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Inflammatory Cytokines and Psoriasis: A Mendelian Randomization Study

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Abstract: Psoriasis, a chronic inflammatory skin disorder, has been posited to be influenced by circulating inflammatory cytokines. However, the causative link remains nebulous. The use of Mendelian Randomization (MR) analysis is gaining popularity in testing the causal impact of exposures on disease outcomes by utilizing data obtained from genome-wide association studies. Using a two-sample Mendelian randomization analysis model, we evaluated the causal relationship between 26 circulating inflammatory cytokines and psoriasis risk based on GWAS meta-analysis summary data. We identified significant causal associations between specific inflammatory cytokines and psoriasis. IL-14 and CTACK were associated with increased risk, while IL-1 receptor antagonist (IL-1ra) and MCP1 showed associations with reduced risk. Notably, IL-14 and CTACK emerged as potential risk factors, while IL-1ra and MCP1 appear to serve as protective factors. No significant effects were observed for IL-2ra, IL-2, IL-6, IL-17, IL-8, IL-10, IL-16, IL-18, MIF, MIG, MIP1a, MIP1b, RANTES, and CXCL9 on psoriasis. The research offers genetic epidemiology evidence that associates psoriasis risk with specific circulating inflammatory cytokines. These findings underscore the potential of cytokine-targeted therapies and the importance of cytokine profiling in clinical practice.

Keyword: Psoriasis; Mendelian randomization; Inflammatory cytokines; GWAS meta-analysis

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1. Introduction

Psoriasis is a prevalent skin condition characterized by chronic inflammation that affects people of all genders. It affects roughly 2-3% of the worldwide population, with the highest occurrence observed between the ages of 40 and 55-70 [1]. The hallmark features of this disease include abnormal epidermal proliferation and incomplete keratinization of the skin epidermis [2]. Its pathogenesis is influenced by genetic, epigenetic, environmental, and immune factors and may be triggered or influenced by various factors such as ultraviolet radiation, infections, trauma, medications, and lifestyle [3]. Diagnosis is typically based on clinical history and physical examination, with histopathological examination occasionally required for confirmation [4]. Therefore, in-depth research into psoriasis's pathogenesis is paramount for its prevention and treatment.

The development of psoriasis is influenced by complex relationships between different types of cells and inflammatory cytokines. Bennett et al., using single-cell transcriptome analysis, reported significant expression of IL-14, IL-18, and IL-32 in individual cell types in psoriasis, in addition to well-known factors [5]. Pio et al. demonstrated that IL-1ra can inhibit the inflammatory process of psoriasis by reducing neutrophil infiltration and the release of proteases, IL-6, and fibrinogen [6]. Furthermore, the chemokine family has a crucial role in the development and progression of psoriasis. An observational study found significant differences in the levels of CTACK in healthy and psoriasis populations [7]. Although several studies have reported an association between inflammatory cytokines and psoriasis, these studies were observational and the evidence presented was a correlation test. There is still a lack of extensive research on the connection between circulating inflammatory cytokines and susceptibility to psoriasis.

Confirming causality between inflammatory cytokines and psoriasis is difficult due to reverse causation and confounding. Mendelian randomization (MR) uses genetic variants as instrumental variables (IVs) to overcome these biases, as alleles are randomly assigned and fixed after conception. We performed two-sample MR using SNPs for 26 circulating cytokines (from GWAS) as IVs, with psoriasis GWAS as the outcome. Seven MR models and odds ratios were applied to estimate associations [8-9]. Our findings provide novel insights into potential therapeutic targets for psoriasis prevention.

2. Method

2.1 Study design and data sources

To assess the causal impact of circulating inflammatory cytokines on psoriasis, we employed a two-sample MR analysis model (**Figure 1**). MR analysis can overcome unmeasured confounding and make stronger causal inferences; thus, it is a good method to assess whether an exposure factor has a causal effect on the development of one disease [10]. The effect of 26 circulating inflammatory cytokines was assessed using a total of seven MR analysis models (CRP, MIP1a, MIP1b, IL-1ra, IL-2ra, IL-2, IL-6, IL-17, IL-8, IL-10, IL-13, IL-14, IL-16, IL-17, IL-18, MCP1, MIF, MIG, CTACK, Eotaxin, GROa, MIP1a, MIP1b, RANTES, TANLN, CXCL9) on psoriasis. We utilized genetic variants that were reported in the most comprehensive meta-analysis of genome-wide association studies (GWAS) related to cytokines in order to investigate the association between these variants and circulating levels of inflammatory cytokines in three separate groups [the Cardiovascular Risk in Young Finns Study (YFS), FINRISK 1997, and FINRISK 2002], including up to 8,293 Finnish participants [11]. The largest GWAS (id: ukb-a-100, https://gwas.mrcieu.ac.uk/datasets/ukb-a-100/) recently published provided the summary statistics data for psoriasis, resulting in the determination of the lifetime risk of developing this condition. This GWAS for psoriasis tested the associations between up to 10,894,596 genotyped SNPs of psoriasis, including a total of 337,159 individuals (3,871 cases and 333,288 controls) of European ancestry.

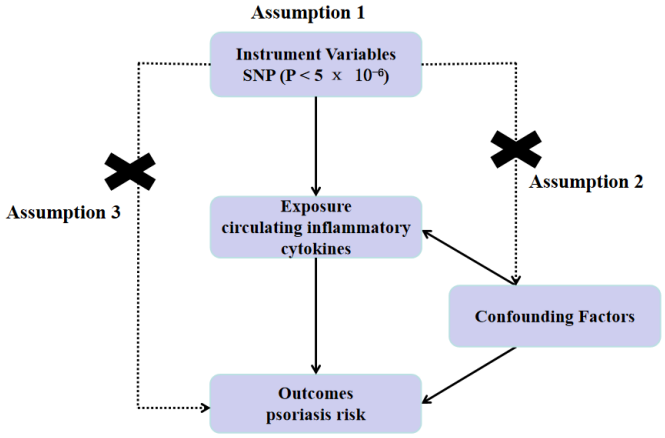


Figure 1. Schematic of the study design in this Mendelian randomization (MR) analysis.

Significant instrumental variables were selected for 26 inflammatory cytokines and psoriasis, and the causalities were then explored. Three basic assumptions of MR analysis were illustrated in this causal directed acyclic graph, namely, relevance, independence, and exclusion restriction.

2.2. SNP selection

We identified single-nucleotide polymorphisms (SNPs) associated with these circulating inflammatory cytokines as instrumental variables (IVs) [$P < 5 \times 10-6$; linkage disequilibrium (LD); $r2 < 0.001$, LD distance > 10,000 kb]. Furthermore, we searched for information on the above IV SNPs in the outcome group (psoriasis) data from the large-scale GWASs (ID: ukb-a-100, https://gwas.mrcieu.ac.uk/datasets/ukb-a-100/). The dataset for psoriasis was derived from the Neale Lab. The studies included in these GWAS meta-analyses had obtained ethical approval from the appropriate institutional review boards. In this study, we only extracted the summarized data from the aforementioned studies; therefore, obtaining the data did not require additional ethics approval.

2.3. Statistical analysis

In this study, a total of 7 methods for Mendelian randomization analysis were used, including fixed-effect and random-effect inverse-variance weighted (IVW), simple median, weighted median, penalized weighted median, MR Egger, and MR Egger (bootstrap). The primary method used to analyze the results was the IVW method, which provides a robust causal estimate even in the presence of heterogeneity. However, in order to meet the MR assumptions, two additional methods, the weighted median estimator and MR-Egger, were used for sensitivity analyses. The weighted median estimator is suitable when more than half of the instrumental variables are valid, while the MR-Egger estimate is unbiased as long as the genetic instrument is not dependent on pleiotropic effects. To assess pleiotropy and heterogeneity of individual SNPs, IVW methods with MR-Egger intercept and Cochran's Q statistic were employed. Pleiotropic effects were considered absent if the intercept did not significantly differ from 0 ($P > 0.05$), and heterogeneity was evaluated using Cochran's Q statistic. If the p-value was less than 0.05, the primary outcome of the study used the IVW method with a multiplicative random-effects model. If the p-value was greater than or equal to 0.05, the primary outcome used the IVW method with a fixed-effects model. The study also included MR-Egger regression to detect and adjust for pleiotropy and to evaluate causality and verify if directional

horizontal pleiotropy contributed to the results. Additionally, a leave-one-out analysis was conducted to assess the robustness of the MR analysis results by examining any outlier SNP. Based on the previous study, a causal relationship was considered significant if three conditions were met: 1) the *P*-value of the IVW method was less than 0.05, 2) the estimates from the IVW, MR-Egger, and weighted median methods were consistent in direction, and 3) the *P*-value of the MR-Egger intercept test was greater than 0.05. All statistical analyses were performed using the "TwoSampleMR" package in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria), and a two-tailed *P*-value less than 0.05 was considered statistically significant.

3. Results

3.1. The characteristics of instrumental variables

In our study, we utilized 565 SNPs that displayed a significant connection to the variation in circulating inflammatory cytokines. These SNPs were used as instrumental variables to estimate the causality relating to circulating inflammatory cytokines and psoriasis.

3.2. The results of circulating CRP on psoriasis

Genetically predicted higher plasma CRP levels showed no association with psoriasis using the IVW method (OR, 1.000; 95% CI, 0.999-1.001, $P = 0.840$, fixed-effect model; OR, 1.000; 95% CI, 0.999-1.001, $P = 0.842$, random-effect model). A similar result was observed in the Simple median method (OR, 1.001; 95% CI, 0.999-1.002, $P = 0.340$), however, Weighted median method (OR, 0.999; 95% CI, 0.998-1.001, $P = 0.315$), Penalised weighted median method (OR, 0.999; 95% CI, 0.998-1.001, $P = 0.322$), and MR Egger regression method (OR, 0.999; 95% CI, 0.997-1.000, $P = 0.059$) showed an opposite results, as showed in **Figure 2**. The intercept indicated evidence of pleiotropy (*P* for intercept 0.020). Cochran's Q test revealed no evidence of heterogeneity across the SNPs for psoriasis (*P* for Cochran's Q of IVW (random effects): 0.388; *P* for Cochran's Q of MR Egger: 0.459).

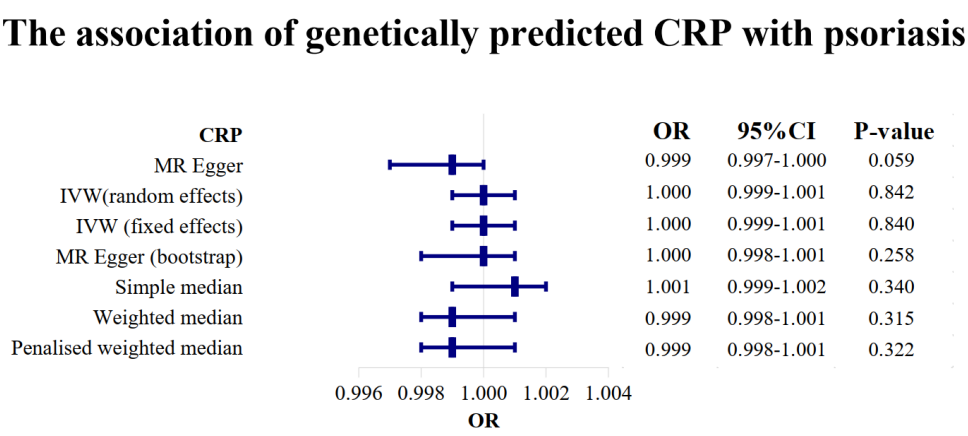


Figure 2. Causal correlations of CRP on psoriasis performed in the form of a forest plot. The change in the odds ratio (OR) of psoriasis per one-SD rise in the CRP level is shown by the OR and 95% confidence interval. The results found no significant causal relationship between CRP and psoriasis.

3.3. The results of circulating inflammatory cytokines (IL family) on psoriasis

In general, IVW is more powerful than the other six methods; so this paper is mainly based on IVW,

complementing the other six methods. The MR analysis based on the IVW method showed that IL14 has a significant causal relationship with the increased risk of psoriasis (OR, 1.002; 95% CI, 1.000-1.003, $P = 0.023$, random-effect model). The MR analysis by MR Egger also showed that IL14 has a causal relationship with the increased risk of psoriasis (OR, 1.002; 95% CI, 0.999-1.004, P = 0.292), although the causal relationship was not significant. According to the interpretation of the results in the methodology, the present study supported a causal relationship between IL14 and psoriasis, as shown in **Figure 3**. It is interesting that IL-1ra showed a causal relationship with a significant decreased risk of psoriasis (OR, 0.998; 95% CI, 0.996-1.000, $P = 0.029$, random-effect model IVW; OR, 0.997; 95% CI, 0.992-1.003, $P = 0.401$, MR Egger). We also investigated the causal relationship between other common IL factors and psoriasis. Unfortunately, we did not find a causal relationship between other IL factors and psoriasis risk, as shown in **Figure 3**.

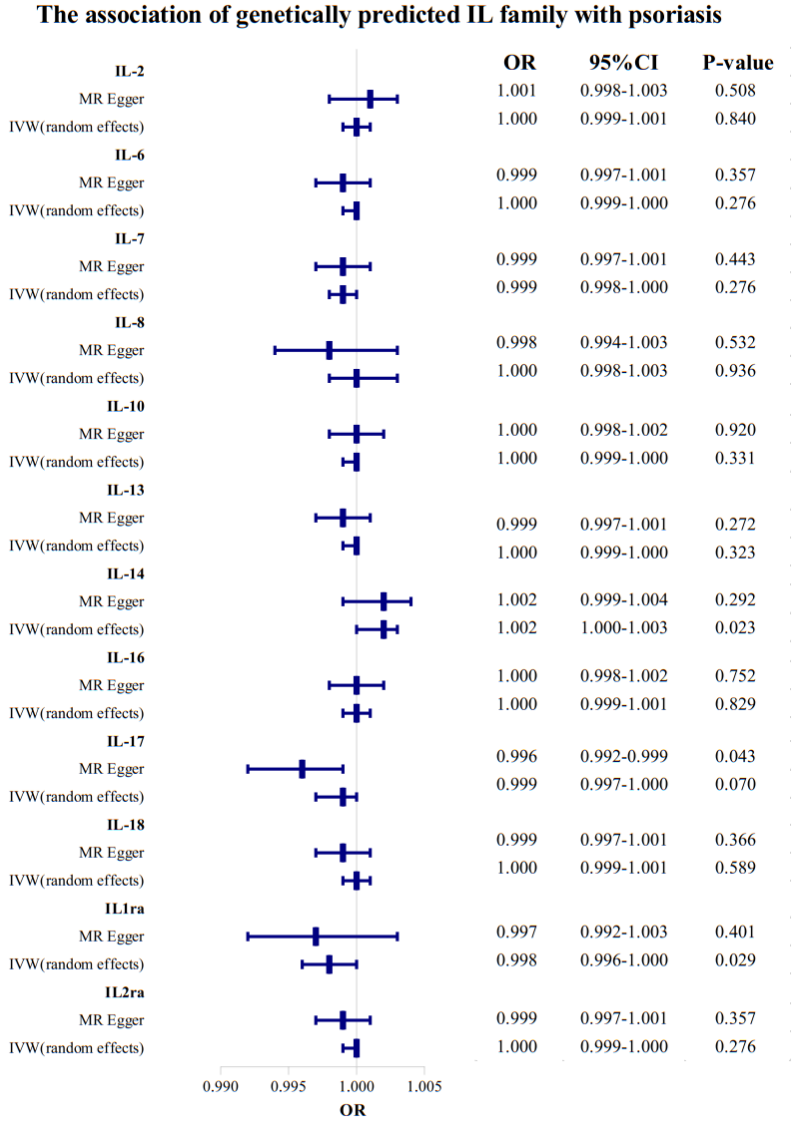


Figure 3. Causal correlations of the interleukin family factors on psoriasis performed in the form of a forest plot. The change in the odds ratio (OR) of psoriasis per one-SD rise in each interleukin factor level is shown by the OR and 95% confidence interval. The results found that IL14 has a significant causal relationship with the increased risk of psoriasis, and IL1ra has a significant causal relationship with the decreased risk of psoriasis.

3.4. The results of circulating inflammatory cytokines (chemokine family) on psoriasis

The MR analysis by IVW models showed that MCP1 has a significant causal relationship with the decreased risk of psoriasis (OR, 0.998; 95% CI, 0.997-0.999, P = 0.000, random-effect model; OR, 0.998; 95% CI, 0.997-0.999, P = 0.002, fixed-effect model). Similar results were observed in the other analysis methods, simple median (OR, 0.997; 95% CI, 0.995-0.999, P = 0.009), weighted median (OR, 0.999; 95% CI, 0.997-1.000, P = 0.096), penalised weighted median (OR, 0.999; 95% CI, 0.997-1.000, P = 0.100), and MR Egger (OR, 0.999; 95% CI, 0.996-1.002, P = 0.372). CTACK (OR, 1.001; 95% CI, 1.000-1.003, P = 0.014, random-effect model; OR, 1.001; 95% CI, 1.000-1.002, P = 0.006, fixed-effect model) with simple median (OR, 1.002; 95% CI, 1.001-1.0044, P = 0.005), weighted median (OR,1.002; 95% CI, 1.001-1.003, P = 0.020), penalised weighted median (OR, 1.002; 95% CI, 1.000-1.003, P = 0.023), and MR Egger (OR, 1.000; 95% CI, 0.998-1.002, P = 0.922) was showed a significant causal relationship with the increased risk of psoriasis, as showed in **Figure 4**. There is no research evidence to suggest that CXCL9, Eotaxin, GROa, MIF, MIG, RANTES, TNFα, TNFβ, and TRAIL were associated with an increased risk of psoriasis, as shown in **Figure 4**.

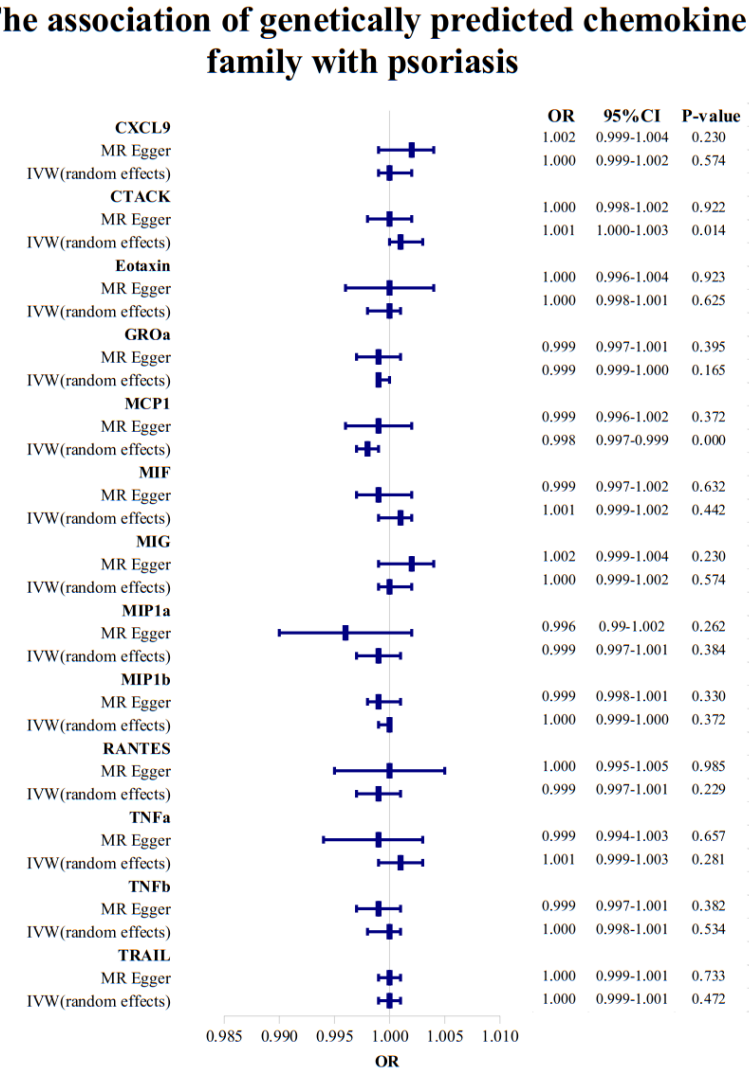


Figure 4. Causal correlations of the chemokine family factors on psoriasis performed in the form of a forest plot. The change in the odds ratio (OR) of psoriasis per one-SD rise in each chemokine level is shown by the OR and 95% confidence interval. The results found that CTACK has a significant causal relationship with the increased risk of psoriasis, and MCP1 has a significant causal relationship with the decreased risk of psoriasis.

3.5. Secondary results associated with selected instruments and sensitivity analyses

There was a suggestion of potential heterogeneity for IL16 (*P* for Cochran's Q of IVW (random effects): 0.05; *P* for Cochran's Q of MR Egger: 0.039). We did not observe methodological heterogeneity in the causal relationship of other inflammatory cytokines to psoriasis. MR-Egger Intercept-test showed that our results were not affected by horizontal pleiotropy (The *P* value in the MR-Egger Intercept-test for each inflammatory cytokines on psoriasis were all more than 0.05, only except for CRP (*P*: 0.020). The leave-one-out sensitivity analysis results suggested that no specific SNP primarily influenced the relationship between inflammatory cytokines and psoriasis.

4. Discussion

This study employed a two-sample Mendelian randomization (MR) approach to systematically evaluate the causal associations between circulating inflammatory cytokines and psoriasis risk. Inverse-variance weighted (IVW) analysis revealed that elevated levels of IL-14 and CTACK were significantly associated with increased psoriasis risk, identifying them as risk factors, whereas higher IL-1 receptor antagonist (IL-1ra) and MCP-1 levels correlated with reduced risk, suggesting protective roles.

These findings are consistent with the established immunopathological landscape of psoriasis. Psoriatic lesions are characterized by aberrant keratinocyte proliferation and differentiation driven by the IL-23/IL-17 axis, further amplified by pro-inflammatory cytokines such as TNF-α and IL-6 [12]. Biologics targeting IL-23 or IL-17 pathways have demonstrated clinical efficacy, and low-dose IL-2 has been shown to restore Treg/Th17 balance [13-14]. In this context, our identification of IL-14 (a less extensively studied cytokine) and IL-1ra (known to be linked to *IL1Ra* gene polymorphisms(6)) provides novel insights into potential therapeutic targets.

Regarding chemokines, previous reports have highlighted aberrant expression of MIF, MIG, OPN, and CXCL9 in psoriasis or psoriatic arthritis, and the MCP-1 promoter polymorphism (-2518 A/G) has been implicated in disease susceptibility and clinical phenotype [15-17]. Our study adds to this evidence by demonstrating a causal relationship for CTACK (risk) and MCP-1 (protection), although no significant associations were observed for IL-2, IL-6, IL-17, IL-8, IL-10, IL-16, IL-18, MIF, MIG, MIP-1α, MIP-1β, RANTES, or CXCL9. Discrepancies between studies may arise from differences in sample size, population composition, or subtype proportions, and may also reflect the heterogeneous effects of circulating versus tissue-level cytokines.

From a biological standpoint, the pathogenic effects of IL-14 and CTACK are likely mediated through immune dysregulation and exacerbated autoinflammation, leading to enhanced release of downstream mediators such as TNF-α and IL-17, which in turn drive keratinocyte hyperproliferation and abnormal cornification. Conversely, the protective actions of IL-1ra and MCP-1 may involve suppression of immune-mediated inflammation, reduction of cutaneous inflammatory mediators, and preservation of skin barrier integrity, underscoring the critical role of immune homeostasis in disease prevention.

Several limitations should be acknowledged. First, the analyses were restricted to European-ancestry populations, limiting generalizability to other ethnic groups. Second, while MR supports causal inference, it cannot delineate the underlying molecular mechanisms, necessitating complementary animal and in vitro studies. Third, the absence of detailed clinical data precluded subgroup analyses; future investigations with richer phenotypic information are warranted.

5. Conclusion

In conclusion, this study provides genetic evidence for causal links between selected circulating inflammatory cytokines and psoriasis, highlighting IL-14, CTACK, IL-1ra, and MCP-1 as potential screening biomarkers. However, these findings require validation in broader populations and further mechanistic exploration.

Disclosure statement

The authors declare no conflict of interest.

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