Dermatology Practical & Conceptual

# Causal Relationship Between Psoriasis and Bullous Pemphigoid: A Mendelian Randomization Analysis

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## ABSTRACT

**Introduction:** Psoriasis and bullous pemphigoid (BP) are the two major types of immune-mediated inflammatory skin diseases. Studies have reported the association between psoriasis and BP; however, no studies have reported whether a causal relationship exists between these two skin diseases.

**Objectives:** In order to explore the causal relationship between psoriasis and BP, we performed a bidirectional two-sample Mendelian randomization (MR) study.

**Methods:** Genome-wide association study (GWAS) data related to psoriasis and BP were collected. The inverse-variance weighted (IVW) method was primarily applied for our MR analysis; MR-Egger, weighted median, simple mode, and weighted mode methods were also used. Heterogeneity, horizontal pleiotropy, and potential outliers were assessed for the MR analysis results.

**Results:** GWAS data for psoriasis (three cohorts) and BP (one cohort) from publicly available trials were selected. Our MR results showed that psoriasis was causally associated with BP, that psoriasis could increase the risk of BP, and that reversed MR showed BP has no causal effect on psoriasis. No heterogeneity or pleiotropy was detected.

**Conclusion:** These findings provided new evidence of the causal relationship between psoriasis and BP. Our MR suggested that psoriasis is potentially causal to BP, which helps us to improve the treatment strategy for patients with psoriasis. The mechanism remains open for further investigation.

## Introduction

Psoriasis is a common chronic inflammatory skin disease [1], with a relatively high incidence and prevalence worldwide. Accordingly, psoriasis affects 2%–3% of adults in the USA and Europe, about 125 million people globally [2, 3]. Studies have reported that patients with severe psoriasis have a significantly increased probability of loss of work, more than four times so, which gives rise to a greater impact on quality of life [4]. Pathologically, the development of psoriasis is mainly attributed to immune dysfunction, vascular injury, disturbance of signal transduction pathway, and imbalance of psoriasis-related gene expression. The most common clinical characteristic in psoriasis is red or pink plaques covered by silvery scales. Emerging studies have gradually illuminated the pathogenesis of psoriasis in the past years. Meanwhile, the etiology of psoriasis still remains largely elusive. A specific aspect of psoriasis progression involves substantial psychological disability, with up to 20% of those affected reporting symptoms of depression [5]. Treatment strategies for patients with psoriasis include topical therapies, oral medications, biologic agents, and phototherapy. For patients with severe disease, which cannot be controlled with the fundamental use of topical therapies (e.g. corticosteroids), systemic biologic agents such as adalimumab, ustekinumab, secukinumab, or ixekizumab more frequently considered [6]. However, given the highly heterogeneous character of psoriasis, biologic therapies are suitable for only a minority of patients.

Bullous pemphigoid (BP) is the major type of pemphigoid, belonging to an autoantibody-mediated blistering skin disease [7]. BP primarily affects the elderly (with an average age of 80 years at presentation), and the death rate is three times higher than that of controls (pemphigus vulgaris), statistically [8]. Tense bullae that appear on erythematous or normal skin are the clinical features of BP [9]. Subepidermal blisters with inflammation are the histological hallmark of BP, and eosinophils are frequently observed in the blister cavity and at the intact basement membrane zone [9]. Corticosteroids, azathioprine, and plasmapheresis are treatment options for BP [10]. Recently, studies have reported the association between BP and other diseases. Accordingly, compared to matched controls, patients with BP have a threefold increased risk of developing pneumonia and pulmonary embolism [8], and between 30% and 50% of BP patients have neurological diseases [11].

As mentioned, psoriasis and BP are common immune-related dermatological diseases, and studies have also reported the association of BP with psoriasis [12]. Whether a causal relationship exists between psoriasis and BP remains unclear.

## Objectives

Mendelian randomization (MR) is an emerging method to determine the existence and the strength of the causal relationship between an exposure and an outcome [13]. In MR, researchers need to choose single nucleotide polymorphisms (SNPs) and use them as instrument variables (IVs) [14]. Different from a randomized controlled trial, which is typically expensive, time-consuming, and sometimes infeasible, MR relies on observational data [14]. In order to identify any causal influence between psoriasis and BP, we carried out a bidirectional MR analysis. Based on genome-wide association studies (GWAS), genetic variants related to psoriasis and BP were screened as instrumental variables (IVs).

## Methods

### Study Design

Figure 1 shows our MR framework. In this study, there were three key assumptions:

1. Relevance Assumption: Single nucleotide polymorphisms (SNPs) that are substantially linked to exposures are used as instrumental variables (IVs).
2. Independence Assumption: These SNPs (IVs) should not show any correlation with the relevant confounding factor.
3. Exclusivity Assumption: These SNPs (IVs) should affect outcomes only through their effect on exposure [15, 16].

### GWAS Summary Data Source

We retrospectively used summary data associated with psoriasis and BP from MRC Integrative Epidemiology Unit Open GWAS database (https://gwas.mrcieu.ac.uk) and FinnGen (https://www.finngen.fi/en/access_results). Accession numbers ebi-a-GCST90018907 (psoriasis 5,072 cases; 478,102 controls) [17], ukb-b-10537 (psoriasis 5,314 cases; 457,619 controls), finn-b-L12_PSORI_VULG (psoriasis 2,802 cases; 212,242 controls); finn-b-L12_PEMPHIGOID_BULL (BP 219 cases; 218,066 controls) summary data were accessed from IEU Open GWAS project database (https://gwas.mrcieu.ac.uk). Our study was conducted by secondary analysis of data from other studies. All participants or their family members provided informed written consent in the original studies. Detailed information of data elements for psoriasis and BP was listed in Table 1.

### Instrumental Variables Selection

Related IVs for MR analysis followed particular principles: SNPs should be associated with exposures at the locus-wide significance level ($P$ <5e-06 for psoriasis,

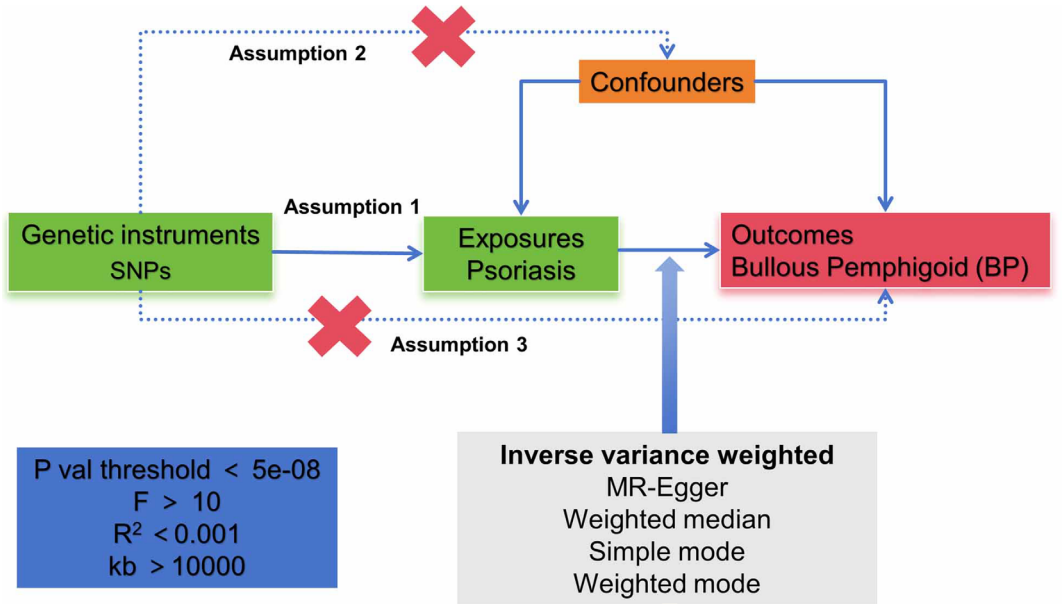


**Figure 1.** The flowchart adhered to the principles of MR analysis as outlined in this study.

**Table 1.** GWAS Summary Data Sources Included in the Study.

| Diseases | GWAS ID | N of Cases | N of Controls | Population | N of SNPs |
|---|---|---|---|---|---|
| Psoriasis | ebi-a-GCST90018907 | 5,072 | 478,102 | European | 15 |
| Psoriasis | ukb-b-10537 | 5,314 | 457,619 | European | 21 |
| Psoriasis | finn-b-L12_PSORI_VULG | 2,802 | 212,242 | European | 10 |
| Bullous pemphigoid | finn-b-L12_PEMPHIGOID_BULL | 219 | 218,066 | European | 14 |

Abbreviations: GWAS: genome-wide association studies; SNPs: single nucleotide polymorphisms.

*P* <5e-08 for BP). In addition, linkage disequilibrium (LD) coefficient $R^2$ should be less than 0.001, not closely related (clumping window more than 10,000 kb) to ensure exposure instrument independence. We used the F statistic to measure the strength of the IVs; the values of F-statistics were more than 10.

## MR Analysis

Causal relationships between psoriasis and bullous pemphigoid (BP) were investigated utilizing Mendelian randomization (MR) and reverse causality analysis (Supplementary Table S1). In the assessment of exposure and outcome, we employed MR with multiple single nucleotide polymorphisms (SNPs) serving as instrumental variables (IVs). Each IV provides an independent estimate of the causal effect, which can be aggregated through a fixed effect, inverse variance-weighted (IVW) meta-analysis. The primary statistical analysis for assessing causal effects was performed using the IVW method, complemented by additional approaches such as simple mode, weighted median, weighted mode, and MR-Egger to further validate the results. The MR-Egger method was applied through a straightforward modification of the previously established weighted linear regression technique. This method was specifically utilized to assess the robustness of the MR findings as a form of validation. [15, 16, 18].

## Sensitivity Analysis

The heterogeneity of the chosen SNPs was evaluated using Cochran's Q test; a p-value of more than 0.05 suggested the lack of heterogeneity. The random effects model was used once significant heterogeneity had been identified. We evaluated the possible bias from horizontal pleiotropy using the weighted median and MR-Egger regression in order to gauge the robustness of the IVW method. The MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) test was used to identify outliers that might have been influenced by horizontal pleiotropy. The causal effect estimates for individual variants were displayed using a scatter plot. Thereafter, we carried out a "leave-one-out" to test the robustness of the results [15, 16, 18].

### Statistical Analysis

All data were analyzed by R software (Version 4.3.2), "Two-Sample MR package" (Version 0.5.8). The statistical significance level is $P$ <0.05. Pooled odds ratios (ORs) with 95% confidence intervals (CI) were calculated.

## Results

### Instrumental Variables

According to the quality control principle as mentioned, SNPs related to psoriasis and BP were adopted as instrumental variables (IVs). Table 1 shows the essential information regarding psoriasis and BP. The SNPs included in the exposure data are detailed in Supplementary Table S2.

### MR Analysis

We conducted a two-sample MR analysis between psoriasis and BP. The IVW MR analysis demonstrated that psoriasis has a causal relationship with the risk of BP (ebi-a-GCST90018907: Figure 2; ukb-b-10537: Figure 3; finn-b-L12_PSORI_VULG: Table 2). Instead, the reversed MR showed that BP has no causal relationship with the risk of psoriasis (Table 3). Using the MR-Egger, the relationships between psoriasis and BP had the same direction (Figure 4A–C).

### Sensitivity Analysis

According to the analysis of Cochran's Q test, our IVW-MR analysis results demonstrated no evidence of heterogeneity among the reported results. Furthermore, the MR-Egger regression and MR-PRESSO analysis results provided evidence that there exists no significant horizontal pleiotropy in our MR analysis (Table 4). The symmetric funnel plot (Figure S1) indicated no evidence of horizontal pleiotropy. We also conducted the leave-one-out method to identify and delete abnormal instrumental variables. The results showed the robustness of our results (Figure S2). These results suggest that the MR analysis results were relatively stable.

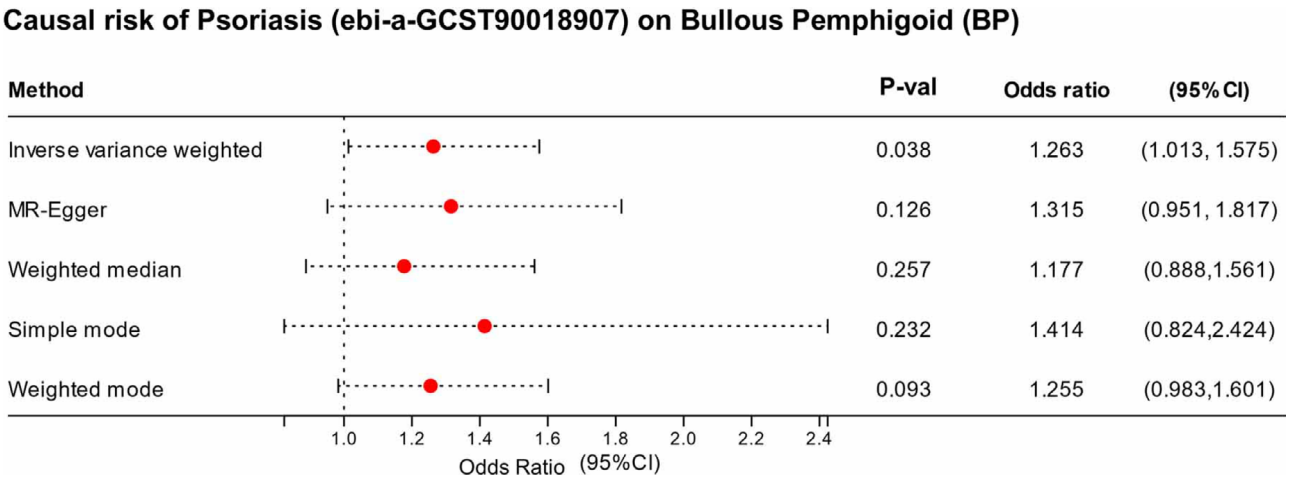


**Figure 2.** Forest Plot of Mendelian Randomization Analysis for Psoriasis (ebi-a-GCST90018907) on BP Risk. Abbreviations: CI: confidence interval; OR: odds ratio.

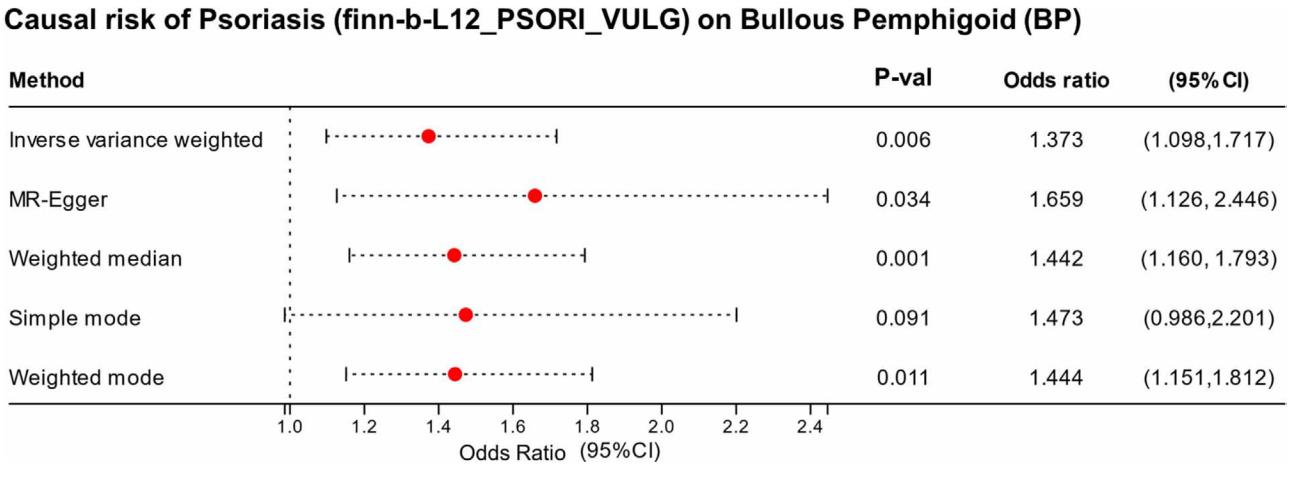


**Figure 3.** Forest Plot of Mendelian Randomization Analysis for Psoriasis (finn-b-L12_PSORI_VULG) on BP Risk. Abbreviations: CI: confidence interval; OR: odds ratio.

**Table 2.** Causal Association of Psoriasis (ukb-b-10537) on BP.

| Methods | OR | 95% CI | P-Value |
|---|---|---|---|
| Inverse-variance weighted | 1.201E+07 | 9.066-1.590e+13 | 0.023 |
| MR-Egger | 1.239E+03 | 1.200e-5-1.281e+11 | 0.459 |
| Weighted median | 1.757E+04 | 3.269e-4-9.445e+11 | 0.282 |
| Simple mode | 1.340E+22 | 8.637-2.070e+43 | 0.055 |
| Weighted mode | 4.542E+03 | 0.001-1.824e+11 | 0.358 |

Abbreviations: BP: bullous pemphigoid; CI: confidence interval; MR: Mendelian randomization; OR: odds ratio.

**Table 3.** Reverse Causality Between BP and Psoriasis.

| BP | Psoriasis ID | Methods | P-Value |
|---|---|---|---|
| BP | ebi-a-GCST90018907 | Inverse-variance weighted | 0.181 |
| | | MR-Egger | 0.722 |
| | | Weighted median | 0.765 |
| | | Simple mode | 0.776 |
| | | Weighted mode | 0.891 |
| BP | ukb-b-10537 | Inverse variance weighted | 0.870 |
| | | MR-Egger | 0.631 |
| | | Weighted median | 0.117 |
| | | Simple mode | 0.126 |
| | | Weighted mode | 0.149 |
| BP | finn-b-L12_PSORI_VULG | Inverse variance weighted | 0.319 |
| | | MR-Egger | 0.917 |
| | | Weighted median | 0.902 |
| | | Simple mode | 0.746 |
| | | Weighted mode | 0.756 |

Abbreviations: BP: bullous pemphigoid; MR: Mendelian randomization.

## Discussion

Our results revealed psoriasis itself is an independent causal factor of BP. In addition, the sensitivity analysis supported the validity of the results. In contrast, our reverse MR analysis showed that BP was not significantly associated with psoriasis progression. Psoriasis is recognized as a systemic autoimmune disorder, with its etiology attributed to a combination of environmental factors, immune dysregulation, and genetic predisposition. [19]. The pathogenesis progression of psoriasis has gradually been expounded: extracellular cytokine pathways and intracellular signaling molecules take part in the progression of psoriasis, collectively [20]. Extracellular cytokine pathways mainly included the tumor necrosis factor (TNF)/ interleukin (IL)-23/IL-17 pathways [21-23]; intracellular signaling pathways of transmission mainly included the nuclear factor kappa B (NF-κB) [24], Janus kinase/signal transducer and activator (JAK-STAT) [25], and mitogen-activated protein kinases (MAPK) pathway [26]. It is reported that psoriasis leads to an increased risk of the pathosis of other organ systems, for example, cardiovascular disease, psoriatic arthritis, obesity, diabetes mellitus, nonalcoholic fatty liver disease, and inflammatory bowel disease, compared with that of the general population [27]. Bullous pemphigoid is characterized by local inflammation and dermal-epidermal separation and belongs to autoantibody-mediated blistering skin disease, with no approved targeted therapy [28]. Immunoprecipitation with BP sera of extracts of cultured keratinocytes identified two hemidesmosomal proteins—BP180 (180 kDa) and BP230 (230 kDa) [29, 30]—both of which have been identified as target antigens in BP. Pathologically, BP180 leads to the release of IL-6 and IL-8 [31]. As mentioned, psoriasis and BP are both skin diseases seen in clinical practice. Our MR study results suggest psoriasis itself might cause BP. Previous case-control studies showed similar results [12, 32]. According to a large-scale population-based cohort study, patients with psoriasis were statistically independently associated with a threefold

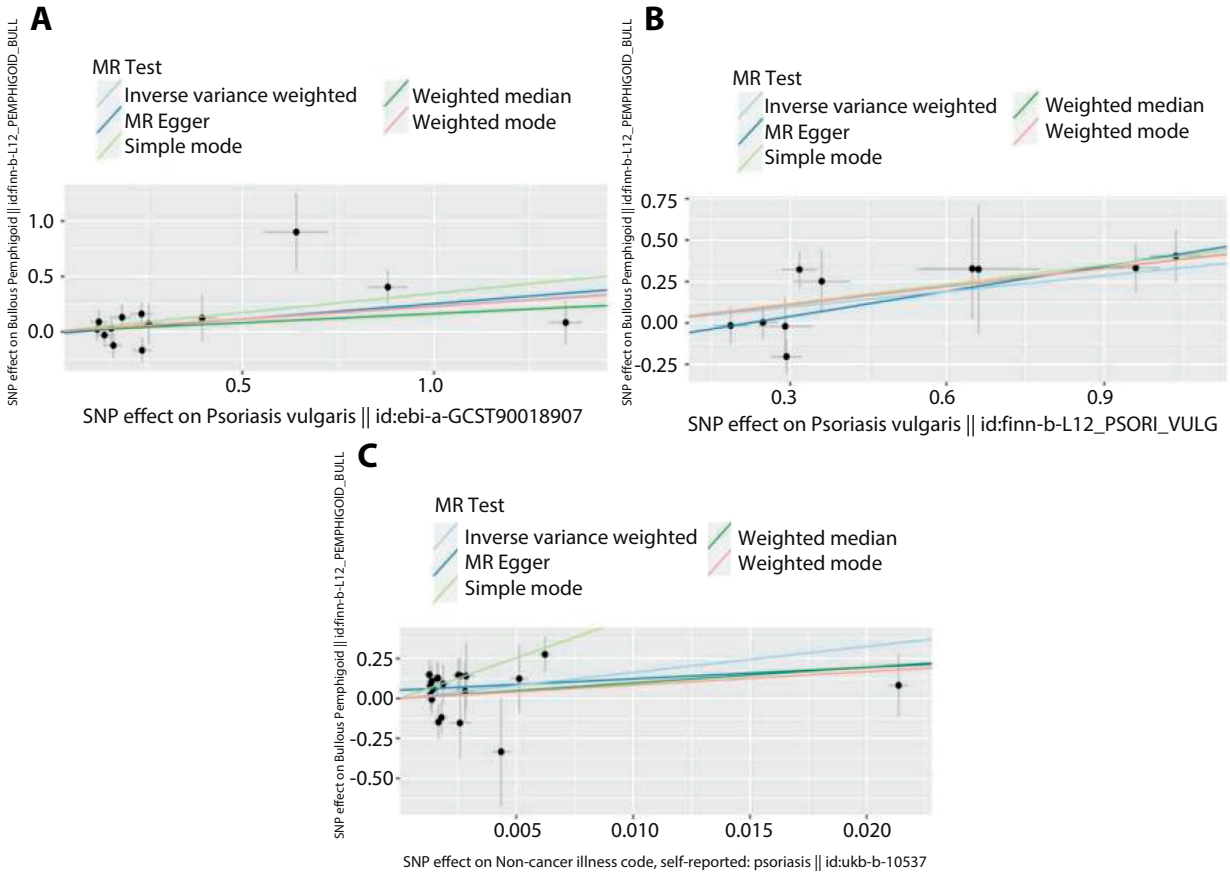


**Figure 4.** Scatter Plots showing Significant Causal Effects among Three Psoriasis Cohorts and BP, respectively: (A) ebi-a-GCST90018907, (B) ukb-b-10537, (C) finn-b-L12_PSORI_VULG.

**Table 4.** Sensitivity Analysis of Our MR Analysis.

| Psoriasis ID | Q | P-value for Cochran Q test | Egger-intercept | P-value for MR-Egger intercept | P-value for MR-PRESSO Global test |
|---|---|---|---|---|---|
| ebi-a-GCST90018907 | 16.227 | 0.181 | -0.020 | 0.738 | 0.226 |
| ukb-b-10537 | 18.495 | 0.489 | 0.051 | 0.148 | 0.417 |
| finn-b-L12_PSORI_VULG | 14.829 | 0.095 | -0.112 | 0.279 | 0.160 |

Abbreviations: MR: Mendelian randomization; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier.

increased risk of BP [12]. In addition, a systematic review and meta-analysis showed a significantly higher rate of psoriasis in patients with BP compared to controls [33]. The literature has also reported the co-occurrence of these two diseases [34].

To date, few studies have reported the potential mechanisms leading to the association between psoriasis and BP. Phototherapy is a prevalent treatment for patients with psoriasis that may lead to autoantibody formation due to the change of the antigenicity of the basement membrane [12]. Utilization of immunosuppressants, such as biologic agents, is another explanation for how psoriasis could increase the risk of BP. The use of biologic agents, for instance, TNF-α inhibitors (e.g., secukinumab or ustekinumab), could contribute to autoimmune processes and may also be a cause of BP development [12, 35]. As mentioned, specific autoantibodies have been identified in BP (BP180, BP230). Although these autoantibodies rarely exist in psoriasis, there may be other autoantibodies stimulated by T cell dysregulation in psoriasis patients. A common characteristic of psoriasis and BP is the disruption of the basement membrane integrity [33]. Our MR analysis indicated that, for psoriasis patients, we should work on preventing BP development early and carefully formulate clinical strategies.

Usually, MR analysis chooses an exposure and an outcome. In our research, we chose three cohorts for psoriasis

in three different GWAS databases; we analyzed the causal association between the three individual cohorts (exposure) and the BP (outcome). Interestingly, these three cohorts obtained similar results, namely that psoriasis has a causal impact on BP. These analyses enhance the robustness of our outcomes.

## Limitations

There are several limitations to our study. First, we were unable to divide the cohorts or perform subgroup analyses due to the original GWAS statistics. Second, our MR analysis only included individuals of the European population. As using a single European population in our MR analysis can limit population stratification bias, caution is needed when interpreting these findings and their applicability to different populations. Third, our results indicated that psoriasis has a causal influence on BP. There was no evidence that BP itself was a casual risk to psoriasis, but this does not mean BP had no impact on psoriasis. The fundamental mechanisms and pathways that contribute to the causal relationship between psoriasis and BP require further investigation and clarification.

As previously mentioned, MR analysis can be conducted using only summary data, i.e., it is unnecessary to use individual-level data [14]. Inverse-variance weighted two-sample Mendelian randomization (IVW-MR) is the most commonly used approach that utilizes genome-wide association studies (GWAS) summary statistics to infer the existence and the strength of the causal effect between an exposure and an outcome. In addition, two-sample MR methods expect the exposure and the outcome GWAS summary statistics to be obtained from independent samples. Estimates from this method can be biased due to weak instruments and to the winner's curse, which can change as a function of the overlap between the exposure and outcome samples. It should be noted that the method we used may bias our results [13, 14].

## Conclusion

Our MR analysis provides evidence that psoriasis has a causal impact on BP. Our findings indicate that we should pay attention to the possibility of BP development so as to improve treatment strategies for patients with psoriasis. Further investigations are required to elucidate the underlying mechanisms between the contributing risk factors of psoriasis to BP.

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