

Causal Relationship of Skin Microbiota on Psoriasis: A Mendelian Randomization Study

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Objective: Epidemiological investigations have indicated an association between skin microbiota imbalance and psoriasis, however, the causal relationship has not been confirmed through Mendelian randomization (MR). MR employed genetic instrumental variables (IVs) to evaluate the causal relationship between skin microbiota and psoriasis, providing new insights for potential treatments.

Methods: Summary statistics for psoriasis and related traits were available from FinnGen R10 and United Kingdom Biobank (UKB) consortium. The genome-wide association studies (GWAS) on skin microbiota in three skin microenvironments came from two population-based German cohorts. Several selection processes were used to determine the optimal instrumental variables. Five MR methods were performed and different sensitivity analyses approaches yield robustness evidence under different assumptions.

Results: 449 SNPs were employed as IVs for 53 bacterial genera, with F-statistics between 20.18 and 42.44, indicating no evidence of weak instrument bias. *Bacteroides* was associated with psoriasis from UKB in IVW (OR, 95% CI: 0.914, 0.869–0.961; $P < 0.001$, $P_{B-H} = 0.007$). The taxon was also associated with psoriasis vulgaris (IVW: OR, 95% CI, 0.918, 0.872–0.967; $P = 0.001$, $P_{B-H} = 0.054$) and psoriasis and related disorders (IVW: OR, 95% CI, 0.915, 0.875–0.957; $P < 0.001$, $P_{B-H} = 0.008$). Consistent causal estimates were identified in terms of both magnitude and direction, indicating a protective effect of *Bacteroides*.

Conclusion: The MR study found that *Bacteroides* in the antecubital fossa may protect against psoriasis, offering genetic proof that skin microbiota helps prevent the condition.

Keywords: skin microbiota, psoriasis, Mendelian randomization, genus *Bacteroides*, autoimmune disease, AD

Introduction

Psoriasis, which includes subtypes such as psoriasis vulgaris, erythrodermic psoriasis, pustular psoriasis, arthropathic psoriasis, and other variants, is a chronic, systemic skin and autoimmune disorder characterized by abnormal proliferation of epidermal keratinocytes and associated inflammation.^{1,2} Global statistics from the World Health Organization indicated that over 125 million individuals worldwide were impacted by psoriasis, with a higher prevalence observed in high-income nations.¹

Researchers have posited that the immune system may play a contributory role in the pathogenesis of psoriasis.^{3,4} The significance of microbiomes in maintaining skin health was growing, with dysbiosis of microbiomes being linked to various skin conditions. It has been proposed that microbiome-related immunological dysregulation may contribute to systemic inflammation.^{5,6} The notion of the gut-skin axis has garnered increased attention in contemporary scholarship, leading to numerous studies investigating the connection between gut bacteria and skin conditions.⁷ Additionally, skin microbiota helps regulate immune responses and maintain skin-resident commensals.⁸ Evidence suggested that skin microbiota imbalance may play a role in psoriasis development.^{9,10} Nevertheless, the epidemiological evidence regarding these associations has been inconsistent, as qualitative studies have identified various bacterial taxa that show significant

increases in psoriatic lesions.¹¹ Consequently, investigating the correlation between psoriasis and skin microbiota, along with the pathophysiology of the disorder, may yield evidence-based therapeutic targets for clinical intervention.

Mendelian randomization (MR) is a statistical method utilized in epidemiological studies to evaluate causal relationships, utilizing single nucleotide polymorphisms (SNPs) as genetic instrumental variables (IVs) that demonstrate robust correlations with exposures, in order to estimate causal associations between exposures and outcomes. The random allocation of genotypes in MR studies helps mitigate the effects of confounding variables.

The selected IVs must meet three core assumptions: Genetic variation is correlated with exposure; the impact of IVs on outcomes remains unaffected by confounding variables. A genetic variation can only affect outcome through a particular exposure. Combined, these two later assumptions are known as the “nonexistent horizontal pleiotropy assumption”.¹²

Previous research has established a causal association between psoriasis and gut bacteria through MR analysis.^{13–15} However, the influence of skin microbiota on the development and progression of psoriasis had not been explored using this method. Therefore, our study sought to explore the potential causal relationship association through MR method, with the aim of identifying novel therapeutic targets for the management of psoriasis.

Methods

Data Sources

Summary statistics for psoriasis and related traits can be obtained in FinnGen R10 cohort (https://www.finnngen.fi/en/access_results) and United Kingdom Biobank (UKB) (<https://pheweb.org/UKB-SAIGE/>) consortium. FinnGen is a project that merges genotype data from Finnish biobanks and health registries with health outcomes data. Diagnostic criteria were established according to International Classification of Diseases, 10th Revision (ICD-10). The summary data from GWAS for psoriasis included 19,345,588 variant loci derived from 10,312 cases and 397,564 controls.¹⁶ We also collected the data from the White British participants in the UKB. The UKB defined psoriasis using ICD-10 according to participants’ medical records and questionnaires, which contained 2,237 psoriasis cases and 398,199 controls. GWAS was accomplished between the binary outcomes and SNPs through SAIGE, a mixed model association test that adjusts for various factors.¹⁷ Detailed information on FinnGen and UKB consortia was shown in Table 1.

The summary GWAS data on skin microbiota in different body parts and skin microenvironments came from two population-based German cohorts. Two cross-sectional studies, KORA FF4 (n = 324) and PopGen (n = 273), collected 1656 skin samples. Based on the sequencing of V1-V2 regions within the 16S ribosomal RNA gene, microbial community profiles were generated. GWAS was carried out on relative abundances of individual bacteria.¹⁸ We limited our analysis at the genus level. Detail information of each taxon or sample was available in Table 1 and Supplement Table 1.

Table 1 Characteristics of Data in Genome-Wide Association Studies

Trait		Case / Control	Data Source
Exposure: skin microbiota	Dry [dorsal and volar forearm (PopGen)], moist [antecubital fossa (KORA FF4 and PopGen)] and sebaceous [retroauricular fold (KORA FF4) and forehead (PopGen)]	KORA FF4 (n = 324) PopGen (n = 273)	https://doi.org/10.1038/s41467-022-33906-5 https://www.finnngen.fi/en/access_results https://pheweb.org/UKB-SAIGE/
Outcome: psoriasis traits	Finngen_R10_L12_PSORI_GUTTATE Guttate psoriasis	389 / 397,564	
	Finngen_R10_L12_PSORI_NAS Other and unspecified psoriasis	1910 / 397,564	
	Finngen_R10_L12_PSORI_PUSTGEN Generalized pustular psoriasis	101 / 397,564	
	Finngen_R10_L12_PSORI_VULG Psoriasis vulgaris	6408 / 397,564	
	Finngen_R10_L12_PSORIASIS Psoriasis	10312 / 397,564	
	Finngen_R10_PSORI_STRICT Psoriasis (vulgaris), strict definition	901 / 397,564	
	ukb_saige_696 Psoriasis and related disorders	2293 / 398,199	
	ukb_saige_696.4 Psoriasis	2237 / 398,199	
	ukb_saige_696.41 Psoriasis vulgaris	1684 / 398,199	

The summary-level data was publicly available from existing, published GWAS, and therefore the ethical approval and informed consent have been trained by all original studies. As the reanalysis was based on previously collected and published data, no additional ethics approval was required.

Instrumental Variable (IV)

In order to verify the authenticity and precision of the findings regarding the causal relationship between the skin microbiota and traits of psoriasis. Optimal instrumental variables were selected through a series of processes: First, the threshold for loci-wide analysis was 1×10^{-5} . Second, 1000 genome reference panels for European were used by default in IEU OpenGWAS to compute the linkage disequilibrium (LD) between SNPs. The parameters for clumping were set to $r^2 < 0.01$, and clumping window size = 10000 kb. Third, to mitigate potential biases in strand orientation or allele coding, we excluded palindromic SNPs with intermediate effect allele frequencies (EAF > 0.42) or with A/T or G/C alleles by `harmonise_data` function. Finally, to verify IVs' strength, the F statistic for each bacterial taxon was computed utilizing the following formula: $F = R^2 * (N-2)/(1-R^2)$, F-statistic exceeding 10 suggests that the presence of weak instrumental bias is not substantial.¹⁹

Additionally, we utilized the PhenoScanner V2 database of human genotype–phenotype associations to analyze the potential associations of SNPs with confounding variables. SNPs found to be associated with these confounders were subsequently manually excluded from the analysis.

Statistical Analysis

Five MR methods were performed and different sensitivity analyses approaches yield robustness evidence under different assumptions. The primary MR analysis employs the inverse variance weighted (IVW) method, utilizing a meta-analysis framework within a multiplicative random effects model. In the absence of horizontal pleiotropy, the IVW method yields the most precise estimates.²⁰ However, numerous unidentified variables contributing to genetic pleiotropy and potentially biasing estimations persist, necessitating the utilization of alternative methodologies to ensure the robustness and validity of findings. The Maximum-likelihood (Maxlik) method, which is similar to IVW, was applied as a complementary method to control pleiotropic effects, without relying on the instrument strength independent of direct effect (InSIDE) assumption. Hypothesizing that horizontal pleiotropy and heterogeneity do not exist. Standard errors will be smaller than IVW, providing unbiased outcomes.²¹ The Robust Adjusted Profile Score (RAPS) is a novel approach that incorporates measurement error in SNP-exposure effects, maintains unbiasedness in the presence of numerous weak instruments, and demonstrates robustness to both systematic and individual pleiotropy among SNPs.²² The weighted median (WM) method enables precise estimation of causal associations even in cases where up to 50% of IVs are invalid. When the InSIDE assumption is violated, weighted model estimates demonstrate greater efficacy in detecting causal effects, reduced bias, and lower rates of type I errors compared to MR-Egger regressions.²³ MR-Egger regression generates estimates based on the assumption of InSIDE, which facilitates the assessment of the presence of pleiotropy. If the intercept term is determined to be zero, it suggests the absence of horizontal pleiotropy ($P_{\text{egger_intercept}} < 0.0$) and the analysis of the MR-Egger regression produces similar results with IVW, but less precise.²⁴

A Cochran Q statistic was used to determine if the IVW meta-analysis was statistically heterogeneous. Heterogeneity can be implied by Q statistics significant at a $P < 0.05$.²⁰ A leave-one-out analysis was conducted to assess the individual impact of each SNP on the aggregated IVW estimates. [Figure 1](#) provided a comprehensive summary of the aforementioned analysis.

The Benjamini–Hochberg method was used to adjust for multiple testing in the primary analysis. The statistical significance of the MR effect estimate was deemed significant if five MR methods had the consistent beta direction, a nominal $P < 0.05$ and Benjamini–Hochberg adjusted $P < 0.1$.

R (v4.3.2) was used for statistical analyses, including TwoSampleMR (v0.5.6) and MendelianRandomization (v0.9.0) packages for MR analyses.

Results

Based on a rigorous selection process, 449 SNPs were identified as IVs for 53 bacterial genera. The F-statistics ranged from 20.18 to 42.44, suggesting the no evidence of weak instrument bias. Detailed information about the selected IVs was shown in [Supplement Table 2](#).

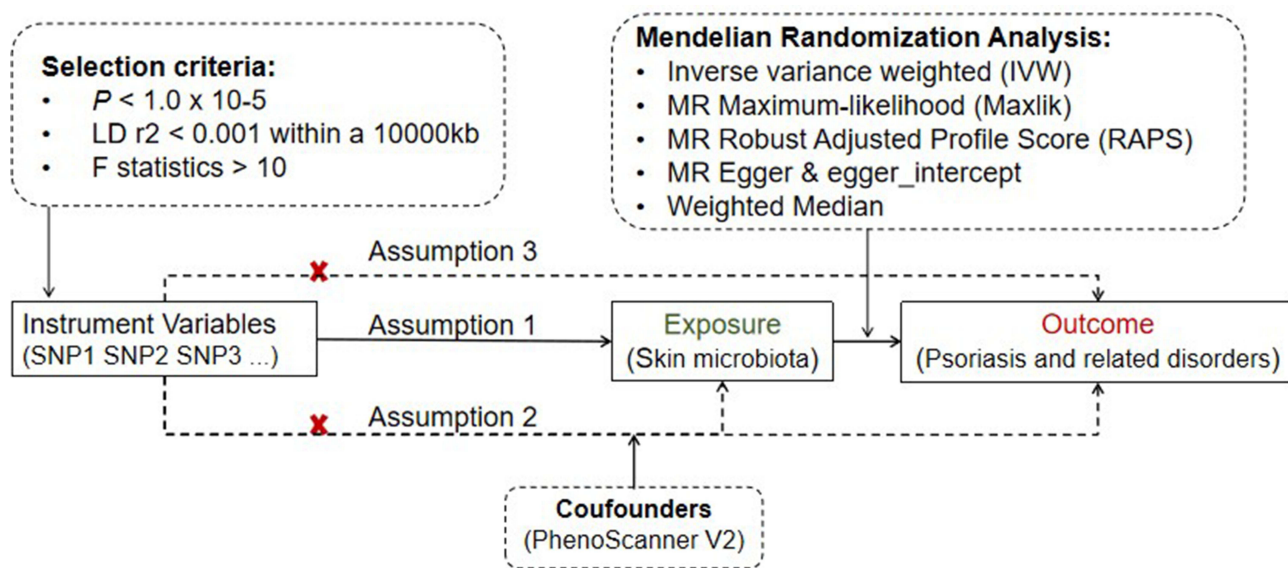


Figure 1 Design of a Mendelian randomization study on the link between skin microbiota and psoriasis and related disorders.

Table 2 showed the findings indicating that a particular bacterial genus, specifically samples from the moist region of the antecubital fossa, maintained statistical significance following B-H correction. *Bacteroides* was associated with psoriasis from UKB in IVW (OR, 95% CI: 0.914, 0.869–0.961; $P < 0.001$, $P_{B-H} = 0.007$), MR Maxlik (OR, 95% CI: 0.914, 0.869–0.961; $P < 0.001$) and MR Raps (OR, 95% CI: 0.915, 0.870–0.931; $P < 0.001$) method. The taxon was also associated with psoriasis vulgaris (IVW: OR, 95% Ci, 0.918, 0.872–0.967; $P = 0.001$, $P_{B-H} = 0.054$) and psoriasis and related disorders (IVW: OR, 95% Ci, 0.915, 0.875–0.957; $P < 0.001$, $P_{B-H} = 0.008$). Consistent causal estimates were identified in terms of both magnitude and direction, indicating a protective effect of *Bacteroides*. The scatter plots illustrating these findings across different tests are presented in Figure 2.

There was no significant heterogeneity observed among the three traits in Cochran's Q test, Table 2. Furthermore, the MR-Egger regression intercepts did not demonstrate evidence of horizontal pleiotropy, as indicated by a P-value greater

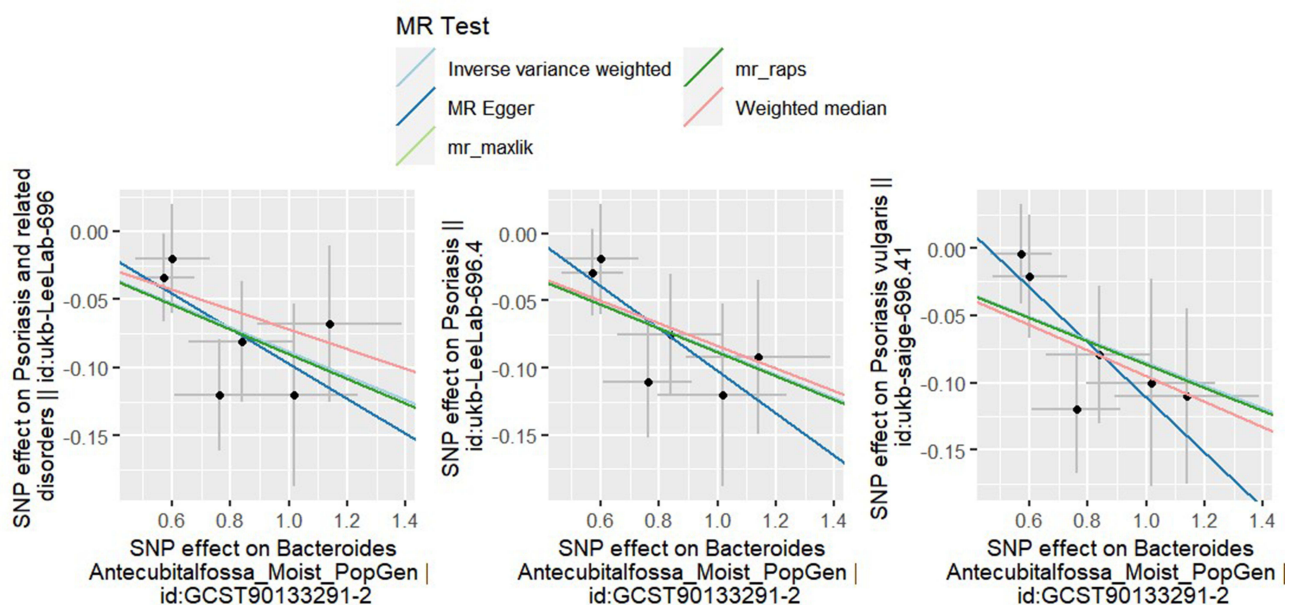


Figure 2 Scatter plots of the 5 Mendelian randomization tests in 3 causal associations from one bacterial feature to 3 psoriasis traits.

Table 2 Significant MR Results of Causal Effects Between Skin Microbiome and Psoriasis and Related Disorders

Exposure	Outcome	Method	Beta	Se	P	P _{B-H}	OR (95% CI)	P _{egger_intercept}	P _{heterogeneity}
Genus <i>Bacteroides</i> Antecubital fossa Moist PopGen id: GCST90133291-2	Psoriasis and related disorders ukb-saige-696	IVW	-0.089	0.023	<0.001	0.005	0.915 (0.875–0.957)	0.689	0.674
		MR-Egger	-0.128	0.095	0.248		0.880 (0.730–1.060)		
		WM	-0.072	0.031	0.020		0.930 (0.875–0.989)		
		MR-Maxlik	-0.090	0.025	<0.001		0.914 (0.871–0.959)		
		MR-RAPS	-0.090	0.026	<0.001		0.914 (0.869–0.961)		
	Psoriasis ukb-Lee Lab-696.4	IVW	-0.087	0.023	<0.001	0.008	0.916 (0.875–0.960)	0.488	0.791
		MR-Egger	-0.158	0.096	0.174		0.854 (0.708–1.030)		
		WM	-0.084	0.030	0.005		0.920 (0.867–0.975)		
		MR-Maxlik	-0.088	0.025	<0.001		0.915 (0.872–0.961)		
		MR-RAPS	-0.088	0.026	0.001		0.915 (0.870–0.931)		
	Psoriasis vulgaris id:ukb-saige-696.41	IVW	-0.085	0.026	0.001	0.054	0.918 (0.872–0.967)	0.319	0.645
		MR-Egger	-0.205	0.109	0.133		0.814 (0.658–1.008)		
		WM	-0.095	0.034	0.006		0.909 (0.850–0.973)		
		MR-Maxlik	-0.087	0.028	0.002		0.917 (0.869–0.968)		
		MR-RAPS	-0.087	0.029	0.003		0.917 (0.867–0.971)		

Notes: P_{egger_intercept}, p value from MR-Egger intercept test; P_{heterogeneity}, p value from Cochran Q statistic.

Abbreviations: MR, Mendelian randomization; IVW, Inverse variance weighted; WM, Weighted Median; Maxlik, Maximum-likelihood; RAPS, Robust Adjusted Profile Score; B-H: Benjamini-Hochberg.

than 0.05, Table 2. And the leave-one-out sensitivity analysis validated that the findings were not influenced by a single SNP, Figure 3.

The Genus *Bacteroides* did not exhibit any significant differences in abundance across the same anatomic location and type of sample in the KORA FF4 cohort. Additionally, there was no observed variation in abundance between the dorsal forearm and volar forearm within the same cohort. Detailed MR results can be found in Supplement Tables 3 and 4.

Discussion

The initial utilization of a comprehensive MR analysis aimed to ascertain the potential contribution of skin microbiota to the susceptibility of psoriasis and related conditions. Through a genetic examination, our research demonstrated a negative correlation between the relative abundance of *Bacteroides* in the antecubital fossa and the likelihood of developing psoriasis, psoriasis vulgaris, and related disorders within the UK Biobank cohort. These findings were consistently robust across various MR methodologies employed.

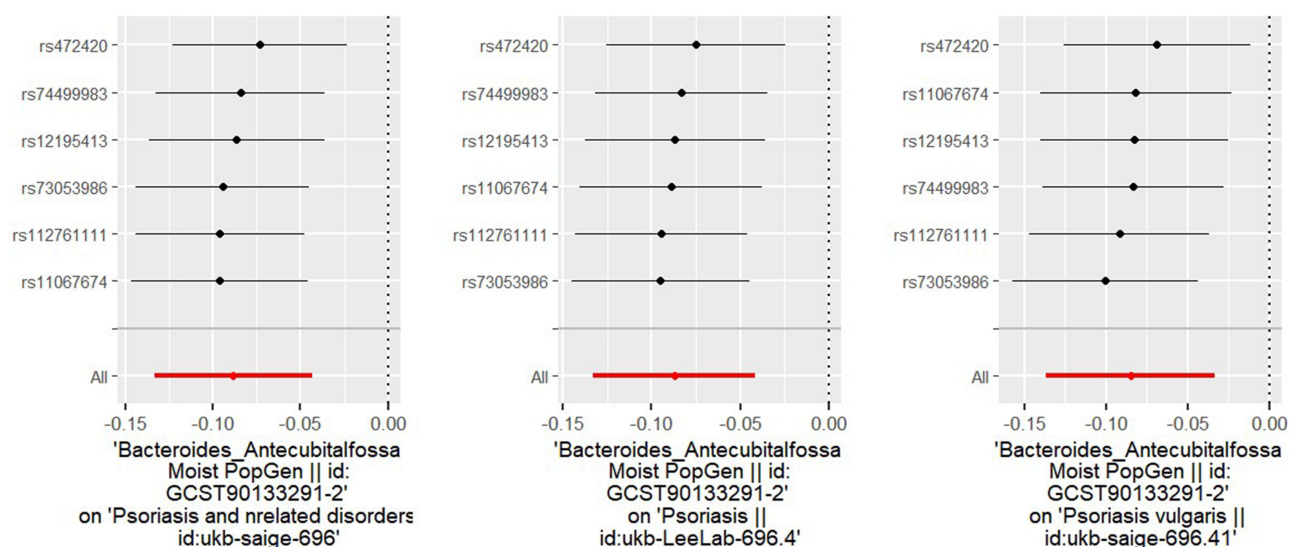


Figure 3 Leave-one-out analysis of the causal effect of bacterial on psoriasis traits. Red lines represented estimations from the inverse variance weighted test.

The Global Burden of Disease (GBD) data indicates that psoriasis was the tenth most prevalent skin disease (0.9%) and the second largest contributor to all combined skin DALYs (0.2%) in 2017. The prevalence of psoriasis was highest in developed Western countries.²⁵ Psoriatic lesions were caused by immunological mediators of the IL-23 and IL-17 pathway, which caused hyperproliferation and abnormal differentiation of epidermal keratinocytes.²⁶ The IL17 family was considered the main inflammatory cytokine for pathogenesis. IL-17A and IL-17F were both upregulated in psoriasis and IL-17C overexpression in keratinocytes promoted psoriasiform skin inflammation.^{27,28} IL-17A could promote the expression of keratin K17 by activating signalers and transcriptional activator 1 (STAT1) and STAT3 pathways and was involved in the pathogenesis of psoriasis.²⁹ An inflammatory cycle was created when cytokines like IL-17 and IL-22 caused excessive keratinocyte proliferation and the production of associated cytokines and chemokines.³⁰

Bacteroides played a significant role in the immune modulation of the human immune system by metabolizing lipids into free short-chain fatty acids (SCFA), such as propionate, acetate, and butyrate. The preceding two metabolites inhibited the release of pro-inflammatory cytokines from neutrophils and macrophages.³¹ Meanwhile, butyrate inhibited the immune response cells' adhesion, proliferation, translocation, and cytokine synthesis, along with the production of reactive oxygen species.³²

Bacteroides was reported to exert beneficial effects in the gut against psoriasis.³³ Recent lectures had suggested that the skin and the gut share some physiological features, although the distinct morphologies of these organs were different,³⁴ hence, studies had also shown that there were certain similar ecological of microflora in the colon and in the skin.³⁵ Our results confirmed that in the skin, *Bacteroides* can also provide anti-inflammatory effects and modulate immune function by utilizing the limited resources of lipids and sebum on the skin to produce SCFA.³⁶

In quantitative studies, *Bacteroides* exhibited a notable elevation in psoriasis lesions when contrasted with unaffected healthy skin. Drago et.al analyzed the cutaneous microbiota in healthy skin, psoriasis, and atopic dermatitis, which indicated that *Bacteroidetes* and *Proteobacteria* were the predominant microbial species present in psoriasis lesions.³⁷ Other studies reported significant differences in the distribution of the minor phylum *Bacteroidetes*.³⁸ However, differences of *Bacteroidetes* levels in psoriasis lesions and healthy skin were not found in a meta-analysis.³⁹ Inconsistent results hint that the mechanism of skin microbiota on psoriasis is still complex.⁴⁰ We confirmed our findings about the protective effect of *Bacteroides* on psoriasis. Future studies should combine qualitative and quantitative studies.

The primary benefit of this study was that confounding factors were less likely to interfere with MR strategies, which has the potential to compensate for the limitations inherent in conventional observational research methods. In addition, according to two-sample MR guidance, there was no overlapping participants in the GWAS summary data were involved in the exposure and outcome. And cases possessed large sample sizes from different cohorts.

Nevertheless, several limitations were present in our study. First, contrary to the outcome, sample size of exposure was less in currently available summary GWAS data of skin microbiota. We will update future studies with larger sample sizes to validate our results. Second, only genus-level analysis was conducted, not species or strain-level analysis. Shotgun metagenomic sequencing can give more accurate and specific results for microbiota GWAS. Third, since most GWAS participants were from Europe and our results showed differences in the results among populations, study results might not be extrapolated to other ethnic groups. Last, as MR analysis relied on untestable assumptions, clinical and experimental validation studies should be conducted in the future to identify the exact mechanism.

Conclusion

This MR study suggested that the possible causal associations that the levels of *Bacteroides*, in antecubital fossa, were protective factors for psoriasis, psoriasis vulgaris, psoriasis and related disorders. These findings provided genetic evidence on supporting skin microbiota, in particular *Bacteroides*, to prevent psoriasis.

Data Sharing Statement

The Summary statistics for psoriasis and related traits can be obtained in FinnGen R10 cohort (https://www.finnngen.fi/en/access_results) and United Kingdom Biobank (UKB) (<https://pheweb.org/UKB-SAIGE/>) consortium. GWAS summary statistics of skin microbiota were available in the GWAS catalogue under accession codes GCST90133164-GCST90133313.

Disclosure

The authors report no conflicts of interest in this work.

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