

CONCISE COMMUNICATION



Association of psoriasis with depression, anxiety, and suicidality: A bidirectional two-sample Mendelian randomization study

Mengyang Chu | Shengxian Shen | Zhenlai Zhu | Zhiguo Li | Yaxing Bai |
Jingyi Ma | Junfeng Hao | Lei Wang | Meng Fu | Erle Dang | Gang Wang |
Shuai Shao

Department of Dermatology, Xijing hospital, Fourth Military Medical University, Xi'an, China

Correspondence

Gang Wang and Shuai Shao, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shannxi 710032, China.

Email: xjwang@fmmu.edu.cn and shaos@fmmu.edu.cn

Funding information

National Natural Science Foundation of China, Grant/Award Number: 82230105, 82030096 and 82173415

Abstract

Psoriasis is a chronic, refractory inflammatory skin disease, with a high prevalence of psychiatric comorbidities, including depression, anxiety, and even suicidality, which may in turn initiate or exacerbate skin inflammation. However, the causal relationships between these comorbidities remain unclear. To investigate the cause-effect relationships between psoriasis and mental disorders including depression, anxiety, and suicidality, we conducted a bidirectional two-sample Mendelian randomization (MR) study utilizing summary statistics from the most comprehensive genome-wide association studies of psoriasis ($n = 306\,123$), broad depression ($n = 500\,199$), major depressive disorder ($n = 173\,005$), anxiety ($n = 17\,310$), and suicide attempts ($n = 50\,264$). Using the random-effects inverse-variance weighted method as primary method, the forward MR analyses indicated that psoriasis was significantly associated with higher odds of broad depression (odds ratio [OR] 1.030, 95% confidence interval [CI] 1.010–1.051, $P = 0.003$) and suggestively associated with an increased risk of major depressive disorder (OR 1.054, 95% CI 1.002–1.109, $P = 0.040$), but not with the risk of anxiety ($P = 0.160$) or suicide attempts ($P = 0.648$). In reverse MR analyses, significant causal impact of broad depression (OR 1.363, 95% CI 1.103–1.684, $P = 0.004$) and major depressive disorder (OR 1.890, 95% CI 1.285–2.781, $P = 0.001$), but not anxiety ($P = 0.787$) and suicide attempts ($P = 0.961$) on psoriasis risk was observed. In addition, the results of primary analysis are consistent across sensitivity analyses, albeit the MR-Egger regression model produced wide CIs and negative results in several analyses. In conclusion, this MR study indicates a bidirectional causal relationship between psoriasis and depression that was previously unrecognized, which highlights the significance of screening for depression in psoriasis patients and initiating appropriate interventions. Further studies are required to elucidate the pathophysiology of the bidirectional causal relationship between these two conditions.

KEYWORDS

Mendelian randomization, mental health, psoriasis

1 | INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by demarcated and scaly erythematous that commonly occur on extensor surfaces of forearms and shins, trunk, and scalp.¹ It affects 2%–3% of the global population and is caused by the interaction between genetic predisposition and environmental factors,² which cannot currently be cured, leading to a substantial burden for individuals and society. Comorbidities of psoriasis have attracted a lot of attention in recent decades, especially in the area of psychological health.

Emerging evidence has suggested that people with psoriasis may be more likely to experience mental health issues, including

depression (up to 20%), anxiety (up to 16%), or even suicidality (12.7%) extending to suicidal behavior, due to the physical and emotional challenges of living with these psoriatic conditions.^{1,3,4} Meanwhile, episodes of psychological stress can also exacerbate psoriasis symptoms.⁵ However, most related findings are observational, and the directionality and causality between psoriasis and mental disorders remain poorly understood, which is of great significance in clinical practice.

To address this, we conducted a bidirectional two-sample Mendelian randomization (MR) study to explore the causal association of psoriasis with depression, anxiety, and suicide attempts. MR uses genetic variations that are closely linked to exposure as a tool to minimize the influence of confounders and reverse causality, providing a

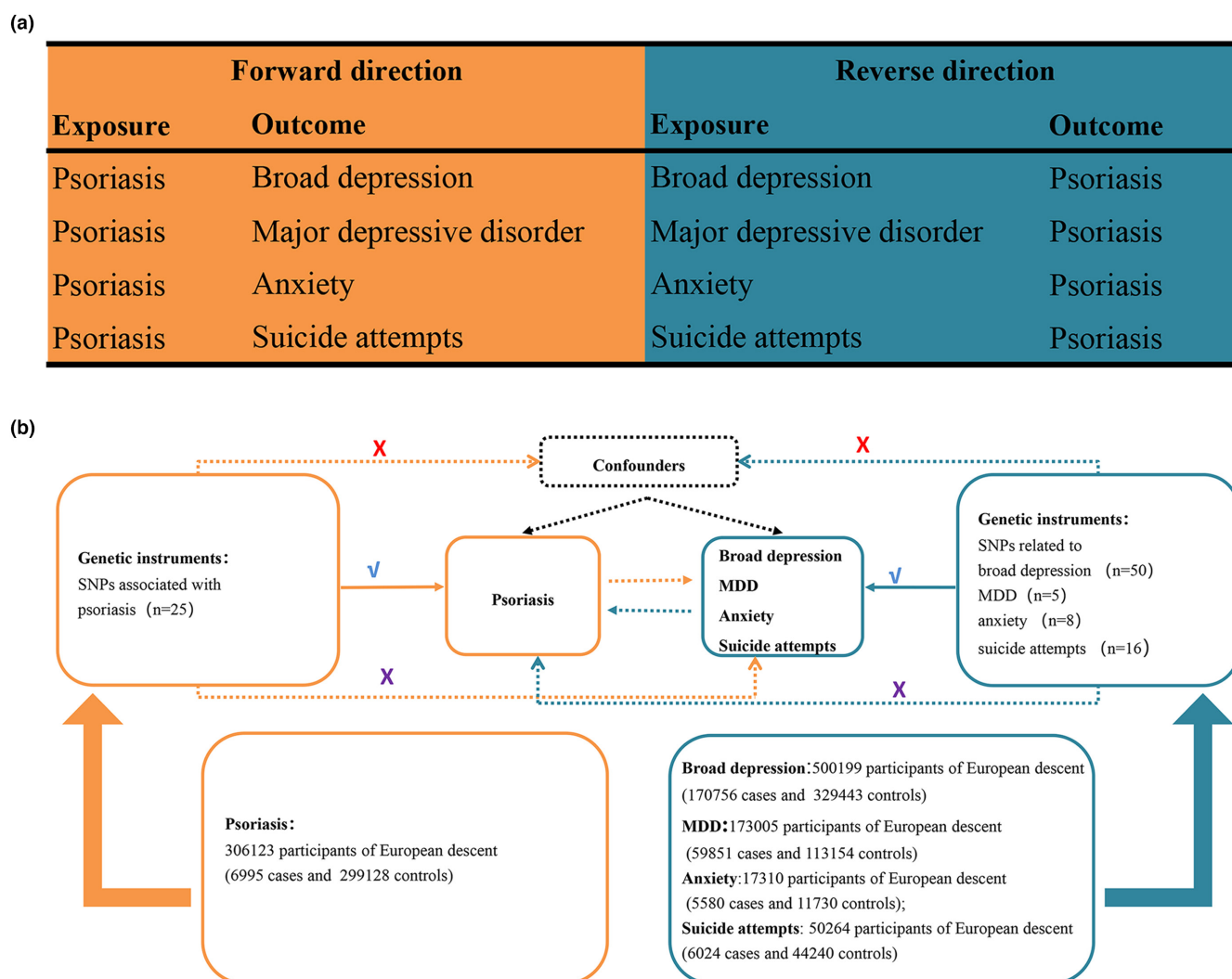


FIGURE 1 Overview of the study design in this bidirectional Mendelian randomization (MR) study. (a) A total of eight MR analyses were performed to investigate the bidirectional relationships between psoriasis and four kinds of mental disorders. (b) Brief description of the study design. Blue ticks indicate that genetic variants were significantly associated with the exposure/outcome. Red crosses indicate that genetic variants were not related to any confounders of the exposure–outcome association. Purple crosses indicate that genetic variants exerted effects on the outcome only via the exposure. MDD, major depressive disorder.

higher level of evidence for clinical decision-making in the management of psoriasis patients.

2 | METHODS

2.1 | Study design

We performed a total of eight MR analyses based on publically available summary-level data of genome-wide association studies (GWASs; Figure 1a). Figure 1b shows the flowchart of this study, among which three principal assumptions were prerequisites. No additional ethical permissions were required, since ethical approval and participant consent had been obtained in all original studies.

2.2 | GWAS summary statistics data sources

GWAS summary statistics for psoriasis were obtained from FinnGen Biobank, including 6995 cases (4321 patients were diagnosed with psoriasis vulgaris, 2571 with arthropathic psoriasis, 258 with guttate psoriasis, 930 with pustular psoriasis, and 1287 with other and unspecified psoriasis) and 299 128 participants without any diagnosis of psoriasis.⁶ For depression, we drew on the summary statistics from a GWAS meta-analysis, which included 170 756 cases and 329 443 control individuals.⁷ In addition, we extracted GWAS summary statistics for major depressive disorder (MDD) with 59 851 cases and 113 154 controls from the meta-analysis carried out by Wray et al.⁸ We obtained genetic instruments for anxiety from another meta-analysis in the Anxiety Neuro Genetics Study Consortium (5580 patients diagnosed anxiety disorder and 11 730

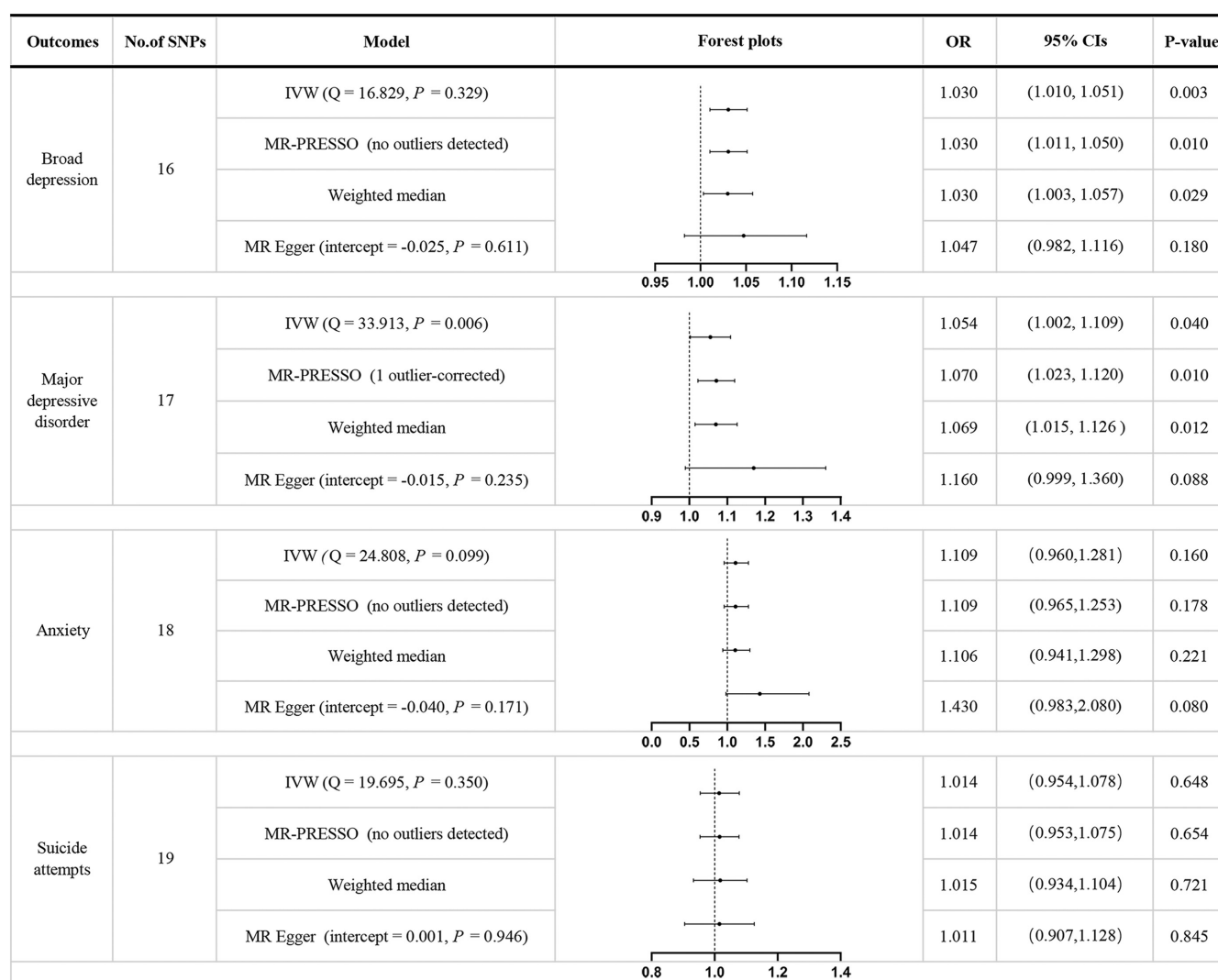


FIGURE 2 Association of psoriasis with the risk of mental disorders in forward Mendelian randomization (MR) analyses. Causal estimates are given as odds ratios (ORs) and 95% confidence intervals (CIs). After a Bonferroni correction, we regarded $P < 0.00625$ ($\alpha = 0.05/8$) as significant evidence of associations, while associations with $P \geq 0.00625$ and < 0.05 were considered as suggesting significance. IVW, inverse variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier; Q, heterogeneity statistic Q.

controls).⁹ We also extracted GWAS summary statistics for suicide attempts released by the recent Lundbeck Foundation Initiative for Integrative Psychiatric Research GWASs.¹⁰ In this study, at least one suicide attempt was recorded in 6024 cases, while 44 240 did not. (Supporting Information Table S1).

2.3 | Single nucleotide polymorphism selection

We selected single nucleotide polymorphisms (SNPs) associated with exposure at genome-wide significance ($P < 5 \times 10^{-8}$) for psoriasis, broad depression and MDD, while a looser threshold of $P < 5 \times 10^{-6}$ for anxiety and suicide attempts. A linkage disequilibrium (LD) clumping algorithm was used with a stringent r^2 cut-off of 0.001 on a 10000kb window. Subsequently, we merged and harmonized the exposure–outcome dataset, and palindromic SNPs

with an ambiguous strand were corrected based on allele frequency information.¹¹ F -statistics of the instruments and the explained phenotypic variance were calculated to evaluate the risk of weak instrument bias.

2.4 | Statistical analyses

The random-effects inverse-variance weighted (IVW) model was used as the main analysis, with several complementary MR methods conducted for sensitivity analysis, including the weighted median estimator method, MR-Egger regression, and MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO). We conducted Cochran's Q statistic, with a value of $P < 0.05$ indicating significant heterogeneity. Furthermore, leave-one-out analysis was performed to assess the stability of the results.

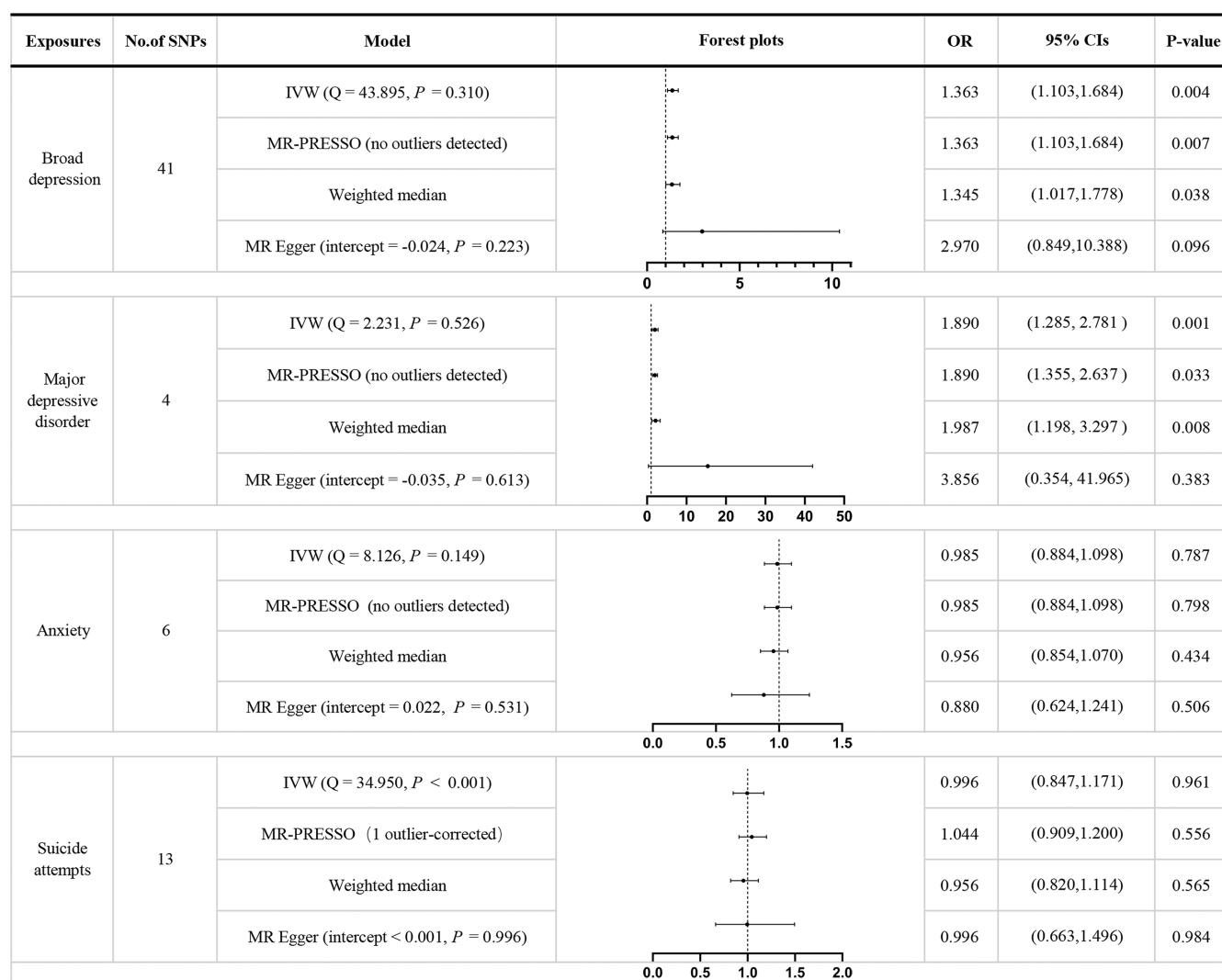


FIGURE 3 Association of mental disorders with the risk of psoriasis in reverse Mendelian randomization (MR) analyses. Causal estimates were given as odds ratios (ORs) and 95% confidence intervals (CIs). After a Bonferroni correction, we regarded $P < 0.00625$ ($\alpha = 0.05/8$) as significant evidence of associations, while associations with $P \geq 0.00625$ and < 0.05 were considered as suggesting significance. IVW, inverse variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier; Q , heterogeneity statistic Q .

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to present the effect estimates. After a Bonferroni correction, we regarded $P < 0.00625$ ($\alpha = 0.05/8$) as significant evidence of associations, while associations with $P \geq 0.00625$ and < 0.05 were considered to suggest significance. All analyses were performed by the TwoSampleMR package (version 0.5.6) and the MR-PRESSO package (version 1.0) in R software (version 4.2.1).

3 | RESULTS

3.1 | Causal effect of psoriasis on depression, anxiety, and suicide attempts

The forward-direction MR analyses indicated that psoriasis was significantly associated with an increased risk of broad depression (OR 1.030, 95% CI 1.010–1.051, $P = 0.003$) and was suggestively associated with higher odds of MDD (OR 1.054, 95% CI 1.002–1.109, $P = 0.040$), but not associated with the risk of anxiety (OR 1.109, 95% CI 0.960–1.281, $P = 0.160$) or suicide attempts (OR 1.014, 95% CI 0.954–1.078, $P = 0.648$) in the random-effects IVW model (Figure 2). Detailed information about the instrumental variables (IVs) involved in forward-direction analyses is shown in Supporting Information Tables S2–S5.

These associations were consistent across most sensitivity analyses. After outlier (rs674451) removal, the OR of MDD per one-unit increase in log-odds of psoriasis liability was 1.070 (95% CI 1.023, 1.120, $P = 0.003$). The scatter plots of causal relationships between psoriasis and four outcomes are shown in Supporting Information Figure S1a. Leave-one-out plots revealed that the results were not driven by any certain extreme SNPs, but rather reflected an overall combined pattern of the associations (Supporting Information Figure S2a).

3.2 | Causal effect of depression, anxiety, and suicide attempts on psoriasis

Correspondingly, the random-effects IVW model provided evidence of a significant causal effect of broad depression (OR 1.363, 95% CI 1.103–1.684, $P = 0.004$) and MDD (OR 1.890, 95% CI 1.285–2.781, $P = 0.001$) on an increased risk of psoriasis, while no associations were observed between either anxiety (OR 0.985, 95% CI 0.884–1.098, $P = 0.787$) or suicide attempts (OR 0.996, 95% CI 0.847–1.171, $P = 0.961$) with psoriasis (Figure 3). Detailed information about the IVs involved in reverse directions analysis is shown in Supporting Information Tables S6–S9.

For the sensitivity analysis, one outlier (rs27721) was shown by MR-PRESSO in the casual estimate of suicide attempts on psoriasis. However, the result remained similar after removal of this outlier (IVW OR 1.044, 95% CI 0.909–1.200, $P = 0.544$). The scatter plots are shown in Supporting Information Figure S1b. Leave-one-out plots also revealed the stability of the results (Supporting Information Figure S2b).

4 | DISCUSSION

This study is the first MR investigation to examine the bidirectional causal relationships between psoriasis and mental disorders. Our results suggest a causal link between psoriasis and an increased risk of depression, but not anxiety or suicide attempts, and vice versa.

The biological connection between psoriasis and depression has not yet been fully understood. To begin with, the cytokine theory, by which inflammatory responses and elevated cytokines can also cause depression, is the most prominent hypothesis for the mechanisms underlying the mental health comorbidities associated with psoriasis.¹² Many studies have shown that high levels of several psoriasis cytokines, most notably IL-6, are also elevated in the plasma and central nervous system of individuals with depression and may exacerbate the progression of mental health disorders.¹³ However, the exact nature of the molecular mechanism remains incompletely understood.

In summary, our findings indicate that appropriate screening and treatment for depression in psoriasis patients might help manage psoriasis symptoms and may lead to better clinical outcomes. Further studies are warranted to elucidate the pathophysiology of the bidirectional causal relationship between psoriasis and depression.

ACKNOWLEDGMENTS

We thank all investigators of the original genome-wide association studies who made their summary statistics available.

FUNDING INFORMATION

This work was supported by grants to Gang Wang and Lei Wang from the National Natural Science Foundation of China (82230105, 82030096, and 82173415).

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

ORCID

Zhenlai Zhu  <https://orcid.org/0000-0001-8518-8222>

Lei Wang  <https://orcid.org/0000-0002-2111-5160>

Gang Wang  <https://orcid.org/0000-0002-5842-8080>

Shuai Shao  <https://orcid.org/0000-0003-0699-1864>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chu M, Shen S, Zhu Z, Li Z, Bai Y, Ma J, et al. Association of psoriasis with depression, anxiety, and suicidality: A bidirectional two-sample Mendelian randomization study. *J Dermatol*. 2023;50:1629–1634. <https://doi.org/10.1111/1346-8138.16941>