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ORIGINAL RESEARCH

Bidirectional Two-Sample Mendelian Randomization Analysis Reveals Causal Associations Between Modifiable Risk Factors and Fibromyalgia

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Introduction: This study aims to investigate the potential causal effects of modifiable risk factors on Fibromyalgia (FM).

Methods: Genetic variants associated with 34 exposure factors were obtained from Genome-wide association studies (GWAS). Summary statistics for FM were acquired from the FinnGen consortium. Bidirectional Mendelian randomization (MR) analysis was conducted between all exposures and outcomes. The inverse-variance weighted (IVW) method was employed as the primary estimation technique. Heterogeneity and pleiotropy were assessed using MR-PRESSO global test, the weighted median, Cochran's Q statistic and MR-Egger.

Results: Depression (OR=2.087, 95% CI: 1.466–2.971), alcohol consumption (OR=1.489, 95% CI: 1.094–2.028), body fat percentage (OR=1.524, 95% CI: 1.153–2.013) and body mass index (BMI) (OR=1.542, 95% CI: 1.271–1.872) were associated with an increased risk of FM among genetically susceptible individuals. Conversely, higher education level (OR=0.404, 95% CI: 0.297–0.549), longer years of education (OR=0.489, 95% CI: 0.290–0.825) and higher household income (OR=0.328, 95% CI: 0.215–0.502) were protective against FM. Additionally, rheumatoid arthritis (OR=1.138, 95% CI: 1.061–1.221) and ankylosing spondylitis (OR=1.079, 95% CI: 1.021–1.140) were identified as important risk factors for FM.

Conclusion: This MR study unveiled a complex causal relationship between modifiable risk factors and FM. Psychosocial factors significantly increase the odds of FM, while obesity and some autoimmune diseases that frequently coexist with FM demonstrate causal associations. Additionally, lifestyle habits such as alcohol consumption are causally related to FM. Further investigation is needed to determine whether risk factors contribute to the pathogenesis of FM through mechanisms involving central sensitization, inflammatory, and hyperalgesia. This study enhances our understanding of the factors that drive FM onset and progression, offering valuable insights for future targeted prevention and treatment strategies.

Keywords: fibromyalgia, modifiable risk factors, causal association, Mendelian randomization

Introduction

FM is a chronic diffuse pain syndrome characterized by multisite pain, severe fatigue, stiffness, sleep disturbances, cognitive deficits, and psychological problems.[1] The prevalence of fibromyalgia worldwide ranges between 2% and 4% across all populations.[2] Unlike nociceptive pain, which results from tissue damage, and neuropathic pain, which arises from nerve damage, nociplastic pain frequently lacks definitive evidence of tissue injury or identifiable pathology within the somatosensory system, and it is often caused by reversible changes in the nervous system. These changes increase the sensitivity of the system that controls which stimuli should be interpreted as pain and which should not. This type of pain is consistent with fibromyalgia as part of the classification group of central sensitization syndrome disorders. As a result,

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FM is classified as a type of nociplastic pain.[3] The pathophysiology of FM is still poorly understood, but it is thought that augmented central nervous system (CNS) pain and sensory processing and altered pain modulation play prominent roles.

The incidence of FM is steadily rising due to population aging in major global economies, escalating psychological stress, and worsening lifestyle habits. There is a growing concern for early identification and improved diagnostics of FM. Psychosocial factors are among the most significant influencers. Notable physical and psychological stresses such as work and school stress, daily life concerns, anxiety, and depression can elevate the incidence of FM,[2] with depression and anxiety potentially affecting 25% to 65% of FM patients.[4] FM is believed to be associated with various autoimmune disorders, including autoimmune hypothyroidism, irritable bowel syndrome(IBS), celiac disease, and most musculoskeletal rheumatologic conditions.[5] A US registry study further suggests a close relationship between hypothyroidism and FM.[6] Additionally, FM often coexists with other chronic diseases that may share similar central mechanisms or arise due to secondary central sensitization, with research indicating FM prevalence in 20% to 30% of patients with inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE).[7] Several analyses have reported that peripheral blood concentrations of pro-inflammatory cytokines, including interleukin (IL)-6, IL-17, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, are associated with the severity of FM symptoms in patients.[8,9] A longitudinal community study revealed that women with insomnia had twice the risk of developing new-onset fibromyalgia, whereas high levels of physical activity conferred protective effects.[10] Overweight or obese women were at a higher risk of developing fibromyalgia compared to women with normal weight.[11] A meta-analysis demonstrated the effectiveness of vitamin D supplementation in reducing scores on the Fibromyalgia Impact Questionnaire.[12] Dietary interventions, including vitamin and mineral supplementation, vegetarian diets, and Mediterranean diets, have shown potential efficacy in alleviating symptoms of FM.[13] Although numerous studies have shown associations between these factors and FM, most of them are cohort or cross-sectional studies. There is substantial heterogeneity in the objectives of these studies, and the associations between various factors and FM may occasionally be contradictory, thereby limiting their capacity to establish a causal relationship.

Mendelian randomization (MR) is a method of causal inference based on genetic variations. This approach allows researchers to analyze the effects of environmental factors, drug treatments, and other influences on human biology and diseases.[14] This study design provides an unbiased estimation of the influence of hypothesized causal variables without requiring traditional randomized controlled trials, which are the gold standard for establishing causality in epidemiology.[15] MR analysis investigates potential causal relationships between exposures and outcomes by utilizing single nucleotide polymorphisms (SNPs) as instrumental variables (IVs). During meiosis, random classification effectively segregates the population of SNPs into effect and control groups for risk factors based on each individual's genetic characteristics, thereby reducing potential confounding effects that might influence traditional multivariate regression methods, akin to randomized controlled trials.[16] Many studies have used the MR method to explore the potential causal relationships between exposure factors and associated diseases, thereby clarifying the causal links between exposures and outcomes. Numerous researchers have applied this approach to determine the relationship between certain exposures and pain. For instance, in studies examining the connections between coffee, alcohol consumption, smoking, and migraine, Yuan S demonstrated through the MR method that smoking is a potential cause of pain.[17] FM, a syndrome with unclear etiology, is associated with depression, sleep disturbances, and other cognitive and somatic symptoms.[18,19] However, there is a lack of causal analysis regarding these associations with FM. In this study, we conducted a two-sample MR analysis using high-quality GWAS data from a large consortium to evaluate the causal effects of various exposures on FM outcomes. Obtaining robust causal inferences regarding these associations is crucial for devising effective intervention strategies.

Materials and Methods

Figure 1 depicts a schematic diagram of the study. In this study, the risk factors were classified into four categories: psychosocial factors, lifestyle factors, obesity-related factors, and autoimmune and inflammatory factors. Subsequently, eligible SNPs were selected to assess the causal relationship between exposure factors and the risk of developing the outcome variable, employing a combination of statistical methods. Exposure factors and outcome variables will be interchanged in each analysis to investigate the presence of reverse causality between them. This study adheres to the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting (Table S1).

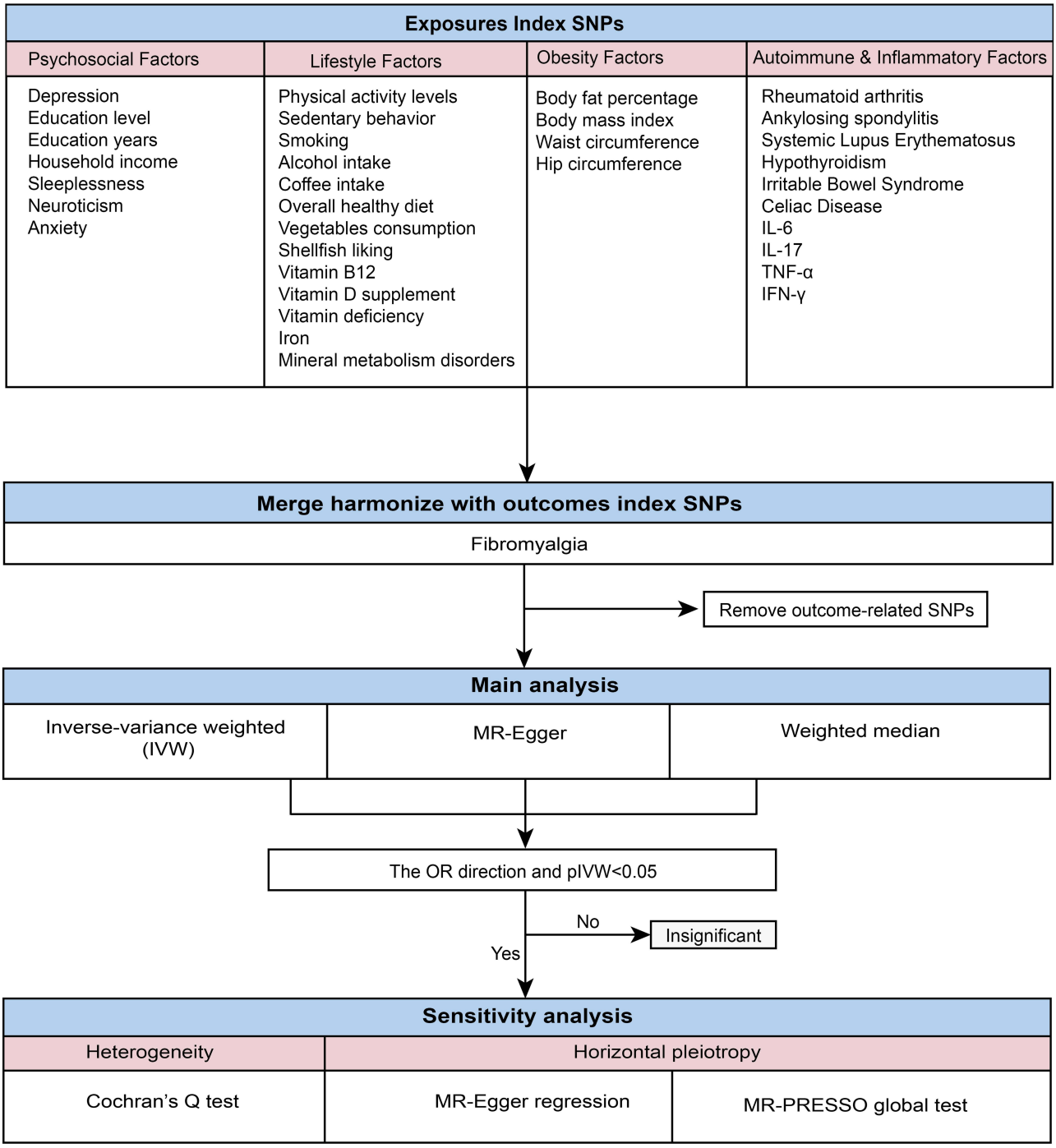

Figure 1 Overall design of the MR analysis in this Mendelian randomization study.
Abbreviations: IVW, inverse-variance weighted; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier; SNPs, single-nucleotide polymorphisms.

Data on Fibromyalgia

The FM dataset was obtained from FinnGen biobank analysis round 10(finngen_R10_M13_FIBROMYALGIA), with a case size of 2689 and a control group of 299,606 individuals and containing 21,303,253 SNPs. The diagnosis of FM was based on ICD-10 – M79.7.

Data on IVs

All exposure-related IVs were derived from GWAS conducted in individuals of European ancestry. IVs pertaining to smoking,[20] household income,[21] education level[22] and education years[23] were obtained from SSGAC (Social Science Genetic Association Consortium). Data on alcohol intake, coffee intake, sleepless, and obesity characteristics (including waist circumference, hip circumference, and body fat percentage) were retrieved from the MRC-IEU.[24] Summary statistics for depression[25] and body mass index (BMI) were obtained from the UK Biobank, while those for vitamin D supplements,[26] physical activity levels,[27] sedentary behavior,[28] overall healthy diet,[29] vegetables consumption,[29] shellfish liking,[30] iron,[31] vitamin B12,[31] IL-6,[32] IL-17,[33] TNF-α,[33] IFN-γ,[33] and neuroticism[34] were derived from relevant GWAS studies. IVs for anxiety, rheumatoid arthritis, SLE, hypothyroidism, IBS, vitamin deficiency, Coeliac disease, disorders of mineral metabolism and ankylosing spondylitis were sourced from the FinnGen Consortium. These GWAS data can be found in Table 1.

Table 1 GWAS Data Sources for Instrumental Variables Selection

Risk Factors	GWAS ID	Sample Size	Ancestry
Psychosocial Factors			
Depression	GCST007342	807,553	European
Education level	ieu-a-1239	766,345	European
Education years	GCST003676	405,072	European
Household income	GCST009523	286,301	European
Sleeplessness	ukb-b-3957	462,341	European
Neuroticism	GCST006476	449,484	European
Anxiety	finngen_R10_KRA_PSY_ANXIETY_EXMORE	346,542	European
Lifestyle Factors			
Physical activity levels	GCST006097	377,234	European
Sedentary behavior	GCST90104345	372,609	European
Smoking	GCST007327	518,633	European
Alcohol intake	ukb-b-5779	462,346	European
Coffee intake	ukb-b-5237	428,860	European
Overall healthy diet	GCST90096893	258,758	European
Vegetables consumption	GCST90096900	428,979	European
Shellfish liking	GCST90094838	155,491	European
Vitamin B12	GCST90012772	19,415	European
Vitamin D supplement	GCST005367	79,366	European
Vitamin deficiency	finngen_R10_VIT_DEF	388,454	European
Mineral metabolism disorders	finngen_R10_E4_MINERAL_MET	354,664	European
Iron	GCST90012683	15,335	European
Obesity Factors			
Body fat percentage	ukb-b-8909	454,633	European
Body mass index	ukb-b-2303	454,884	European
Waist circumference	ukb-b-9405	462,166	European
Hip circumference	ukb-b-15590	462,117	European
Autoimmune & Inflammatory Factors			
Rheumatoid arthritis	finngen_R10_M13_RHEUMA	276,465	European
Ankylosing spondylitis	finngen_R10_M13_ANKYLOSPON	297,932	European
Systemic Lupus Erythematosus	finngen_R10_SLE_FG	308,307	European
Hypothyroidism	finngen_R10_E4_HYTHY_AI_STRICT	344,168	European
Irritable Bowel Syndrome	finngen_R10_K11_IBS	339,710	European
Coeliac disease	finngen_R10_K11_COELIAC	398,506	European
IL-6	GCST90274815	14,743	European
IL-17	GCST004442	7,760	European
TNF-α	GCST004426	3,454	European
IFN-γ	GCST004456	7,701	European

Genetic Instruments Selection

Initially, if the number of SNPs meeting the significance threshold of 5×10^{-8} was less than 3.[35,36] A more lenient threshold of 1×10^{-5} was established accordingly. Secondly, SNPs that were not in linkage disequilibrium (LD) with other SNPs ($r^2 < 0.01$ within a clumping window of 10,000 kb) were employed as instruments for these diseases. Proxy SNPs with LD set to $r^2 > 0.8$ were utilized in cases where no SNP in the resulting dataset met this criterion. To ensure the robustness of the selected SNPs, we also calculated the F-statistic, which was deemed sufficiently strong at 10 to mitigate any weak instrumental bias.[37]

Statistical Analysis

The fixed-effects inverse variance weighting (IVW) approach was employed as the primary analysis method to assess the causal effects of multiple SNPs.[38,39] The direction of sensitivity analyses using IVW analyses is aligned with that of the sensitivity analyses using MR-Egger and weighted median analyses. If instrumental variables can directly influence the results independently of exposure factors, it violates the principle of Mendelian randomization, indicating the presence of horizontal pleiotropy in the test outcomes. Thus, the simple median method, weighted median method, and MR Egger regression method were employed to validate the findings and assess stability. IVW methods yield highly effective outcomes, contingent upon the validity of all instrumental variables.[39] The weighted median approach yields consistent effect estimates when < 50% of genetic variation is invalid,[38] whereas the MR-Egger approach offers estimates adjusted for pleiotropic effects, albeit with reduced statistical efficacy,[40] The Cochran Q test was employed to assess heterogeneity among instrumental variables, where a P-value > 0.05 indicates low heterogeneity likelihood.[41] The MR Egger intercept test was utilized to evaluate the existence of horizontal pleiotropy, with a statistically significant intercept term suggesting its presence in the study.[40] Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) were employed to identify outliers, and if detected, the analysis was rerun to identify after outlier removal.[40] If the global p value remained significant, Radial MR was additionally employed to identify and eliminate outliers.[42] "Leave-one-out" sensitivity analyses were performed to evaluate the impact of individual genetic variations on the overall causal effect by systematically excluding one SNP at a time.[43] All statistical analyses were conducted using the "TwoSampleMR" package in R software version 4.3.2, and the results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The significance level was set at α=0.05.

Results

MR analysis was conducted to assess the presence of a causal relationship between risk factors and FM. Detailed results can be found in Table S2. We identified several risk factors influencing FM (Table 2, Figures 2 and 3). The characteristics of the selected SNPs are presented in Table S3. Given that the F-statistics for all SNPs ranged from 10.78 to 113289.22, we observed a low risk of substantial weak instrumental bias.

Psychosocial Factors

The results of the causal analysis of FM-related psychosocial factors are shown in Table 2 and visualized in Figures 2 and 3. Several psychosocial factors were associated with increased odds of developing fibromyalgia (FM). Depression (OR=2.087, 95% CI: 1.466–2.971, P= 4.480×10^{-5}) significantly contributed to FM. Conversely, education level (OR=0.404, 95% CI: 0.297–0.549, P= 6.780×10^{-9}), years of education (OR=0.489, 95% CI: 0.290–0.825, P= 0.007), and household income (OR=0.328, 95% CI: 0.215–0.502, P= 2.640×10^{-7}) were inversely associated with FM odds. Educational attainment and years of schooling represent distinct aspects of educational background, and cross-validation was conducted using diverse source databases. No significant association was observed between sleeplessness, neuroticism, anxiety, and the likelihood of FM.

Table 2 Main Results of the MR Analysis

Risk Factors	nNSPs	Method	OR (95% CI)	SE	p value
Psychosocial factors					
Depression	40	IVW	2.087 (1.466, 2.971)	0.180	4.48×10^{-5}
Education level	256	IVW	0.404 (0.297, 0.549)	0.156	6.78×10^{-9}
Education years	61	IVW	0.489 (0.290, 0.825)	0.267	7.32×10^{-3}
Household income	109	IVW	0.328 (0.215, 0.502)	0.216	2.64×10^{-7}
Sleeplessness	32	IVW	5.277 (2.040, 13.649)	0.485	6.03×10^{-3}
Neuroticism	7	IVW	0.604 (0.112, 3.252)	0.859	5.57×10^{-1}
Anxiety	10	IVW	2.076 (1.145, 3.767)	0.304	1.62×10^{-2}
Lifestyle factors					
Physical activity levels	18	IVW	0.624 (0.179, 2.171)	0.636	4.59×10^{-1}
Sedentary behavior	7	IVW	0.527 (0.250, 1.108)	0.379	9.13×10^{-2}
Smoking	125	IVW	1.625 (1.131, 2.334)	0.185	8.69×10^{-3}
Alcohol intake	88	IVW	1.489 (1.094, 2.028)	0.157	1.14×10^{-2}
Coffee intake	35	IVW	0.674 (0.334, 1.359)	0.358	2.70×10^{-1}
Overall healthy diet	15	IVW	1.373 (0.790, 2.386)	0.282	2.61×10^{-1}
Vegetables consumption	25	IVW	1.187 (0.487, 2.891)	0.454	7.06×10^{-1}
Shellfish liking	28	IVW	1.061 (0.874, 1.288)	0.099	5.51×10^{-1}
Vitamin B12	19	IVW	0.997 (0.800, 1.243)	0.113	9.79×10^{-1}
Vitamin D supplement	7	IVW	1.211 (0.676, 2.170)	0.191	2.98×10^{-1}
Vitamin deficiency	26	IVW	1.019 (0.957, 1.086)	0.032	5.55×10^{-1}
Mineral metabolism disorders	20	IVW	0.990 (0.900, 1.088)	0.048	8.28×10^{-1}
Iron	21	IVW	0.990 (0.812, 1.206)	0.101	9.18×10^{-1}
Obesity factors					
Body fat percentage	335	IVW	1.524 (1.153, 2.013)	0.142	3.04×10^{-3}
Body mass index	333	IVW	1.542 (1.271, 1.872)	0.099	1.13×10^{-5}
Waist circumference	316	IVW	1.229 (0.944, 1.600)	0.135	1.26×10^{-1}
Hip circumference	362	IVW	1.146 (0.938, 1.399)	0.102	1.82×10^{-1}
Autoimmune & inflammatory factors					
Rheumatic arthritis	21	IVW	1.138 (1.061, 1.221)	0.036	3.00×10^{-4}
Ankylosing spondylitis	13	IVW	1.079 (1.021, 1.140)	0.028	6.77×10^{-3}
Systemic Lupus Erythematosus	6	IVW	1.041 (0.956, 1.133)	0.043	3.54×10^{-1}
Hypothyroidism	137	IVW	1.058 (0.982, 1.140)	0.038	1.36×10^{-1}
Coeliac disease	19	IVW	1.016 (0.976, 1.058)	0.020	4.28×10^{-1}
Irritable Bowel Syndrome	20	IVW	1.227 (1.025, 1.469)	0.092	2.60×10^{-2}
IL-6	12	IVW	1.105 (0.885, 1.381)	0.114	3.78×10^{-1}
IL-17	16	IVW	1.141 (0.928, 1.404)	0.106	2.11×10^{-1}
TNF-α	11	IVW	0.926 (0.794, 1.081)	0.079	3.32×10^{-1}
IFN-γ	11	IVW	0.983 (0.783, 1.233)	0.116	8.79×10^{-1}

Abbreviations: IVW, Inverse-Variance Weighted; nSNPs, Number of Single-Nucleotide Polymorphisms; SE, Standard Error.

Lifestyle Factors

The causal analysis of lifestyle factors on FM are presented in Table 2 and visualized in Figures 2 and 3. Alcohol intake (OR=1.489, 95% CI: 1.094–2.028, P= 0.011) was significant factor predisposing to FM. Vitamin D supplement was not associated with the risk of FM. In the IVW analysis, no significant causal relationships were identified between the odds of developing fibromyalgia and various factors, including physical activity levels, sedentary behavior, coffee intake, smoking, disorders of mineral metabolism (serum or plasma iron levels), vitamin deficiency (serum or plasma vitamin B12 levels), and dietary habits, such as overall healthy diet, vegetable consumption, and shellfish consumption.

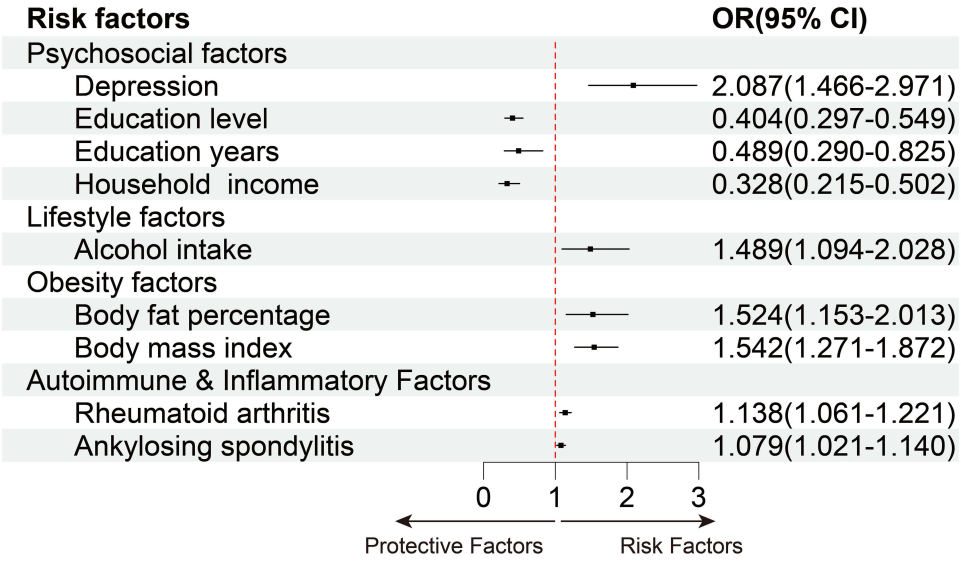

Figure 2 Forest plot to visualize the causal effect of related risk factors on FM.
Abbreviation: OR, odds ratio; CI, confidence interval.

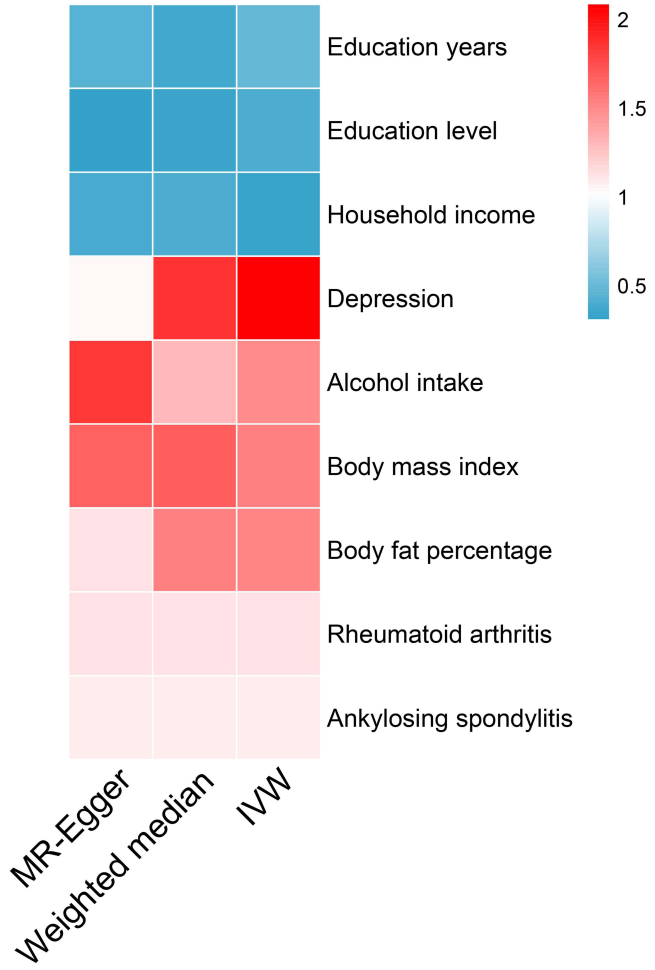

Figure 3 Heatmap of significant exposure OR values identified through IVW, MR-Egger, and Weighted Median analyses. The color of each block represents the OR values of each MR analysis, OR < 1 is shown in blue and OR > 1 is shown in red.

Obesity Factors

The results of the causal analysis of FM-related obesity factors are shown in Table 2 and visualized in Figures 2 and 3. Body fat percentage (OR=1.524, 95% CI: 1.153–2.013, P= 0.003) was associated with higher odds of FM. IVW analysis revealed an association between high BMI and FM odds. After removing outliers using MR-PRESSO, the causal link between BMI and FM remained significant (OR=1.542, 95% CI: 1.271–1.872, P=1.126× 10^{-5}). There was no association between waist/hip circumference and the odds of FM.

Autoimmune and Inflammatory Factors

The causal analysis of autoimmune and inflammatory factors on FM are presented in Table 2 and visualized in Figures 2 and 3. RA (OR=1.138, 95% CI: 1.061–1.221, P=3.000× 10^{-4}) was meaningful facilitators to FM. IVW analysis revealed an association between ankylosing spondylitis and FM odds (OR=1.067, 95% CI: 1.001–1.138). Following outlier removal with MR-PRESSO, the causal association between ankylosing spondylitis and FM remained significant (OR=1.079, 95% CI: 1.021–1.140, P= 0.007). No causal relationship exists between FM and SLE, autoimmune hypothyroidism, celiac disease, IBS, or inflammatory cytokines (IL-6, IL-17, TNFα, INF-γ).

Reverse MR Analysis

We analyzed FM as the exposure and various risk factors as the outcomes. The causal analysis results were presented in Table S4. The potential reverse associations of smoking (OR = 1.007, 95% CI: 1.002–1.013, P = 0.008), hypothyroidism (OR = 1.024, 95% CI: 1.004–1.043, P = 0.018), and IBS (OR = 1.070, 95% CI: 1.032–1.110, P = 2.794 × 10^{-4}) with FM were identified. No evidence supported a reverse causal relationship between FM and other risk factors.

Sensitivity Analysis

Neither Cochran's Q test nor the MR-PRESSO global test revealed any significant heterogeneity for various risk factors and FM. No horizontal pleiotropy was detected by the MR-Egger intercept test. The results of sensitivity analyses are shown in Table 3.

Table 3 Heterogeneity and Pleiotropy of the Causal Effects on FM

Exposures	Cochrane's *Q* Test		MR-Egger Intercept Test		MRPRESSO Global Test *p* value
	Q-Value	p_Q	Intercept	$p_{intercept}$	
Psychosocial factors					
Depression	45.7963	0.2109	0.0209	0.5393	0.2254
Education level	193.7582	0.9856	0.0007	0.9301	0.9862
Education years	62.0319	0.3015	−0.0010	0.9647	0.3092
Household income	129.3430	0.0791	−0.0026	0.8566	0.0840
Lifestyle factors					
Alcohol intake	101.8938	0.1313	−0.0052	0.6558	0.1258
Obesity factors					
Body mass index	266.8291	0.9964	−0.0015	0.7654	0.9970
Body fat percentage	252.6678	0.9917	−0.0012	0.8346	0.9938
Autoimmune & Inflammatory Factors					
Ankylosing spondylitis	16.3926	0.1739	0.0018	0.9474	0.1982
Rheumatoid arthritis	15.0934	0.7710	0.0019	0.8790	0.7202

Abbreviations: MR-PRESSO, Mendelian Randomization-Pleiotropy Residual Sum and Outlier.

Discussion

Despite the refinement of fibromyalgia diagnostic criteria, the pathogenesis and diagnostic criteria remain controversial, leading to a substantial number of physicians being unable to effectively recognize the disease or develop treatment strategies. Fibromyalgia, as a syndrome, often accompanies multiple comorbidities. To gain a deeper understanding of potential causality, we utilized the MR approach to assess the relationship between lifestyle, psychosocial factors, obesity, autoimmune and inflammatory factors, and fibromyalgia. The present study identified depression and alcohol consumption as risk factors for FM, while individuals with higher education level and household income had a reduced risk. Moreover, elevated body fat percentage and BMI were shown to significantly elevate FM risk. Rheumatoid arthritis and ankylosing spondylitis also contribute to FM. Our reverse MR analysis suggests that FM may act as a promoter of smoking behavior, IBS, and autoimmune hypothyroidism.

Previous studies have indicated a significant association between FM and psychological or psychiatric disorders.[2] However, the role of psychological disorders in the etiology of FM remains unclear. With the advancement of functional brain imaging techniques, it has been observed that emotional processing in depressed patients is topologically shifted toward the insular cortex, which is implicated in pain perception.[44] Several monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, are implicated in both depression and pain.[45] Therefore, the primary etiological hypothesis suggests that these neurotransmitters share common underlying pathophysiological processes and neurobiological mechanisms. Our findings suggest that depression could potentially have a causal role in FM. Interventions targeting depression might consequently lower the odds of FM. Additionally, in the management of depression concurrent with somatic pain syndromes, a systematic evaluation and network meta-analysis of 36 randomized clinical trials involving 11,930 fibromyalgia patients demonstrated that duloxetine (120 mg) exhibited superior efficacy in alleviating both pain and depression.[46] FM is not merely an unpleasant sensory experience but is considered to involve levels of education and cognition, in accordance with the modern biopsychosocial model of medicine.[19] Our study revealed a causal relationship between education level and years of education with FM. Notably, higher education was identified for the first time as an independent protective factor against FM. This finding may be attributed to individuals with lower education level resorting to maladaptive coping strategies when experiencing pain, which includes overreacting to pain stimuli, avoidance, and catastrophizing. These behaviors impact the intensity of subjective pain sensation and lead to heightened activation of relevant brain regions.[47–49] Additionally, we observed reduced odds of FM prevalence among populations with higher household incomes, consistent with findings from a cross-sectional study conducted in Spain.[50] Several studies have indicated an association between sleep disorders, neuroticism, and anxiety with an elevated risk of FM.[51–53] However, our investigation did not uncover evidence supporting a causal relationship between these factors and the risk of FM. These findings imply that insomnia, neuroticism, and anxiety might exert their influence on FM through other pathways.

Riley and King reported that up to 25% of pain patients use alcohol for analgesia,[54] however, its analgesic effect is linked to susceptibility to alcohol dependence. Currently, strong evidence linking alcohol to FM is lacking. However, our analysis using MR analysis revealed a causal relationship between alcohol intake and increased FM risk. Several studies have demonstrated that alcohol activate similar neuronal circuits, potentially contributing to pain signaling dysregulation.[55] Certain data suggest that it may trigger inflammatory factors that influence central and peripheral pain sensitization.[56] Our study did not identify a causal link between vitamin D intake and FM. Large-scale clinical trials are needed to assess the clinical effectiveness of vitamin D supplementation in preventing and treating FM. While some studies suggest that coffee intake is linked to improved quality of life in FM patients,[57] we did not find evidence of a causal relationship in our study. Evidence indicates that smoking behavior may be a risk factor for specific chronic pain conditions. The results of our MR analysis did not support a causal relationship between smoking behavior and the odds of FM. Although animal studies support the analgesic effects of tobacco and nicotine, findings from human studies are less consistent.[58] Our MR analysis suggested that FM may serve as a predisposing factor for smoking behavior. Existing studies primarily examine the impact of nicotine and tobacco on pain, whereas the initial experimental study by Ditre and Brandon revealed that situational pain could strongly motivate smoking behavior.[59] While some meta-analyses have confirmed that exercise can improve the quality of life in patients with FM,[60] our MR analysis of physical activity,

sedentary behavior, and FM did not reveal a significant causal relationship. This lack of association may be due to the varying therapeutic effects of different types and intensities of exercise on FM. Recent evidence suggests that imbalances in nutrients, including micronutrients and vitamins, may contribute to the odds of FM.[61] Although our MR analysis of mineral metabolism disorders and vitamin deficiencies did not establish a clear cause-and-effect relationship, certain mineral and vitamin supplements might mitigate oxidative stress and bolster the immune system, potentially benefiting FM treatment. Exacerbation of FM symptoms has been associated with carbohydrate-rich diets.[62] Our MR analysis did not reveal a causal relationship between specific diets, such as the Mediterranean diet, vegetable-rich diets, or shellfish intake, and FM. However, numerous studies confirm the beneficial effects of a healthy diet in alleviating FM symptoms,[61] indicating that various nutrients can influence these symptoms. The exact mechanisms underlying these effects warrant further investigation.

Obesity is a growing concern in global health, with varying prevalence across different geographical regions, and it is strongly linked to musculoskeletal disorders.[63] In this study, we also found a causal relationship between higher body fat percentage, BMI, and FM. Systematic evaluation studies have demonstrated a significant association between obesity and the severity of FM pain, providing various mechanisms to explain this relationship. The most direct association is that obesity can cause joint and muscle overload, leading to widespread input of injurious stimuli from the periphery, which can induce central sensitization.[2] Obese individuals have been found to have significantly lower pain thresholds and a stronger correlation between body weight and pain sensitivity.[64] Studies have demonstrated that circulating levels of leptin, a hormone derived from excess body fat in obese individuals, are associated with pain in postmenopausal women and FM patients.[65] MR studies did not reveal a causal relationship between waist and hip circumference and FM. Different fat distributions exhibit distinct metabolic properties; subcutaneous fat, for example, has lower basal lysis and lipolytic stimulation compared to visceral fat, potentially reducing the release of free fatty acids into the bloodstream.[66] It remains unclear whether the risk of disease varies depending on the site of subcutaneous fat accumulation.

Pain is a significant clinical feature of rheumatoid arthritis (RA), typically characterized by predominantly nociplastic pain in patients, which involves enhanced central nervous system pain and sensory processing.[67] Through MR analysis, we identified a causal link between RA and FM. This explains why, despite achieving excellent inflammation control in RA, patients still experience significant pain and fatigue, driven by enhanced central system sensitization that is unresponsive to peripheral treatments, potentially contributing to the persistence of pain.[68] Central sensitization refers to an enhanced responsiveness of neurons in the central nervous system to normal or subthreshold stimuli and is considered a key factor in the odds of FM. Evidence suggests that FM patients experience altered diffuse pain processing in the brain, indicating increased activation in brain regions specifically responsible for pain.[69] The functional activation and connectivity of endogenous pain inhibition signals are also altered in FM patients, leading to an imbalance in the nociceptive pain modulation system.[70] Additionally, reduced μ-opioid receptor availability has been observed in the medulla, amygdala, and dorsal cingulate cortex of FM patients.[71] Furthermore, in terms of nociception, FM patients exhibit reduced gray matter in cortical and subcortical regions, such as the cingulate cortex, orbitofrontal cortex, and insula, which are involved in processing noxious stimuli. However, the causal relationship between these changes and chronic pain or hyperalgesia remains unclear.[19] A retrospective study from Taiwan revealed that ankylosing spondylitis patients have an increased risk of FM,[72] a finding corroborated by our MR analysis, suggesting a significant causal association between ankylosing spondylitis and FM. Mechanistic studies have primarily centered on central sensitization and hyperalgesia, with one study confirming the induction of type I helper T cells (TH1) to the spinal cord in ankylosing spondylitis patients, resulting in pain hypersensitivity.[73,74] Hyperalgesia, defined by heightened pain sensitivity, is a hallmark of fibromyalgia. This condition may be driven by an overabundance of excitatory neurotransmitters involved in pain modulation within the brain and spinal cord.[75] While the precise causes of these nociceptive changes are difficult to determine, it is evident that fibromyalgia is unlikely to arise from a single etiological factor. Inflammatory conditions, particularly neuroinflammation, can activate peripheral nociceptors in C-fibers. Sustained input from these nociceptors can lead to increased excitability and synaptic plasticity in neurons along the central nociceptive pathway, resulting in central sensitization. Numerous studies now support the critical role of central sensitization in maintaining FM symptoms, and centrally acting drugs such as pregabalin and duloxetine have been shown to alleviate FM symptoms.[46] FM is more prevalent in patients with SLE, contributing to pain and physical dysfunction in this population.

We did not identify a causal relationship between SLE and FM by MR analysis, and some studies indicate that FM and SLE activity are not related, and that FM symptoms such as pain in these patients may lead to misinterpretation of SLE activity,[76] which requires further large-scale clinical studies. Other autoimmune-related diseases, such as autoimmune hypothyroidism, IBS, and celiac disease, are often associated with FM.[5] Our MR analysis did not reveal a causal relationship, but reverse causality was observed with hypothyroidism and IBS. Additionally, some studies have shown that a significant proportion of FM patients have thyroid antibodies,[77] and there is a reverse relationship between FM and IBS, which may be linked to the gut microbiota and the gut-brain axis.[78]

Although FM has not traditionally been classified as an inflammatory disease, emerging evidence suggests that low-grade systemic inflammation may play a role in its pathogenesis. Elevated concentrations of pro-inflammatory cytokines, including IL-6, IL-17, IFN-γ, and TNF-α, have been shown to relate with symptom severity in the peripheral blood of FM patients.[8,79] Although our IVW analysis did not establish a causal relationship between these cytokines and FM, this does not rule out the potential involvement of inflammatory factors in the pathogenesis of FM. There is a strong correlation between alcohol consumption, obesity, depression, and inflammation. Metabolites of alcohol can activate immune cells and promote cellular damage by increasing oxidative stress, among other effects.[80,81] These disturbances can, in turn, activate the pain-transducing nervous system. Adipocytes produce pro-inflammatory cytokines that can sustain and amplify pain,[82] potentially explaining the role of obesity as a causative factor in FM. The coexistence of depression with immune-mediated inflammatory diseases is well established, and the close interplay between peripheral and central immune responses suggests shared pathophysiological mechanisms.[83] Depression can heighten the organism's sensitivity to cytokines released in response to various stressors, prolonging the inflammatory process. This prolonged inflammation may contribute to the dysregulation of pain, potentially underlying the pathogenesis of FM in the context of depression. Our Mendelian Randomization analysis did not identify a causal relationship between inflammatory factors and fibromyalgia. This may be due to the inherent complexity of the inflammatory and immune response systems, as well as the possibility that the inflammatory factors we selected as exposure variables did not comprehensively cover the entire spectrum.

Naturally, our study has limitations; the study population consisted predominantly of individuals of European descent and may not fully represent individuals from diverse ethnic backgrounds. Most MR studies have utilized a single exposure-related genetic variable, yet certain risk factors such as obesity can significantly vary with age, potentially introducing bias. Diagnostic criteria for FM are subjective, although the current use of ICD-10 criteria is relatively reasonable, it still has some limitations. Additionally, some exposure data were sourced from the Finnish database, potentially leading to population overlap.

In conclusion, this MR study systematically investigated the causal relationships between FM and four factors: psychosocial factors, lifestyle habits, obesity, and autoimmune and inflammatory factors. We found that psychosocial factors can influence the odds of FM, and that obesity, along with some autoimmune diseases that frequently coexist with FM, may have a causal relationship with the condition. Additionally, lifestyle habits such as alcohol consumption are causally linked to the odds of FM. Further investigation is needed to determine whether risk factors such as depression, alcohol consumption, and obesity contribute to the pathogenesis of FM through mechanisms involving central sensitization, inflammatory immune responses, and hyperalgesia. This study deepens our understanding of the factors influencing FM onset and progression, offering valuable insights for future targeted prevention and treatment strategies.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

As per the regulations outlined in the People's Republic of China's "Notice on the Implementation of Ethical Review Measures for Life Science and Medical Research", our study falls under the exemption criteria specified in Section 4 of the regulation. Therefore, ethics approval was not required for this research, as it met the following conditions:

a. Exemption Premise: The study exclusively utilized publicly available data, specifically summary-level data from Genome-Wide Association Studies (GWAS), which does not involve sensitive personal information, pose harm to individuals, or compromise their privacy.
b. Exemption Provision: Our research adheres to the exemption circumstances outlined in Section 4 of the regulation: We utilized lawfully obtained publicly available data for our analysis.
   The data used in this study were fully anonymized, ensuring the privacy and confidentiality of individuals.
   Our research focuses on analyzing existing data and does not involve interventions, human biological samples, or activities related to reproductive cloning, genetic manipulation, or germ cells.

Due to the nature of our study and its compliance with the exemption criteria, explicit ethics approval was not required. Since the study utilized publicly available data, informed consent from individual participants was not obtained. However, we ensured that all accessed and analyzed data were fully de-identified and in strict compliance with the terms of use and guidelines of the data source. We affirm that this research was conducted in accordance with all applicable laws, regulations, and ethical standards.

Author Contributions

All authors contributed to the data analysis and the drafting or revision of the article. They have agreed on the journal to which the article will be submitted, provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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