



## The Causal Association Between Medication Intake and Increased Risk of Psoriasis

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**ABSTRACT** **Introduction:** Psoriasis is a chronic, inflammatory, and papulo-squamous skin disorder without a radical cure. Although previous observational analyses have discovered a relationship between medication intake and increased risk of psoriasis, they are susceptible to confounders.

**Objectives:** We intend to ascertain if there is a causal association between specific medication intake and increased risk of psoriasis by utilizing the Mendelian randomization (MR) method.

**Methods:** We obtained the genome-wide association study (GWAS) data for medication intake (23 types, N = 1809) from UK Biobank samples. And we sourced the GWAS data for psoriasis from the 8<sup>th</sup> release of the FinnGen database, which included 8,075 psoriasis cases and 330,975 healthy control cases. Then a two-sample MR study was performed to determine their causal association, and inverse-variance-weighted MR (IVW-MR) was applied to calculate the effect estimates.

**Results:** The IVW-MR analysis uncovered a positive correlation between the intake of HMG CoA reductase inhibitors and the increased risk of psoriasis (odds ratio [OR] = 1.167, 95% confidence interval [CI] = 1.084-1.257). Similarly, the use of thyroid preparations (OR=1.080, 95% CI=1.026-1.138), nonsteroidal anti-inflammatory and antirheumatic products (OR=1.406, 95% CI=1.037-1.908), anilides (OR=1.379, 95% CI=1.004-1.894), antihistamines for systemic use (OR=1.341, 95% CI=1.104-1.630), and antihypertensives (OR=1.099, 95% CI=1.016-1.190) were associated with an increased risk of psoriasis. We did not find evidence from IVW-MR for other associations.

**Conclusions:** Our study offers a causal testimony that the intake of HMG CoA reductase inhibitors, thyroid preparations, nonsteroidal anti-inflammatory and antirheumatic products, anilides, antihistamines for systemic use, and antihypertensives will potentially increase the risk of psoriasis.

## Introduction

Psoriasis is a chronic, inflammatory, and papulo-squamous skin disorder. Psoriasis vulgaris is the most common subtype, accounting for approximately 90% of cases [1]. Clinically, it is characterized by sharply demarcated salmon-pink plaques in individuals with white skin but gray plaques in those with black skin, both covered by silvery scales [2]. According to a systematic review [3], the prevalence of psoriasis varied widely across different regions, ranging from 0.09% in Tanzania to 5.1% in the USA. The distribution of psoriasis patients was also unequal regarding race, age, and geography. For instance, it occurred more commonly in Caucasians, adults, and individuals from wealthy countries [2-4]. Furthermore, psoriasis patients often experienced poor self-esteem, anxiety, depression, insomnia, and even suicidality because of their unsightly external appearance [5-8], which placed a heavy burden on individuals and society.

A previous study indicated that the intake of certain medications might induce psoriatic lesions on normal skin in psoriasis patients or trigger psoriasis in predisposed individuals, even in those without a family history of this disease [9]. These medications included nonsteroidal anti-inflammatory drugs (NSAIDs), penicillins, antimalarial drugs, psychotropic drugs, and others [10]. Psoriasis is closely associated with various comorbidities. For example, studies have demonstrated that psoriasis patients had a risk of developing metabolic syndromes such as type II diabetes, hypertension, atherogenic dyslipidemia, and nonalcoholic fatty liver, that was at least twice as high as that of healthy individuals [11]. Besides, psoriasis patients were susceptible to coronary atherosclerosis and even coronary artery disease [12,13]. Moreover, a meta-analysis indicated that psoriasis patients had a tremendously increased risk of asthma, inflammatory bowel disease, chronic kidney disease, and end-stage renal disease [14-16]. In such cases, they should treat not only the primary illness but also the associated complications. However, medications used for treating its complications may, in turn, exacerbate psoriasis. Consequently, regardless of the patient's disease control status, clinicians need to evaluate the potential effects of medication intake on the occurrence, recurrence, or aggravation of psoriasis.

## Objectives

It is widely accepted that genetic variants are randomly distributed during meiosis and scarcely influenced by environmental factors. Unlike traditional observational analyses, the Mendelian randomization (MR) study leverages this advantage of genetic variants by utilizing them as instrumental variables, thereby mitigating limitations such as potential confounders, information biases, and reverse causality to the greatest extent [17]. Accordingly, we conducted an MR study and explored the causal association between medication intake and increased risk of psoriasis in this article.

## Methods

### Source of Genome-wide Association Study (GWAS) Data and Harmonization

Our MR study included 23 types of medications in the exposure group, derived from the GWAS data and used to quantify the future risk associated with medication use. The study samples were drawn from the UK Biobank (UKB) and consisted of 502,616 participants with medication records during their first visit to the UKB evaluation [18]. Out of the 6,745 types of medications recorded in the UKB, 1,809 were reported by at least ten individuals and subsequently included in the GWAS. These medications were integrated into 23 categories and underwent a series of quality control measures to form the aggregated GWAS data. We obtained these GWAS data and used the "format\_data" function of the TwoSampleMR package to transform them into a recognizable format. To select instrumental variables for each medication GWAS, we applied the following thresholds: 1) The P-value was less than 5e-08; 2) We conducted clump analysis with an  $r^2 = 0.001$  and kb=10000 setting; 3) We calculated the F statistic for each instrumental variable, and those with an F value less than ten were eliminated [19]. The calculation formula was as follows [20] where N is the sample size and  $r^2$  the variance explained by IVs:

$$\frac{r^2(N-2)}{(1-r^2)}$$

Since we required at least four single nucleotide polymorphisms (SNPs) as instrumental variables for subsequent analysis, we set a P-value threshold of  $P < 5e-07$  in case the medications GWAS yielded insufficient instrumental variables after screening and normalization. If still inadequate, we would adjust the cutoff point to  $P < 5e-06$ .

The study focused on psoriasis as the primary outcome of interest. We obtained the GWAS data for psoriasis from the 8th release of the FinnGen database [21], where the PhenoCode for psoriasis was L12\_PSORIASIS (<https://finngen.gitbook.io/documentation/>). The dataset included 8,075 cases and 330,975 controls, with a total sample size of 339,050. FinnGen conducted a series of quality control measures on the GWAS data (DOI: <https://doi.org/10.1101/2022.03.03.22271360>). And we used National registries to define psoriasis cases.

We harmonized the exposure and outcome groups data to ensure that the effect allele was consistently related to the same allele. This was achieved using the effect allele frequency (EAF) to deduce the orientation of all SNPs on the forward strand. SNPs with incorrect effects or reference alleles, and those with ambiguous palindromic sequences that EAF could not resolve, were excluded from further analysis.

### Mendelian Randomization and Sensitivity Test

To validate the primary MR analysis method, we performed MR-PRESSO analysis [22] with an element set to 10,000 to identify and remove outliers. We simultaneously conducted MR analysis and computed p values. The data with outliers removed were the corrected data for subsequent studies. Inverse-variance-weighted (IVW) was chosen as the primary MR method due to its robustness and reliability [23]. The results obtained through IVW were considered the main MR results. At the same time, we conducted four additional MR methods (MR-Egger, simple mode, weighted median, and weighted mode) to complement IVW and to observe if their results were consistent with those of IVW.

To ensure the reliability of the MR results, we performed sensitivity analyses after obtaining them. We employed the MR-Egger intercept method to test whether they were affected by horizontal pleiotropy [24]. A P value less than 0.05 was considered evidence of horizontal pleiotropy, indicating unreliable results. We evaluated heterogeneity using the Cochran Q test with IVW and MR-Egger. A p-value less than 0.05 indicated the presence of heterogeneity among the instrumental variables. Since IVW can effectively handle heterogeneity, we should regard its results as the main MR results [23].

## Results

### Causality of Medicine Intake on Psoriasis Occurrence

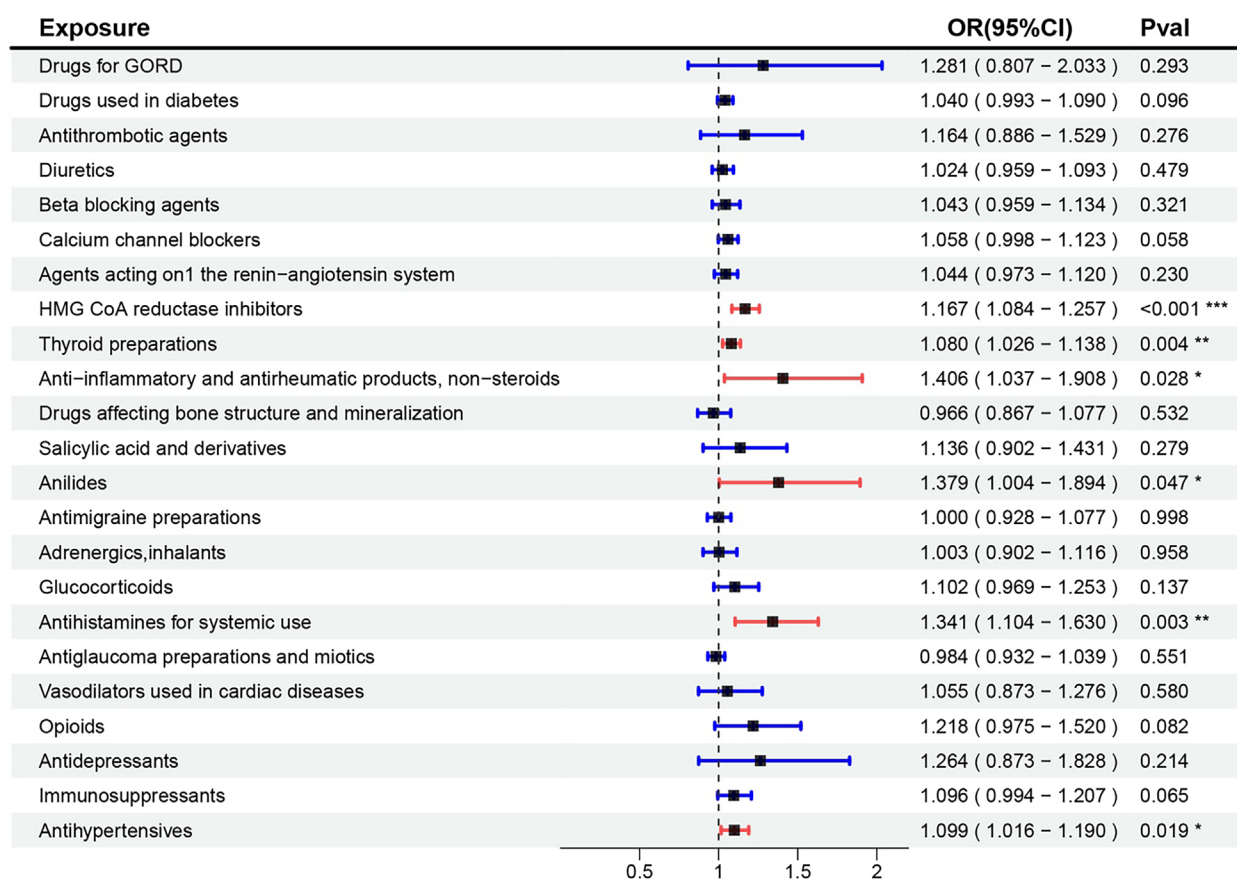
After conducting IVW on 23 different types of medications, we identified six of them as significant risk factors for psoriasis ( $P < 0.05$ ). Supplementary Table 1 provided all the drug IDs and their corresponding detailed names. As depicted in Figure 1, the intake of HMG-CoA reductase inhibitors (OR=1.167, 95% CI: 1.084-1.257,  $P < 0.001$ ) substantially increased the risk of developing psoriasis. Thyroid preparations (OR=1.080, 95% CI: 1.026-1.138,  $P = 0.004$ ) and antihistamines for systemic use (OR=1.341, 95% CI: 1.104-1.630,  $P = 0.003$ ) also showed significant associations. Additionally, NSAIDs and antirheumatic products (OR=1.406, 95% CI: 1.037-1.908,  $P = 0.028$ ), antihypertensives (OR=1.099, 95% CI: 1.016-1.190,  $P = 0.019$ ), and anilides (OR=1.379, 95% CI: 1.004-1.894,  $P = 0.047$ ) contributed to the occurrence or aggravation of psoriasis. Supplementary Table 2 provided detailed outcomes of the other four MR methods.

### Sensitivity Analyses

For the IVW-MR analysis, the Cochran Q test indicated no heterogeneity among the reported results ( $P > 0.05$ ). Moreover, the MR-Egger regression analysis demonstrated that overall horizontal pleiotropy did not significantly affect the results obtained through IVW-MR ( $P > 0.05$ ). Supplementary Table 2 provided the integrated outcomes of MR PRESSO and detailed sensitivity analyses. Based on these findings, we could assert their causal relationship's credibility.

## Conclusions

Psoriasis is an immune-mediated chronic inflammatory skin disease mainly affecting the knees, elbow, trunk, and scalps, which presents with well-demarcated erythematous plaques covered by silvery-white scales. Medication-provoked psoriasis can be classified into two types. Medication-induced psoriasis often occurs in patients with no family or personal history of psoriasis, whose lesions typically subsided after ceasing medication use [25]. Medication-aggravated psoriasis usually affects patients with a history of psoriasis or a genetic predisposition, generally exacerbating their existing lesions or developing new ones [25]. However, identifying medication-related triggers for psoriasis flares in clinical practice can be challenging for various reasons. For example, variations in the absorption rate and half-time period among different medications may lead to an inconspicuous temporal relationship [26]. As mentioned earlier, MR analysis can



**Figure 1.** The forest plot displayed the results of a two-sample Mendelian randomization analysis, investigating the relationship between the intake of 23 different types of medications and the risk of psoriasis. The effect estimates were presented as odds ratios. CI = confidence interval; OR = odds ratio.

effectively dispose of this drawback, making it a more credible tool for causal estimation between medication intake and the increased risk of psoriasis.

Psoriasis patients are susceptible to developing cardiovascular episodes [12,13]. Statins, also known as HMG-CoA reductase inhibitors, are commonly prescribed to lower cholesterol levels and decrease the incidence of cardiovascular diseases. However, there is an ongoing debate among researchers regarding the relationship between statin use and psoriasis. Some studies suggested that statins had beneficial effects on plaque psoriasis and could reduce its severity [27,28]. Conversely, others argued that there was insufficient evidence that using oral statins as an auxiliary treatment could reduce the severity of psoriasis [29]. Psoriasis patients with hypercholesterolemia may even worsen their pre-existing psoriasis after using statins due to the activation of signal transducer and activator of transcription 3 (STAT3) [30]. These studies also stated that statins could result in the deterioration of psoriasis lesions [31,32]. Our study found that statin intake increased the risk of triggering or exacerbating psoriasis, providing genetic evidence for exploring the concrete pharmacological mechanism of statins in psoriasis patients.

Pruritus is a common symptom experienced by most psoriasis patients and can significantly impact their quality of life. Itching often leads to the scratching of psoriatic lesions, further intensifying the itch and creating a vicious cycle of “itching-scratching,” ultimately worsening skin inflammation. In clinical practice, dermatologists use antihistamines to alleviate itch in skin disorders. Few large-scale, randomized, controlled trials have examined whether antihistamines use increases the risk of psoriasis. Some case reports have suggested that fexofenadine and terfenadine may exacerbate psoriasis [33,34]. Our research provided theoretical evidence that antihistamines use may be a risk factor for psoriasis, but the underlying reason for this remained unclear. Further pharmacological studies are required to elucidate the mechanism of this adverse reaction.

Recent studies have shed light on the relationship between psoriasis and thyroid disease. For instance, hypothyroidism was highly prevalent in psoriasis patients [35]. Hashimoto’s thyroiditis was also more prevalent in psoriasis patients (especially in females) than in healthy people [35-37]. Levothyroxine is usually used to treat hypothyroidism and Hashimoto’s thyroiditis. To date, few studies

have investigated the effect of thyroid preparations on psoriasis lesions. Our results suggested, for the first time, that thyroid preparations may contribute to the onset of psoriasis, which can guide future research in exploring the role of thyroid preparations in the occurrence, recurrence, and exacerbation of psoriasis.

Hypertension was reported to have a higher risk of psoriasis incidence (HR: 1.54, 95% CI: 1.47-1.61,  $P < 0.001$ ) and was also known to be more challenging to control in psoriasis patients [38,39]. Antihypertensives are mainly divided into five categories: diuretics,  $\beta$ -receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Our study did not find a correlation between these medicines and an increased risk of psoriasis. In contrast, the remaining minorities, such as sympatholytic agents (reserpine, clonidine), direct vasodilators (hydrazine), and  $\alpha$ 1-receptor blockers (prazosin, terazosin), were implicated. For example, a large population-based, case-control study found no connection between the use of  $\beta$ -blockers and an increased risk of psoriasis [40]. However, clonidine may increase the risk of psoriasiform eruption by decreasing intracellular cyclic AMP and promoting the proliferation of epidermal cells [41]. Taking urapidil resulted in the observation of a similar lesion [42]. These findings were consistent with the results of our study, which instructed us to choose appropriate antihypertensives medications for psoriasis patients.

Acetaminophen and aspirin are two of the most widely used NSAIDs. Shaowei Wu et al. reported that regular acetaminophen users may increase the risk of developing psoriasis and psoriatic arthritis [43]. This phenomenon may be attributed to its inhibition of arachidonic acid metabolism via the cyclo-oxygenase pathway, resulting in the accumulation of leukotrienes and aggravating psoriasis [10]. Notably, acetaminophen belongs to both NSAIDs and anilides. This finding aligned with our study outcomes, which indicated NSAIDs and anilides were associated with a greater risk of psoriasis. These results reminded clinicians that aspirin may be a safer alternative to acetaminophen when prescribing NSAIDs to psoriasis patients in the short term. However, clinicians should still pay attention to psoriasis occurrence when patients use NSAIDs for a long time [43].

This reliable evidence emphasizes the importance of rational medication administration, which is crucial in preventing and managing psoriasis. However, we acknowledge that our research has some limitations. Firstly, the study samples were predominantly of European populations, so the results may not be generalizable to other racial populations. Moreover, the risk factors for disease onset may not align with its prognosis or severity. In other words, the value of our research findings lies in the prevention instead of treatment for psoriasis. Finally, like any other MR research, the

instrumental variable assumptions cannot be empirically verified, but we have conducted sensitivity analyses to ensure no heterogeneity or horizontal pleiotropy.

Our study offers a causal testimony that the intake of HMG CoA reductase inhibitors, thyroid preparations, non-steroidal anti-inflammatory and antirheumatic products, anilides, antihistamines for systemic use, and antihypertensives are substantially associated with the increased risk of psoriasis.

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