A Bidirectional Mendelian Randomization Study on the Causal Association between Psoriasis and Psychiatric Disorders

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Abstract [**Objectives**] To investigate the potential causal relationship between psoriasis and common mental disorders, and to provide genetic epidemiological evidence for the early intervention of mental comorbidities. [**Methods**] Based on publicly available large-scale GWAS data, a bidirectional Mendelian randomization (MR) approach was employed to assess the causal associations between psoriasis and major depressive disorder (MDD), bipolar disorder, schizophrenia, and anxiety disorders. The inverse variance weighted (IVW) method served as the primary analytical tool, supplemented by sensitivity analyses using MR - Egger and weighted median methods. Additionally, a subgroup analysis was conducted for psoriatic arthritis (PsA). [**Results**] Forward MR analysis revealed a significant positive causal association between the genetic predisposition to psoriasis and bipolar disorder as well as MDD, whereas no significant causal relationship was observed with schizophrenia or anxiety disorders. The reverse MR analysis found no causal effect of mental disorders on psoriasis. Subgroup analysis of PsA indicated that its genetic predisposition was significantly associated with the risk of bipolar disorder. The results of various sensitivity analyses and pleiotropy tests supported the robustness of the conclusions. [**Conclusions**] This study provides genetic evidence supporting a causal link between psoriasis and both MDD and bipolar disorder. In particular, patients with PsA are at a higher risk of developing bipolar disorder, highlighting the need to strengthen early screening and intervention for mental health in clinical management.

Key words Psoriasis, Mental disorders, Major depressive disorder, Bipolar disorder, Mendelian randomization

1 Introduction

Psoriasis is a common chronic immune-mediated inflammatory skin disease, with a global prevalence ranging from approximately 0.09% to 11.43%. It not only severely impairs the skin appearance and physiological function of patients but also significantly increases their psychosocial burden and reduces their quality of life[1-2]. Genetic factors play an important role in the pathogenesis of psoriasis, and genome-wide association studies (GWAS) have identified multiple susceptibility loci associated with the disease[3]. In recent years, the association between psoriasis and psychiatric disorders has gained increasing attention. However, previous observational studies have been susceptible to confounding factors and reverse causality, and the causal relationship remains unclear[4]. The Mendelian randomization method, which utilizes genetic variations as instrumental variables, can effectively circumvent the aforementioned research limitations and provide reliable evidence for revealing causal associations. Therefore, based on large-scale GWAS data, this study employs a bidirectional MR approach to systematically evaluate the causal relationship between psoriasis and various psychiatric disorders. It further analyzes the associated risks of the psoriatic arthritis (PsA) subtype, aiming to provide a theoretical basis for the precise prevention and management of psychiatric comorbidities in psoriasis.

2 Data and methods

GWAS summary data for psoriasis, PsA, and four psychiatric disorders were obtained from the GWAS Catalog, IEU OpenGWAS, PGC, and FinnGen databases. All study participants were of European ancestry to minimize population stratification bias. Single nucleotide polymorphisms (SNPs) significantly associated with the exposure factors ($P < 5 \times 10^{-8}$) and independent of each other ($r^2 < 0.001$) were selected as instrumental variables. The inverse-variance weighted (IVW) method was used for the primary causal effect estimation, supplemented by sensitivity analyses including MR - Egger regression and the weighted median method. Heterogeneity among the instrumental variables was assessed using Cochran's Q test, and horizontal pleiotropy was evaluated via the MR - Egger intercept test.

3 Results and analysis

3.1 Basic characteristics of study subjects and instrumental variables This study incorporated GWAS summary statistics for six phenotypes, including psoriasis, psoriatic arthritis (PsA), and four common psychiatric disorders (major depressive disorder, bipolar disorder, schizophrenia, and anxiety disorders). The sources, sample size composition, and population characteristics of the respective study data are presented in Table 1. All study participants were of European ancestry, with a total sample size reaching 902 341, ensuring sufficient statistical power.

According to the predefined instrumental variable selection criteria, 34 SNPs significantly associated with psoriasis were initially identified from the GWAS data for psoriasis. After removing those in linkage disequilibrium (LD), 28 independent SNPs were ultimately included as instrumental variables. Similarly, 29 SNPs were initially screened from the GWAS data for psoriatic arthritis, and after LD pruning, 24 instrumental variables were finally retained. The number and strength assessment results of the instrumental variables for each exposure factor are presented in Table 2. The F statistics for all instrumental variables exceeded 10, indicating no significant weak instrument bias.

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Table 1 Characteristics of GWAS datasets used in this study

Phenotype	Data source	Cases	Control number	Total sample size	Publication year
Psoriasis	FinnGen	9 267	327 892	337 159	2021
Psoriatic arthritis (PsA)	FinnGen	3 984	209 895	213 879	2021
Major depressive disorder (MDD)	PGC	59 851	157 733	217 584	2019
Bipolar disorder	PGC	20 352	31 358	51 710	2019
Schizophrenia	PGC	33 640	43 456	77 096	2018
Anxiety disorder	IEU OpenGWAS	31 977	186 815	218 792	2020

Table 2 Instrumental variable selection and strength

Exposure factors	Number of primary SNPs	Number of SNPs after removal of LD	Range of *F* statistic	Is there a weak instrumental variable
Psoriasis	34	28	31.6 – 89.4	No
Psoriatic arthritis	29	24	28.2 – 76.9	No
MDD	44	35	29.7 – 102.3	No
Bipolar disorder	30	27	33.1 – 91.5	No
Schizophrenia	41	32	26.4 – 84.7	No
Anxiety disorder	36	29	30.8 – 97.6	No

NOTE An *F* statistic > 10 indicates sufficient strength of the instrumental variables, with no significant weak instrument bias.

3.2 Main Mendelian randomization analysis results for psoriasis and psychiatric disorders Using psoriasis as the exposure factor, Mendelian randomization analyses were conducted for four psychiatric disorders, respectively. Results from the inverse variance weighted (IVW) method revealed that genetic predisposition to psoriasis was significantly positively associated with the risk of MDD ($OR = 1.08$, 95% CI: 1.01 – 1.15, $P = 0.027$), and also showed a significant positive causal relationship with the risk of bipolar disorder ($OR = 13.54$, 95% CI: 2.43 – 75.37, $P = 0.002$). These findings suggest that increased genetic risk for psoriasis significantly elevates the risk of developing both MDD and bipolar disorder (Table 3). In contrast, no significant causal associations were observed between psoriasis and schizophrenia ($OR = 3.52$, 95% CI: 0.22 – 55.71, $P = 0.372$) or anxiety disorders ($OR = 0.65$, 95% CI: 0.16 – 2.63, $P = 0.546$) (Table 3).

Table 3 Causal effects of psoriasis on psychiatric disorders

Exposure	Outcome	Methods	*OR*	95% *CI*	*P*
Psoriasis	MDD	IVW	1.08	1.01 – 1.15	0.027
Psoriasis	MDD	Weighted median	1.06	1.00 – 1.13	0.041
Psoriasis	MDD	MR – Egger	1.04	0.89 – 1.21	0.613
Psoriasis	Bipolar disorder	IVW	13.54	2.43 – 75.37	0.002
Psoriasis	Bipolar disorder	Weighted median	11.27	1.98 – 64.19	0.006
Psoriasis	Schizophrenia	IVW	3.52	0.22 – 55.71	0.372
Psoriasis	Anxiety disorder	IVW	0.65	0.16 – 2.63	0.546
PsA	Bipolar disorder	IVW	1.05	1.01 – 1.08	0.005

The forest plot provided a visual representation of the causal effect estimates of psoriasis on different psychiatric disorders. The results showed that the point estimates for the effect of psoriasis on both MDD and bipolar disorder were located to the right of $OR = 1$, and their 95% confidence intervals did not cross the line of no effect, indicating significant positive causal associations. In contrast, the 95% confidence intervals for the effect estimates on schizophrenia and anxiety disorders both crossed $OR = 1$, suggesting that the differences were not statistically significant (Fig. 1).

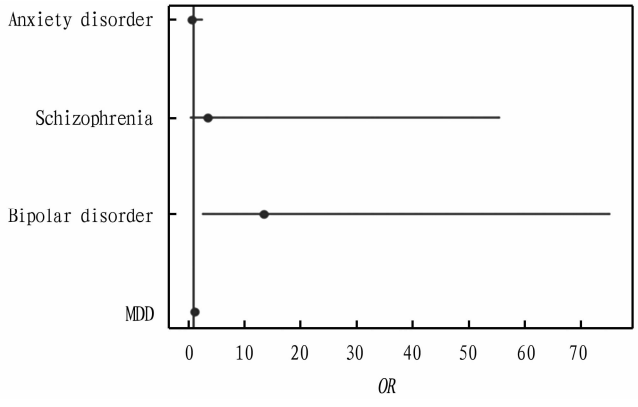

Fig. 1 Forest plot of causal effects of psoriasis on psychiatric disorders

3.3 Sensitivity analysis and causal effect robustness assessment To assess the robustness of the primary analysis results, sensitivity analyses were further conducted using the weighted median method and MR – Egger regression. The results showed that in the analyses of psoriasis with MDD and psoriasis with bipolar disorder, the direction of the causal effects obtained by the different methods was completely consistent. Furthermore, the effect estimates from the weighted median method were close to the IVW results (Table 3), indicating good robustness of the core

conclusions.

The MR scatter plot showed that the instrumental variables (SNPs) associated with psoriasis generally exhibited a positive distribution trend between exposure effects and outcome effects. The slope of the inverse variance weighted (IVW) regression line was positive, indicating that the direction of influence of the genetic instrumental variables on psoriasis and MDD risk was consistent, further supporting the reliability of the main analysis results (Fig. 2).

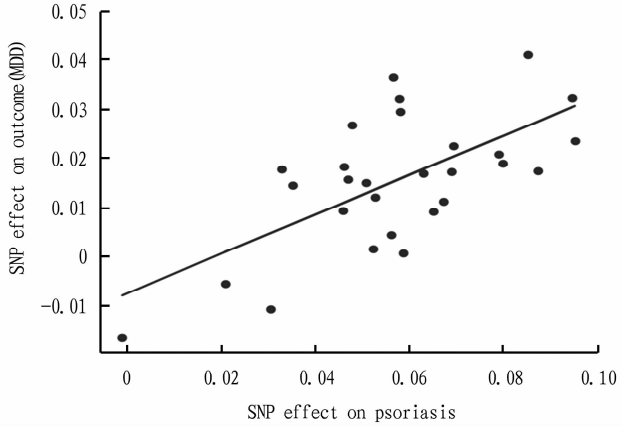

Fig. 2 MR scatter plot of causal relationship between psoriasis and MDD

3.4 Results of heterogeneity and pleiotropy tests The results of Cochran's Q test indicated that no significant heterogeneity was observed among the instrumental variables in the analyses of psoriasis and each psychiatric disorder ($P>0.05$) (Table 4). The MR – Egger intercept test also showed no significant directional pleiotropy ($P>0.05$), suggesting that the effect of the instrumental variables on the outcome was primarily mediated through the exposure factor (psoriasis) and did not occur via other pathways.

Table 4 Heterogeneity and pleiotropy tests

Exposure – Outcome	Cochran's Q	P value	MR – Egger intercept	P value
Psoriasis – MDD	27.14	0.312	0.004	0.421
Psoriasis – Bipolar disorder	25.89	0.284	−0.006	0.367
Psoriasis – Schizophrenia	29.77	0.198	0.009	0.254
Psoriasis – Anxiety	26.41	0.301	−0.002	0.512

The funnel plot results showed that the causal effect estimates of each instrumental variable were distributed nearly symmetrically on both sides of the precision axis, with no obvious bias observed. This further supports that the MR analysis results in this study were not affected by significant directional pleiotropy (Fig. 3).

3.5 Psoriatic arthritis (PsA) subgroup analysis In the subgroup analysis of psoriatic arthritis, the IVW results revealed a significant positive causal association between genetic predisposition to PsA and the risk of developing bipolar disorder (OR = 1.05, 95% CI: 1.01 – 1.08, P = 0.005) (Table 3). No statistically significant causal relationships were observed for major depressive disorder, schizophrenia, or anxiety disorders. Further

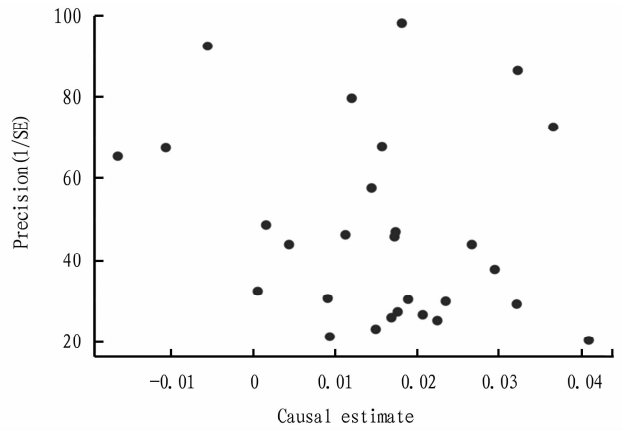

Fig. 3 Funnel plot of causal relationship between psoriasis and psychiatric disorders

sensitivity analysis results indicated that the direction of the effect between PsA and bipolar disorder remained consistent across different analytical methods, suggesting that the findings from this subgroup analysis are reliable and robust.

4 Discussion

Based on large-scale GWAS summary data and employing a bidirectional Mendelian randomization approach, our study systematically evaluated the potential causal relationships between psoriasis and several common psychiatric disorders at the genetic level. The results demonstrated significant positive causal associations between genetic predisposition to psoriasis and both MDD and bipolar disorder, while no statistically significant causal links were observed with schizophrenia or anxiety disorders. Subgroup analysis of PsA further indicated that its genetic susceptibility is significantly associated with the risk of developing bipolar disorder. These findings provide key genetic epidemiological evidence for understanding the pathogenesis of psychiatric comorbidities in psoriasis and offer new insights for precise clinical prevention and management.

We found that genetic predisposition to psoriasis significantly increases the risk of developing MDD, and this result remained consistent across multiple MR analytical methods with no significant directional pleiotropy observed, indicating that the causal association is relatively robust. This finding aligns with previous epidemiological studies. From a mechanistic perspective, psoriasis is primarily characterized by immune-mediated chronic inflammation. Inflammatory pathways such as the IL-23/IL-17 axis and TNF-α may contribute to the development and progression of depressive disorders by affecting central nervous system function[5-6].

Our findings provide genetic-level support for the causal direction of "psoriasis → depressive disorder," offering genetic evidence for the mechanistic hypothesis that inflammation mediates psychiatric comorbidity. In addition, we observed a significant positive causal association between genetic predisposition to psoriasis and bipolar disorder, suggesting that bipolar disorder may be

another type of psychiatric comorbidity requiring focused attention in psoriasis patients, in addition to depressive disorders. The underlying mechanisms may involve broader immune-inflammatory dysregulation and overlapping genetic susceptibility, though further research is needed to elucidate these pathways.

However, we did not find significant genetic causal associations between psoriasis and schizophrenia or anxiety disorders in this study. This suggests that the correlations reported in previous observational studies may be more influenced by non-genetic factors such as environmental exposures, psychological stress, and disease burden[7-8]. In the PsA subgroup, genetic susceptibility was significantly associated with the risk of bipolar disorder, indicating that psoriasis patients with articular involvement may face a higher risk of psychiatric comorbidity. In clinical management, enhanced screening and early intervention for mental health should be implemented for such patients, with particular attention to symptoms related to emotional disorders.

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ical significance, phased rehabilitation training establishes distinct training objectives aligned with the stages of rotator cuff injury recovery, emphasizing both safety and efficacy. The training protocol is highly practical and does not require specialized equipment, thereby facilitating its clinical implementation and broader application. Concerning research limitations, this study was conducted at a single center with a relatively small sample size and a brief follow-up duration, whereas long-term efficacy was not assessed. Consequently, further studies are necessary to validate these findings.

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