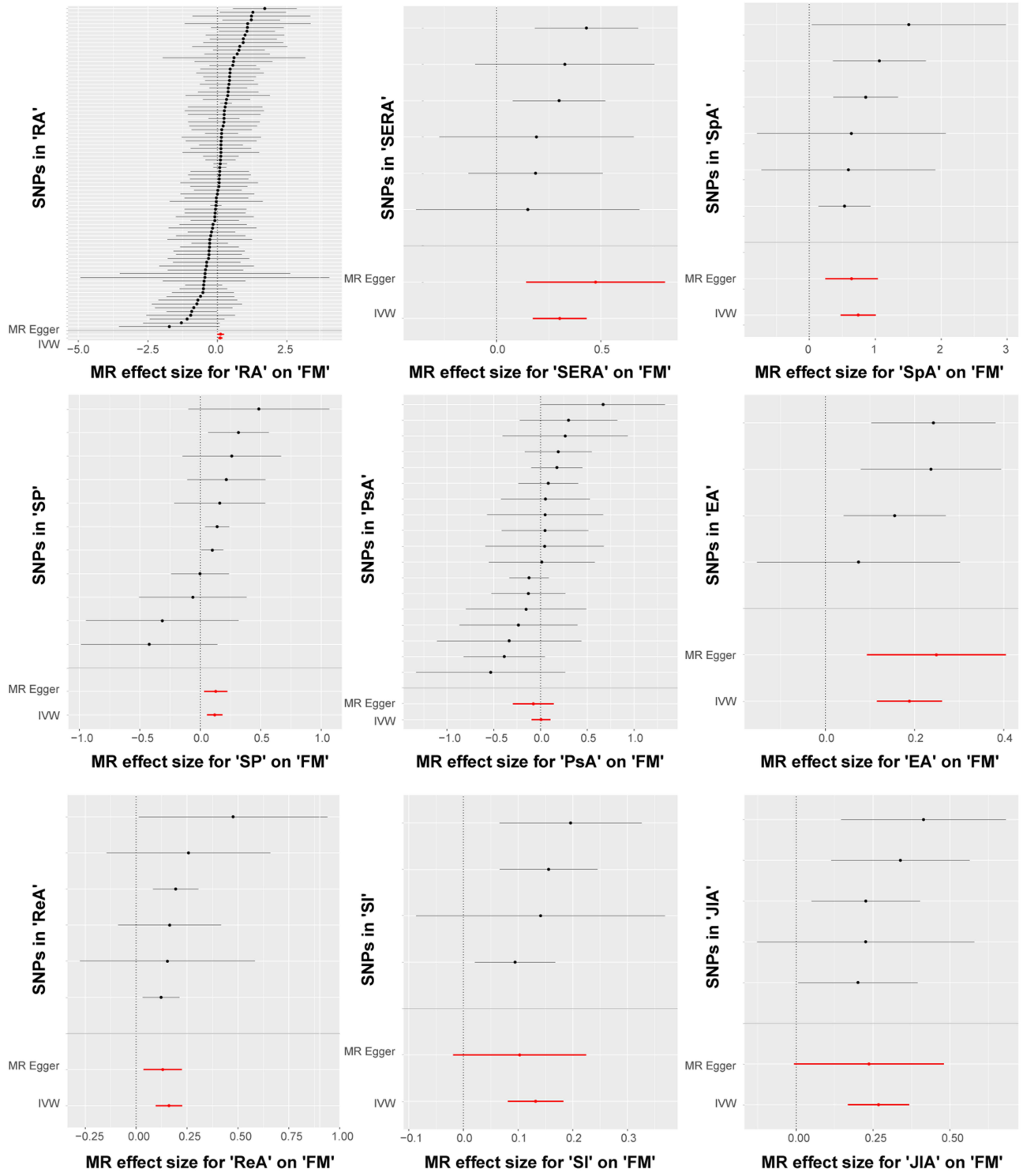

Figure 2 Forest plot of positive MR results for causal relationship between IA subtypes and FM. Forest plots display the causal effect sizes of IA subtypes on FM using MR methods. IVW estimates are highlighted in red, while MR-Egger estimates are shown for comparison.

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis; PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis; JIA, Juvenile Idiopathic Arthritis; MR, Mendelian Randomization.

Sensitivity Analysis

Sensitivity analyses revealed no significant heterogeneity (all Cochran's Q test $p_{\text{heterogeneity}}$ >0.05) and leave-one-out analyses were robust. Although the MR-Egger intercept suggested horizontal pleiotropy for all investigated phenotypes

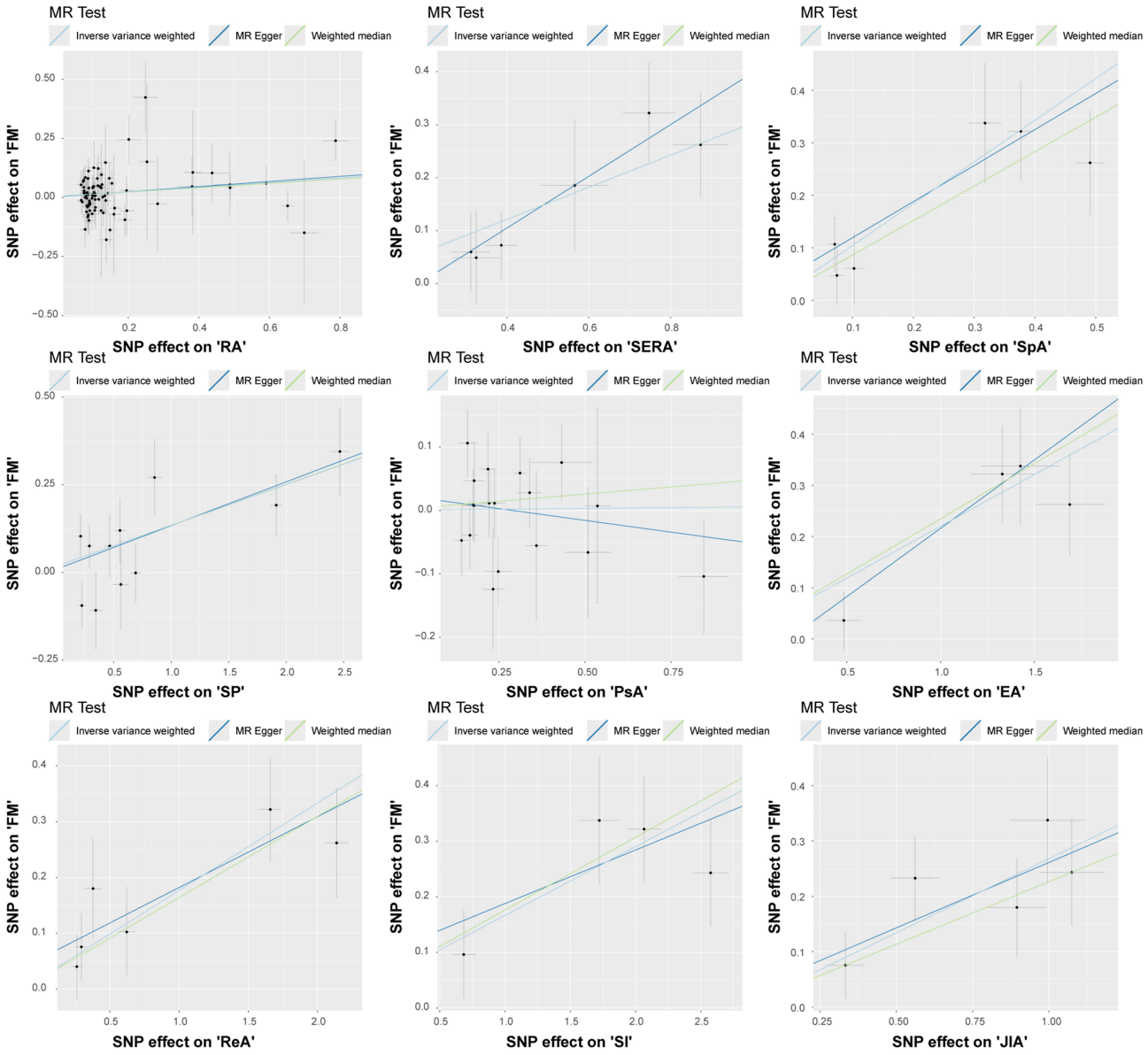

Figure 3 Scatterplot of positive MR results for causal relationship between IA subtypes and FM. Scatter plots illustrate the SNP effects on IA subtypes (RA, SERA, SpA, SP, PsA, EA, ReA, SI, JIA) against their effects on FM. Lines represent causal effect estimates using IVW, MR-Egger, and weighted median methods.

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis; PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis; JIA, Juvenile Idiopathic Arthritis; MR, Mendelian Randomization.

except SI ($p_{\text{intercept}}$ >0.05 for SI; $p_{\text{intercept}}$ <0.05 for all others), the overall conclusions remained unchanged. The sensitivity analysis results are shown in Table 3. The funnel plot of the positive MR results for the causality between IA subtypes and FM is shown in Figure 4 below. The "Leave-one-out" plots are shown in Figure 5 below.

Discussion

This study aimed to investigate the causal relationship between IA and FM using MR, addressing a significant gap in existing literature. Previous systematic reviews have highlighted the high prevalence of FM among IA patients, with approximately one in five individuals affected. Moreover, this comorbidity is associated with increased disease activity, as evidenced by elevated tender joint counts and patient-reported global assessments.[20] However, due to the limitations inherent in observational studies, the causal nature of this association has remained undetermined. This study addresses such limitations by employing MR and leveraging genetic instrumental variables, providing more robust evidence that IA

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Table 3 Results of Sensitivity Analysis

Exposure	Outcome	MR-Egger Intercept			Cochrane's Q		
		Intercept	SE	P value	Cochran's Q	Q_df	P value
RA	FM	−0.002	0.011	0.815	79.535	84	0.618
SERA		−0.098	0.089	0.334	2.071	5	0.839
SpA		0.029	0.043	0.539	3.173	5	0.673
SP		−0.01	0.041	0.814	12.036	10	0.283
PsA		0.027	0.032	0.415	16.808	17	0.467
EA		−0.075	0.087	0.48	2.224	3	0.527
ReA		0.039	0.044	0.428	3.029	5	0.695
SI		0.058	0.112	0.656	2.209	3	0.53
JIA		0.024	0.089	0.801	2.249	4	0.69

Notes: The MR-Egger intercept provides evidence for horizontal pleiotropy, while Cochran's Q-statistic assesses heterogeneity across SNPs. A non-significant MR-Egger intercept suggests no pleiotropy, and the Cochran's Q p-value indicates the consistency of causal estimates.

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis; PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis; JIA, Juvenile Idiopathic Arthritis; MR, Mendelian Randomization; SE, Standard Error; SNP, Single Nucleotide Polymorphism.

may directly contribute to the development of FM. The results indicate a strong causal relationship between several IA subtypes, including RA, SERA, SpA, SP, EA, ReA, SI, and JIA, and the development of FM, while no such relationship was observed for PsA. These findings further underscore the role of immune-mediated inflammation in the pathogenesis of FM. Given these findings, the next logical step is to explore the underlying biological mechanisms by which IA may contribute to FM. We hypothesize that this relationship may be mediated through three primary mechanisms: (1) chronic inflammation, (2) dysregulation of the gut-brain axis, and (3) alterations in amino acid metabolism. These mechanisms not only provide insight into the pathophysiological links between IA and FM but also suggest promising therapeutic targets for future research.

Specifically, chronic inflammatory processes, particularly those observed in conditions like RA, SpA, and SERA, contribute to central sensitization and altered pain processing, which are central to the pathophysiology of FM. During the inflammatory process, in which the central nervous system becomes hypersensitive to pain signals, may exacerbate pain perception and reduce quality of life. For instance, Sarzi-Puttini et al elucidate that pain in RA not only arises from joint inflammation but also induces neuroendocrine responses that perpetuate neurogenic inflammation and cytokine release, leading to sustained hyperalgesia.[21,22] Similarly, studies by Cao et al[23] and Tapia-Haro et al[24] underscore the critical role of proinflammatory cytokines and central nervous system alterations in FM development. Furthermore, Oktayoglu et al[25] identify that elevated levels of high mobility group box 1 (HMGB1) protein are associated with decreased quality of life and increased psychological distress in FM patients, suggesting a link between inflammatory markers and FM severity. Mokhemer et al[26] demonstrated that stem cell therapy can modulate inflammatory pathways and improve behavioral outcomes in FM models, indicating potential therapeutic mechanisms that address both inflammation and neurogenesis. The evidence highlights the complex interplay between peripheral inflammation and central pain processing, further strengthening the notion that immune-mediated inflammation is integral to FM's pathophysiology.

Another essential mechanism in this relationship is the gut-brain axis. Dysbiosis-induced systemic inflammation and microbial metabolites, including short-chain fatty acids and bile acids, within the gut-brain axis contribute to neuroinflammation and central pain sensitization, thereby exacerbating conditions such as EA and FM. The systemic inflammatory processes in EA may aggravate FM through alterations in gut microbiota. Dysbiosis in the gut microbiota, as discussed by Esquerre et al[27] and Shen et al,[28] has been demonstrated to exacerbate systemic inflammation, thereby contributing to neuroinflammation and central pain sensitization. Collins et al[29] and Liu et al[30] also highlight how gut-derived signaling molecules influence pain pathways by modulating both peripheral and central sensitization. Additionally, microbial metabolites, such as short-chain fatty acids and bile acids, can affect intestinal barrier integrity

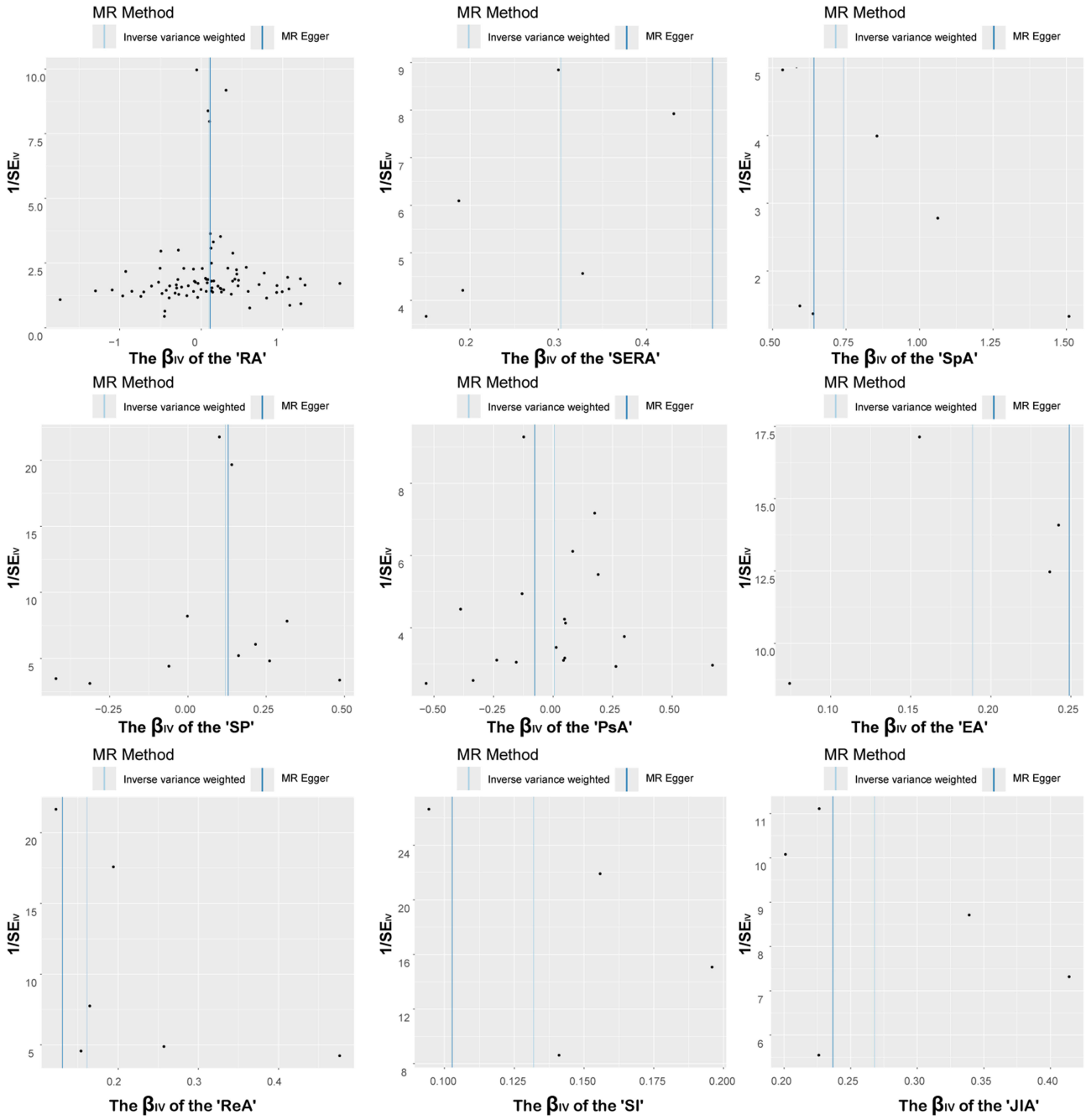

Figure 4 Funnel plot of positive MR results for causal relationship between IA subtypes and FM. Funnel plots illustrate the distribution of SNP effects on IA subtypes and FM. The symmetry of the plots reflects the absence of directional pleiotropy, and the vertical line represents the IVW estimate. Points clustered symmetrically around the IVW line suggest robust causal estimates.

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis; PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis; JIA, Juvenile Idiopathic Arthritis; MR, Mendelian Randomization; SNP, Single Nucleotide Polymorphism.

and contribute to the systemic inflammatory state, which could trigger FM in turn.[31,32] These findings emphasize the systemic nature of inflammation and its pivotal role in modulating pain processing via the gut-brain axis.

The potential contribution of amino acid metabolism to FM pathogenesis is highlighted by its disruption in JIA. In JIA, chronic inflammation leads to alterations in tryptophan metabolism and imbalances within the kynurenine pathway. Both factors influence neurotransmitter regulation and central pain processing, thereby increasing the risk of FM development. Chronic inflammation in JIA patients may lead to alterations in amino acid metabolism, notably affecting

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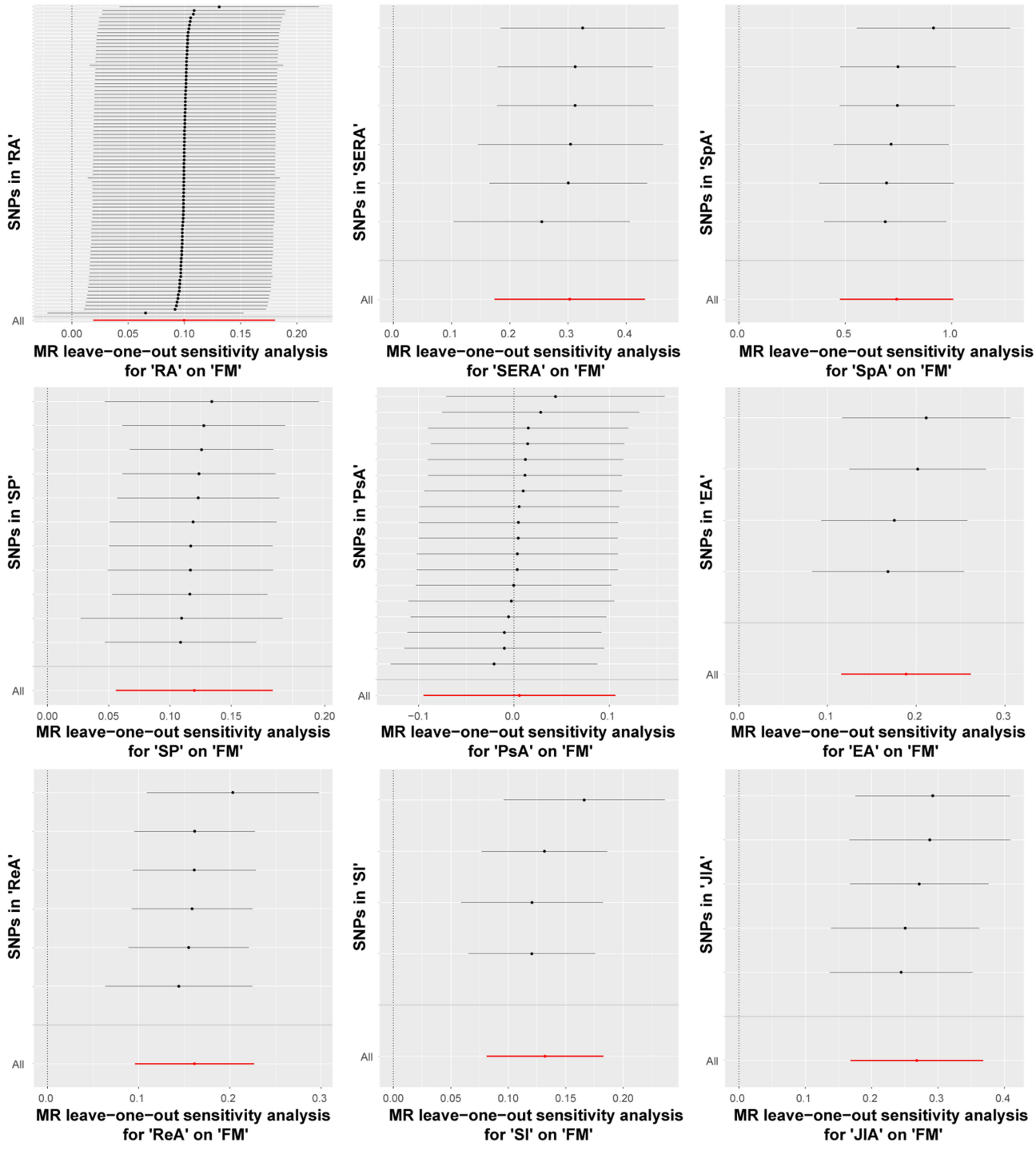

Figure 5 "Leave-one-out" plots of positive MR results for causal relationship between IA subtypes and FM. Leave-one-out sensitivity analyses demonstrate the impact of individual SNPs on the causal estimates for the association between IA subtypes and FM. Each horizontal line represents the causal estimate excluding one SNP at a time, with the red line indicating the overall estimate. Consistency across lines suggests robust results.

Abbreviations: FM, Fibromyalgia; RA, Rheumatoid Arthritis; SERA, Seronegative Rheumatoid Arthritis; SpA, Spondyloarthritis; SP, Spinal Arthritis; PsA, Psoriatic Arthritis; EA, Enteropathic Arthritis; ReA, Reactive Arthritis; SI, Sacroiliitis; JIA, Juvenile Idiopathic Arthritis; MR, Mendelian Randomization; SNP, Single Nucleotide Polymorphism.

pathways involved in neurotransmitter synthesis. Korte-Bouws et al[33] have demonstrated that JIA patients with high disease activity exhibit dysregulated tryptophan metabolism, a critical process for serotonin production, which plays a crucial role in modulating both pain perception and immune response. Similarly, Alfaro-Rodríguez et al[34] have shown that imbalances within the kynurenine pathway, driven by proinflammatory cytokines, contribute to both pain and

depressive symptoms in FM. These metabolic disruptions, resulting from prolonged inflammatory states, may predispose individuals to FM by affecting central pain processing and neurotransmitter regulation.

In contrast, this study found no significant causal relationship between PsA and FM, making PsA the only IA subtype in this study to exhibit a non-significant association with FM. This result suggests that the pathophysiological mechanisms of PsA may not directly influence FM pathogenesis, or alternately, the effect size may be too small to achieve statistical significance. A potential explanation lies in the distinct clinical and immunopathological features of PsA. Unlike other forms of IA, PsA is characterized by a predominant association with enthesitis and axial involvement, with a relatively lower systemic inflammatory burden compared to conditions such as RA and EA.[35] Furthermore, the immunological profile of PsA, primarily driven by the *IL-23/Th17* axis, differs significantly from the pro-inflammatory pathways associated with *TNF-α* and *IL-6*, which are more closely linked to FM pathogenesis.[36]

This study has its own set of limitations: (1) The validity of causal inferences is dependent on the robustness of the genetic instruments used. (2) The genetic data are primarily derived from specific populations, which limits the generalizability to ethnically diverse groups. (3) Additionally, the study does not take gene-environmental interactions into consideration, such as the influence of diet, physical activity, or psychological stress. (4) While the MR design minimizes confounding from post-onset factors, our findings represent the effect of the genetic liability to IA subtypes in general; we could not assess potential effect modification by specific disease subsets, severity states, or treatments within each IA category using summary-level data.

In summary, this study provides convincing evidence that most IA subtypes exert varying degrees of causal influence on FM pathogenesis, advancing our understanding of the systemic effects of inflammatory diseases and the interconnections between peripheral inflammation and central pain modulation. Clinically, these findings underscore the importance of early identification and targeted interventions to mitigate the risk of FM in IA patients. Effective management of chronic inflammation and central sensitization could reduce the burden of these coexisting conditions. The study supports personalized medicine approaches, where therapeutic interventions can be tailored to individual patients based on their specific inflammatory profiles. Furthermore, it highlights the necessity of a multidisciplinary approach, integrating expertise from both rheumatology and pain management to optimize patient outcomes. The robustness of the MR analysis strengthens the generalizability of these findings, although further studies are required to explore the underlying mechanisms in diverse populations and clinical settings.

Conclusion

In summary, this study provides compelling evidence for the causal role of chronic inflammation, particularly in RA, EA, and JIA, in the development of FM. The central mechanisms driving this relationship include neuroinflammation, central sensitization, and the gut-brain axis. Our findings emphasize the need for early identification and intervention in IA patients at risk for FM, focusing on both inflammatory and central pain pathways. Furthermore, targeting gut microbiota may offer new therapeutic strategies for managing FM in individuals with IA. While this study represents an important step in understanding the relationship between IA and FM, further research is needed to elucidate the underlying molecular mechanisms and explore potential therapeutic interventions.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics Statement

This study utilized publicly available summary-level genetic data obtained exclusively from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). As documented by the IEU Open GWAS initiative, all original GWAS contributing data to this repository received prior ethical approval from relevant IRBs or national ethics committees. Informed consent was obtained from all participants in the original studies, explicitly permitting the anonymized use of their genetic data for secondary research. In accordance with Article 32(1) and 32(2) of the Ethical Review Measures for Life Sciences and Medical Research Involving Humans (jointly issued by China's National Health Commission, Ministry of Education,

Ministry of Science and Technology, and National Administration of Traditional Chinese Medicine on February 18, 2023), research involving legally acquired public data or open-access databases with anonymized information is exempt from further ethical review. As this study solely repurposed pre-approved, publicly available, and non-identifiable data from IEU Open GWAS, it falls under this exemption.

Consent for Publication

The manuscript is original, has not been previously published, and is not under consideration elsewhere. All necessary permissions for third-party content have been obtained and properly credited. The manuscript will be published and made publicly available in accordance with the journal's publication policy.

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Disclosure

Zhong Zhang is now affiliated with The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, People's Republic of China. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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