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Assessing the causal relationship between psoriasis vulgaris and urolithiasis

A two-sample Mendelian randomization study

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Abstract

Psoriasis has been suggested to be associated with urolithiasis. However, the existing literature is based on observational studies, which provide limited evidence for the causal relationship between these two conditions. This research aims to evaluate the causal association between psoriasis vulgaris and urolithiasis using 2-sample Mendelian Randomization (MR) analysis. Exposures and outcomes were sourced from genome-wide association study data. The psoriasis vulgaris dataset included 5072 patients and 4,78,102 controls. The urolithiasis dataset included 5347 patients and 2,13,445 controls. We used the inverse-variance weighted (IVW) method as our primary analytical strategy, augmented by MR-Egger regression and the weighted median method. Cochran *Q* test, MR-Egger regression, leave-one-out analysis and Steiger filtering were also conducted to evaluated the stability and credibility of the results. The IVW analysis showed a significant association between psoriasis vulgaris and urolithiasis (odds ratio [OR] = 1.073, 95% confidence interval [CI] = 1.017–1.131, $P = .010$). The results of weighted median analysis (OR = 1.071, 95% CI = 1.013–1.133, $P = .017$) and MR-Egger regression (OR = 1.072, 95% CI = 0.992–1.158, $P = .12$) indicated a consistent directional causality with the IVW analysis. There was no significant horizontal pleiotropy or heterogeneity in the analysis. Steiger filtering further confirmed the accuracy of the directional causality. In conclusion, this MR study supports a causal association between psoriasis vulgaris and urolithiasis.

Abbreviations: CI = confidence interval, GIV = genetic instrumental variable, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: causal relationship, Mendelian randomization, psoriasis vulgaris, urolithiasis

1. Introduction

Psoriasis is an inflammatory skin disorder which impacts approximately 3% of the global population.[1] The predominant variant of this condition is psoriasis vulgaris, which constitutes over 80% of all psoriasis instances.[2] This form is marked by erythematous, scaly plaques that may result in significant physical discomfort as well as psychological distress.[3] Previous studies have reported its associations with various comorbidities, including diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease and inflammatory bowel disease.[3,4]

Urolithiasis is a common urological disease and is associated with significant morbidity, including renal colic and the risk of kidney damage. It has been reported to be associated with many diseases, such as diabetes mellitus, cardiovascular disease and metabolic syndrome.[5] Recent studies have proposed a potential association between psoriasis and urolithiasis, indicating that patients with psoriasis may exhibit a higher incidence of urolithiasis.[6,7] However, the existing literature comprises observational studies, which are influenced by confounding factors and provide limited causal evidence regarding this association.

The present study aims to evaluate the causal relationship between psoriasis vulgaris and urolithiasis utilizing Mendelian randomization (MR) analysis. Randomized controlled trials are golden standards to evaluate the causal relationship, whereas they are often limited by the large costs and ethics.[8] In the absence of RCTs, MR analyses minimize the influence of confounding variables, thereby offering a more robust understanding of the causal relationship than observational studies.[9] To our knowledge, this is the first study to examine the causal link between psoriasis vulgaris and urolithiasis.

JL and ZJ contributed to this article equally.

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The datasets generated during and/or analyzed during the current study are publicly available (https://gwas.mrcieu.ac.uk/).

Since all the data used relied solely on publicly available data, ethical approval was not required.

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2. Materials and methods

In this study, we focused on exposures and outcomes derived from European population. Specifically, psoriasis vulgaris (ID: ebi-a-GCST90018907) and urolithiasis (ID: finn-b-N14_UROLITHIASIS) were sourced from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/) as the exposure and outcome variables, respectively. The psoriasis vulgaris dataset included 5072 patients diagnosed with psoriasis vulgaris and 4,78,102 controls.[10] The urolithiasis dataset included 5347 patients diagnosed with urolithiasis and 2,13,445 controls. The classification of psoriasis vulgaris and urolithiasis cases was based on the International Classification of Diseases, 10th Revision (ICD-10) codes.

The execution of the MR study adhered to 3 essential assumptions.[11] Firstly, genetic instrumental variables (GIVs) are required to demonstrate a strong correlation with the exposure. Secondly, all confounding factors affecting the relationship must be independent. Lastly, GIVs should affect outcomes exclusively through the exposure factors.

Initially, we extracted single nucleotide polymorphisms (SNPs) which exhibited a significant association with psoriasis vulgaris from the pooled GWAS database, adhering to a significance threshold of $P < 5 \times 10^{-8}$. Subsequently, we confirmed the independence of GIVs by implementing screening criteria which utilized parameters of $r^2 = 0.001$ and kb = 10,000 to eliminate potential linkage disequilibrium interference. To avoid the inclusion of weak GIVs, SNPs with F values below 10 were excluded.[12]

We evaluated the causal link between the exposure and outcome variables utilizing 3 methodologies: the inverse-variance weighted (IVW) method, MR-Egger regression and the weighted median method. The IVW method was designated as the principal technique for analyzing pooled effects.[13] In addition, the credibility and robustness of the findings were further evaluated by MR-Egger regression and the weighted median method.[14,15] To enhance the credibility of our results, we employed Bonferroni correction to account for multiple testing.[16]

To assess the stability and credibility of the findings, we implemented a series of quality control measures. Initially, Cochran Q test was utilized to evaluate the heterogeneity among SNPs.[17] Additionally, pleiotropic effects were evaluated using MR-Egger regression, where an intercept significantly different from zero suggests significant horizontal pleiotropy.[18] Furthermore, we conducted a leave-one-out analysis to evaluate the cumulative effect of the remaining SNPs by sequentially excluding each SNP to determine its impact on the association. Lastly, we employed Steiger filtering for directionality test to confirm the accuracy of the directional causality. If the GIV accounts for more variance in the exposure than in the outcome, the orientation is designated as "TRUE".

All statistical analyses were executed by R software 4.4.0. utilizing the "TwoSampleMR" package. All statistical analyses were 2-tailed with a significance threshold set at $P < .05$. Since all the data used relied solely on publicly available data, ethical approval was not required.

3. Results

A total of 14 SNPs were identified as GIVs for the MR analysis after exclusion of SNPs exhibiting linkage disequilibrium. During the harmonization process, 5 SNPs were further excluded due to incompatible alleles or palindromic structures. The F values for all retained SNPs surpassed the threshold of 10 and no SNP was excluded. Ultimately, 9 SNPs were included in the analysis.

The IVW analysis showed that psoriasis vulgaris was linked to an elevated risk of urolithiasis (odds ratio [OR] = 1.073, 95% confidence interval [CI] = 1.017–1.131, $P = .010$; Fig. 1). Notably, this causal relationship remained significant after applying Bonferroni correction ($P = .010$). The weighted median analysis also indicated estimates that were directionally consistent (OR = 1.071, 95% CI = 1.013–1.133, $P = .017$), while the findings of MR-Egger regression did not surpass standard significance thresholds (OR = 1.072, 95% CI = 0.992–1.158, $P = .12$; Fig. 1).

Cochran Q test showed no significant heterogeneity among the SNPs ($P = .39$) and the MR-pleiotropy test yielded a negative result ($P = .97$), further substantiating the reliability of our findings (Table 1). Scatter plots generated from all 3 MR methodologies illustrated a consistent positive correlation between psoriasis vulgaris and urolithiasis (Fig. 2). Furthermore, the funnel plot exhibited a lack of asymmetry in the analysis, suggesting the absence of directional horizontal pleiotropy (Fig. 3). The leave-one-out analysis exhibited that no single SNP disproportionately affected the overall causal inference (Fig. 4). Finally, the directionality test confirmed that the variance explained by psoriasis vulgaris was significantly greater than that attributed to urolithiasis ($P < .001$), thereby reinforcing the validity of the proposed causal direction (Table 1).

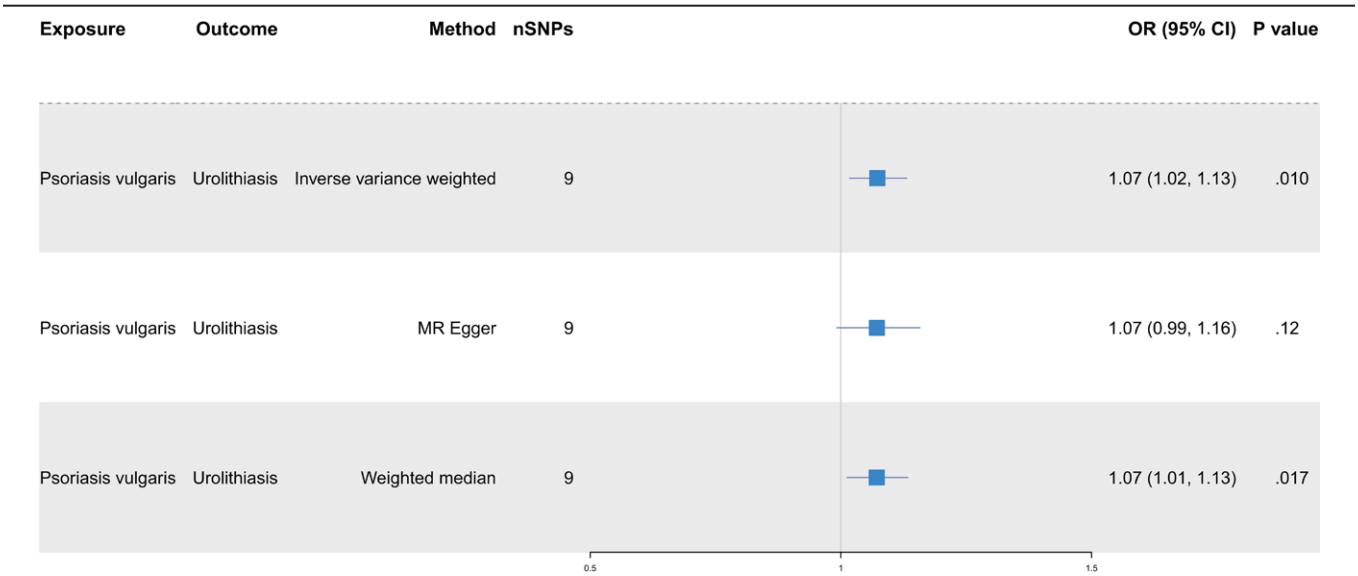

Figure 1. Causal association between psoriasis vulgaris and urolithiasis. SNP = single nucleotide polymorphism.

Table 1

Heterogeneity, horizontal pleiotropy and directionality test of the Mendelian randomization analysis.

Heterogeneity		Horizontal pleiotropy		Directionality test	
Q	*P*	Egger intercept	*P*	Correct causal direction	*P*
8.509	.39	5.113×10^{-4}	.97	TRUE	1.130×10^{-66}

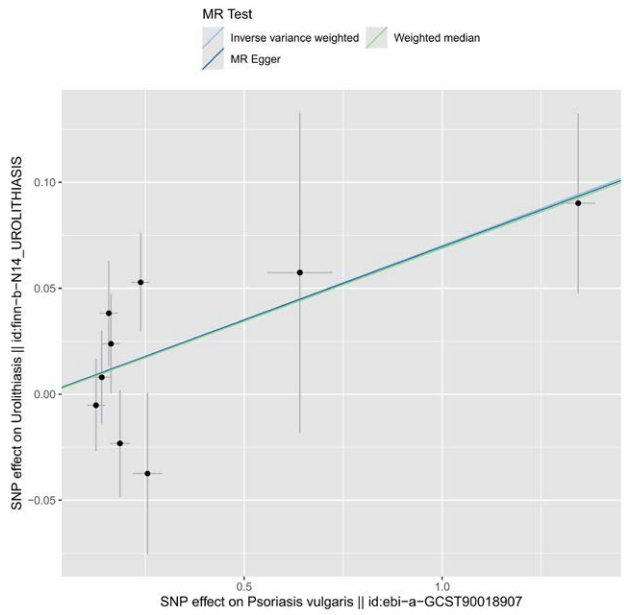

Figure 2. Scatter plot for Mendelian randomization analysis between psoriasis vulgaris and urolithiasis.

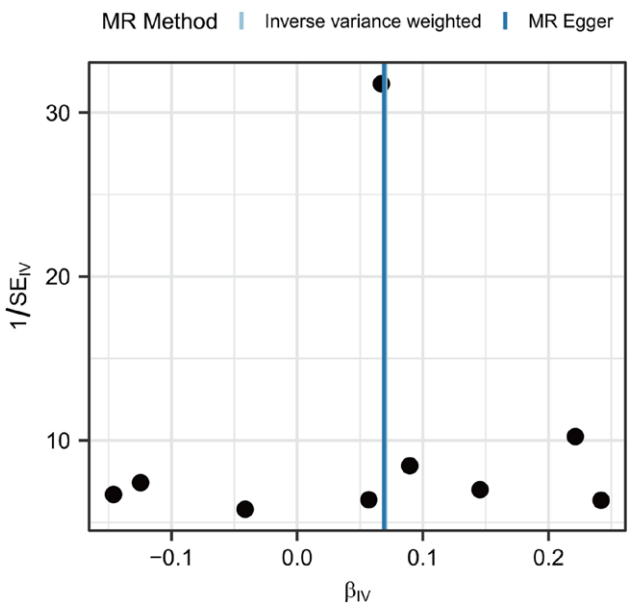

Figure 3. Funnel plot for Mendelian randomization analysis between psoriasis vulgaris and urolithiasis.

4. Discussion

The findings of the MR analysis exhibited a significant causal association between psoriasis vulgaris and urolithiasis. Specifically, the IVW method demonstrated that psoriasis vulgaris was correlated with an increased risk of urolithiasis (OR = 1.073, 95% CI = 1.017–1.131, *P* = .010). To our knowledge, this study represents the first application of MR analysis to explore this association.

Previous reports have suggested an association between psoriasis and urolithiasis. For instance, Oguz et al[7] reported a higher frequency of urolithiasis in patients with psoriasis compared to those without, while Sugihara et al[6] found a significantly elevated prevalence of urolithiasis in psoriasis patients undergoing biologic therapy as assessed through CT imaging. However, these studies were limited by their observational nature, lacking definitive causal evidence. Our research provides support for the hypothesis that psoriasis vulgaris was a risk factor of urolithiasis.

The underlying mechanisms by which psoriasis may contribute to urolithiasis remain to be fully elucidated. Oguz et al[7] noted that psoriasis patients exhibit metabolic abnormalities, including hypocitraturia, hyperuricosuria, and hypernatriuria. Both hypocitraturia and hyperuricosuria are established risk factors of urolithiasis,[19] while hypernatriuria has also been associated with increased stone formation.[20] These metabolic disturbances may partially elucidate the observed association, although the precise mechanisms warrant further investigation.

This study aligns with existing literature that emphasizes the systemic implications of psoriasis and its potential influence on various comorbidities. Psoriasis, recognized as a chronic inflammatory skin disorder, has been linked to a range of systemic conditions, including metabolic syndrome and cardiovascular diseases, and now, urolithiasis. A critical pathway implicated in psoriasis is the immune response, particularly the involvement of T lymphocytes and pro-inflammatory cytokines such as IL-17 and TNF-α,[4] both of which are known to exacerbate inflammatory processes in psoriasis. Elevated levels of TNF-α have also been documented in patients with calcium oxalate kidney stones,[21] suggesting that psoriasis and urolithiasis may share certain inflammatory mechanisms. Nevertheless, a definitive immunological connection between psoriasis and the formation of urinary stones has not yet been established and need further investigation.

Despite the rigorous methodologies employed in this study, several limitations must be acknowledged. Firstly, the datasets utilized were derived exclusively from European populations, which may limit the generalizability of the results to broader populations. Secondly, the reliance on bioinformatics and computational methodologies without the inclusion of wet lab experiments restricted our understanding of the mechanistic pathways linking psoriasis vulgaris to urolithiasis. Lastly, the analysis was confined to psoriasis vulgaris, necessitating further exploration of the relationship between other psoriasis variants and urolithiasis.

5. Conclusions

In summary, our research supports the causal link between psoriasis vulgaris and urolithiasis, highlighting the necessity for vigilant monitoring and management of urolithiasis risk in individuals with psoriasis vulgaris. Future studies should prioritize clinical validation and delve into the underlying mechanisms, as well as develop targeted interventions aimed at mitigating this risk.

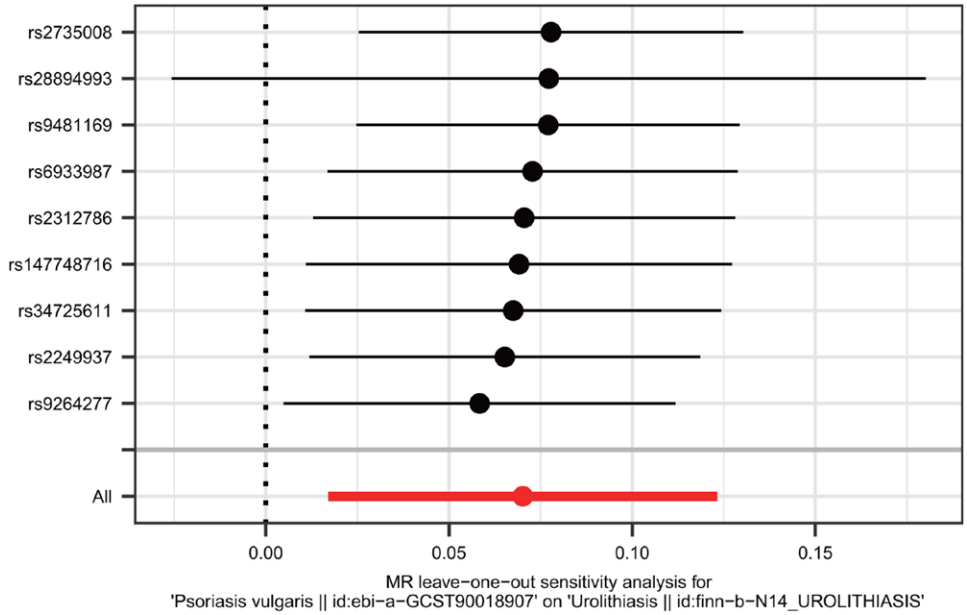

Figure 4. Leave-one-out plot for Mendelian randomization analysis between psoriasis vulgaris and urolithiasis.

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Author contributions

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