



# Bidirectional causal relationships between the skin microbiome and psoriasis Insights from Mendelian randomization analysis

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### **Abstract**

Psoriasis is a chronic inflammatory skin disease affecting 2% of the global population. Recent research suggests the skin microbiome plays a critical role in psoriasis. Skin microbiome data were obtained from the KORA FF4 study in Germany, and psoriasis data from FinnGen genome-wide association study summary statistics. Forward and reverse 2-sample Mendelian randomization (MR) analyses were conducted to assess causal relationships. Forward MR analysis identified several microbial features as risk factors for psoriasis, including the family Neisseriaceae in sebaceous skin (OR = 1.036, 95% CI: 1.010-1.062, P = .0054), ASV011 in dry skin (OR = 1.024, 95% CI: 1.000-1.048, P = .0490), and the order Clostridiales in moist skin (OR = 1.016, 95% CI: 1.000-1.032, P = .0449). Protective features included ASV016 (OR = 0.972, 95% CI: 0.949-0.994, P = .0136) and ASV053 (OR = 0.973, 95% CI: 0.954-0.992, P = .0054) in dry skin. Reverse MR analysis confirmed psoriasis as a significant risk factor for changes in the skin microbiome, with notable associations in the dry skin region for asv002 (OR = 1.266, 95% CI: 1.061-1.510, P = .027) and genus: Haemophilus (OR = 1.364, 95% CI: 1.065-1.746, P = .013). This study reveals bidirectional causal relationships between the skin microbiome and psoriasis, highlighting specific microbial features such as Neisseriaceae and Clostridiales as potential risk factors. Further research is needed to develop treatments that modulate the skin microbiome to improve psoriasis outcomes.

**Abbreviations:** GWAS = genome-wide association studies, IVs = instrumental variables, MR = Mendelian randomization, PRESSO = Pleiotropy Residual Sum and Outlier, SNPs = single nucleotide polymorphisms.

Keywords: dysbiosis, Mendelian randomization, microbial features, psoriasis, skin microbiome

## 1. Introduction

Psoriasis is a chronic inflammatory skin disease affecting approximately 2% of the global population. [1] It is characterized by red, scaly patches on the skin, significantly impacting the quality of life of affected individuals. The pathogenesis of psoriasis is multifactorial, involving genetic susceptibility, environmental factors, and immune system dysregulation. [2,3]

Recent research has shown that the skin microbiome plays a crucial role in the onset and progression of psoriasis.<sup>[4]</sup> The skin microbiome consists of a collection of microorganisms living on the skin, which are essential for maintaining skin health and immune function.<sup>[5]</sup> The skin microbiome of psoriasis patients differs significantly from that of healthy individuals, with changes in bacterial diversity and composition.<sup>[6]</sup>

A 20-year study in Japan found that infections are an important risk factor for psoriasis, with an incidence rate of 3.5% to 8.3%. [7-9] Recent studies have emphasized the significant role of the microbiome in the development and exacerbation of psoriasis. Research indicates that the onset of psoriasis is associated

with streptococcal infections.<sup>[10]</sup> Although streptococcal infections are usually self-limiting, psoriasis can recur with infection recurrence.<sup>[11]</sup> Dysbiosis of the skin microbiome is linked to psoriasis.<sup>[12]</sup> Approximately 60% of psoriasis patients have Staphylococcus aureus colonization in lesional areas, compared to only 5% to 30% on normal skin. Furthermore, the lipophilic yeast Malassezia has been associated with the severity of psoriasis.<sup>[13]</sup> In the skin of psoriasis patients, beneficial bacteria such as Propionibacterium and Lactobacillus are found to be reduced.<sup>[14,15]</sup>

To better understand the causal relationship between the skin microbiome and psoriasis, Mendelian randomization (MR) analysis has been introduced. MR is a method in epidemiology used to assess causal relationships between risk factors and disease outcomes. [16] It simulates a randomized controlled trial by using genetic variants as instrumental variables, independent of the confounding factors that typically affect observational studies. This is a powerful tool because it provides evidence of causality rather than mere association, helping to identify potential intervention targets to improve health outcomes. Given the

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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strong correlation between the skin microbiome and psoriasis, we employed the Mendelian Randomization method to evaluate the bidirectional causal effects between them, aiming to uncover potential causal links and provide direction for clinical treatment and research.

#### 2. Materials and methods

#### 2.1. Study design

Our study explores the bidirectional causal relationship between the skin microbiome and psoriasis using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs). The validity of MR analysis relies on 3 core assumptions: the relevance assumption, which requires a strong association between the IV and the exposure; the independence assumption, which ensures that the IV is independent of confounding factors affecting both the exposure and the outcome; and the exclusion restriction assumption, which stipulates that the IV influences the outcome solely through the exposure. [17] Through this rigorous study design, we aim to gain deeper insights into the role of the skin microbiome in the pathogenesis of psoriasis.

#### 2.2. Skin microbiome data

The data for this study were sourced from an epidemiological study conducted in Germany, aimed at investigating the impact of cardiovascular diseases, metabolic diseases, and environmental factors on health. In the KORA FF4 study, approximately 1656 samples were collected. [18] These samples included various skin microenvironments, such as dry environments (forearm),

moist environments (antecubital fossa), and sebaceous gland-rich environments (forehead and retroauricular crease).

Skin samples were collected using standard operating procedures and analyzed using high-throughput 16S rRNA gene sequencing. Data processing was performed with the DADA2 tool for filtering and denoising, generating high-resolution operational taxonomic units (OTUs), and classification was annotated through the Ribosomal Database Project.

Genotype data were derived from genome-wide association studies (GWAS) and underwent quality control using the PLINK tool. Distance-based redundancy analysis and generalized linear models were used to assess associations between microbial features and genetic variations.

Meta-analyses were conducted using METAL and METASOFT tools, employing fixed-effect meta-analysis weighted by sample size.

Data processing and analysis primarily utilized R language and associated packages, including phyloseq, vegan, and mvabund. These steps ensured high data quality and reliability, laying a solid foundation for subsequent Mendelian randomization analysis.

#### 2.3. Psoriasis data

Summary statistics for psoriasis were obtained from the FinnGen GWAS summary statistics (https://results.finngen.fi/en). FinnGen is a large-scale biobank research project that combines genomic data with health records to identify gene variants associated with diseases. This project integrates biobank samples and extensive health records from Finland. The study includes a large cohort of European ancestry, with 103,312 cases and 397,564 controls, accessible.

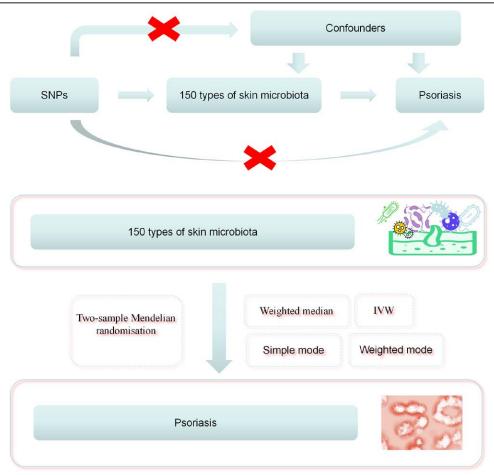


Figure 1. Schematic diagram illustrating the Mendelian randomization process.

## 2.4. Selection of instrumental variables

We selected effective IVs based on 3 fundamental assumptions. First, IVs were identified according to the genome-wide significance threshold (P value <  $5 \times 10^{-8}$ ). Then, SNPs exhibiting linkage disequilibrium were excluded using criteria of  $R^2$  < 0.001 and Kb = 10,000. Different thresholds were set for various exposures to ensure a sufficient number of SNPs.<sup>[19]</sup> Subsequently, PhenoScanner was used to exclude SNPs significantly associated with confounders, initially mitigating the impact of horizontal pleiotropy.<sup>[20]</sup> To avoid bias from weak

instruments, only IVs with an *F* statistic >10 were considered strong instruments. Finally, GWAS data from each skin microbiome dataset and psoriasis dataset were harmonized with the selected IVs.

#### 2.5. Statistical analysis

We employed bidirectional 2-sample MR analysis to investigate the potential bidirectional causal effects of 150 skin microbiome

	nsnp	method	pval		OR(95% CI)
Univariate microbial feature (family: neisseriaceae) at the forehead (sebaceous skin)	7	MR Egger	0.236		1.195 (0.922 to 1.550
	7	Weighted median	0.043		1.034 (1.001 to 1.069
	7	Inverse variance weighted	0.005		1.036 (1.010 to 1.062
	7				1.047 (0.996 to 1.100
		Simple mode	0.122	-	
	7	Weighted mode	0.154	io	1.039 (0.992 to 1.088
Univariate microbial feature (asv: asv011) at the dorsal forearm (dry skin)	8	MR Egger	0.743	H-H	1.016 (0.929 to 1.111
	8	Weighted median	0.019	•	1.027 (1.005 to 1.051
	8	Inverse variance weighted	0.049	•	1.024 (1.000 to 1.048
	8	Simple mode	0.135	•	1.030 (0.995 to 1.067
	8	Weighted mode	0.115		1.027 (0.998 to 1.058
Univariate microbial feature (asv: asv016) at the dorsal forearm (dry skin)					
Univariate microbial leature (asv. asvU16) at the dorsal forearm (dry skin)	8	MR Egger	0.047	н	0.860 (0.764 to 0.968
	8	Weighted median	0.144	•	0.977 (0.946 to 1.008
	8	Inverse variance weighted	0.014	•	0.972 (0.949 to 0.994
	8	Simple mode	0.518	H <b>a</b> it	0.982 (0.930 to 1.036
	8	Weighted mode	0.613	He H	0.986 (0.935 to 1.039
Univariate microbial feature (asv: asv053) at the dorsal forearm (dry skin)	5	MR Egger	0.416	No.	0.972 (0.915 to 1.032
Univariate microbiai leature (asv. asv053) at the dorsal forearm (dry skin)				7	
	5	Weighted median	0.078	•	0.978 (0.954 to 1.002
	5	Inverse variance weighted	0.005	•	0.973 (0.954 to 0.992
	5	Simple mode	0.310	•	0.981 (0.949 to 1.014
	5	Weighted mode	0.247		0.979 (0.951 to 1.009
University microbial feature (sev. sev/02) at the demail fercore (do, skip)	10			H-H	
Univariate microbial feature (asv: asv063) at the dorsal forearm (dry skin)		MR Egger	0.761	-	0.985 (0.896 to 1.083
	10	Weighted median	0.067	•	0.982 (0.964 to 1.001
	10	Inverse variance weighted	0.034	•	0.984 (0.969 to 0.999
	10	Simple mode	0.368	4	0.982 (0.945 to 1.020
	10	Weighted mode	0.407		0.983 (0.947 to 1.021
112 - 21 - 2 - 12 - 12 - 12 - 12 - 12 -					
Univariate microbial feature (asv: asv070) at the dorsal forearm (dry skin)	7	MR Egger	0.411	÷-	1.064 (0.929 to 1.219
	7	Weighted median	0.055	•	0.975 (0.951 to 1.001
	7	Inverse variance weighted	0.044	•	0.974 (0.950 to 0.999
	7	Simple mode	0.260	•	0.974 (0.934 to 1.015
	7	Weighted mode	0.337		0.981 (0.946 to 1.017
Univariate microbial feature (order: clostridiales) at the antecubital fossa (moist skin)	14	MR Egger	0.074	ļe-	1.051 (1.000 to 1.106
	14	Weighted median	0.333	•	1.010 (0.989 to 1.032
	14	Inverse variance weighted	0.045	•	1.016 (1.000 to 1.032
	14	Simple mode	0.060		1.039 (1.002 to 1.07)
	14	Weighted mode	0.906		0.998 (0.962 to 1.035
Univariate microbial feature (family: clostridiales) at the incertae (moist skin)	14	MR Egger	0.074	<b>101</b>	1.051 (1.000 to 1.106
	14	Weighted median	0.325	•	1.010 (0.990 to 1.032
	14	Inverse variance weighted	0.045	•	1.016 (1.000 to 1.03)
	14	Simple mode	0.077	_	1.039 (0.999 to 1.080
	14	Weighted mode	0.911		0.998 (0.960 to 1.037
Univariate microbial feature (genus: streptococcus) at the antecubital fossa (moist skin)	10	MR Egger	0.085	-	→ 1.397 (1.001 to 1.949
	10	Weighted median	0.252	<del></del>	1.081 (0.946 to 1.235
	10	Inverse variance weighted	0.020	<b>→</b>	1.126 (1.019 to 1.244
	10	Simple mode	0.621		1.057 (0.855 to 1.308
	10	Weighted mode	0.559	<del></del>	1.063 (0.873 to 1.294
Univariate microbial feature (family: flavobacteriaceae) at the dorsal forearm (dry skin)	9	MR Egger	0.172	-	1.137 (0.963 to 1.342
	9	Weighted median	0.039	•	1.033 (1.002 to 1.065
	9	Inverse variance weighted	0.030		1.031 (1.003 to 1.059
	9	Simple mode		in the	
	9	Simple mode	0.163		1.049 (0.987 to 1.114
			_	<b>(●+</b>	1.050 (0.990 to 1.114
	9	Weighted mode	0.143		
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	9		0.143 0.559	<u> </u>	1.049 (0.903 to 1.218
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)		Weighted mode	0.559	_	
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	7 7	Weighted mode MR Egger Weighted median	0.559 0.365	_	1.018 (0.980 to 1.05)
Univariate microbial feature (asv: asv002) at the antecubital fessa (moist skin)	7 7 7	Weighted mode  MR Egger  Weighted median  Inverse variance weighted	0.559 0.365 <b>0.024</b>	1	1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06)
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	7 7 7 7	Weighted mode  MR Egger  Weighted median Inverse variance weighted  Simple mode	0.559 0.365 <b>0.024</b> 0.732	1	1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07)
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	7 7 7	Weighted mode  MR Egger  Weighted median  Inverse variance weighted	0.559 0.365 <b>0.024</b>	1	1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07)
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)  Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7	Weighted mode  MR Egger  Weighted median Inverse variance weighted  Simple mode	0.559 0.365 <b>0.024</b> 0.732	1	1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.06)
	7 7 7 7	Weighted mode  MR Egger  Weighted median  Inverse variance weighted  Simple mode  Weighted mode	0.559 0.365 <b>0.024</b> 0.732 0.787	•	1.049 (0.903 to 1.218 1.018 (0.980 to 1.057 1.032 (1.004 to 1.061 1.011 (0.953 to 1.073 1.008 (0.953 to 1.076 1.082 (0.970 to 1.208
	7 7 7 7 7 4	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median	0.559 0.365 <b>0.024</b> 0.732 0.787 0.292 <b>0.036</b>		1.018 (0.980 to 1.05: 1.032 (1.004 to 1.06: 1.011 (0.953 to 1.07: 1.008 (0.953 to 1.06: 1.082 (0.970 to 1.20: 1.038 (1.002 to 1.074
	7 7 7 7 7 4 4	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted	0.559 0.365 <b>0.024</b> 0.732 0.787 0.292 <b>0.036</b> <b>0.010</b>		1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.06) 1.082 (0.970 to 1.20) 1.038 (1.002 to 1.07)
	7 7 7 7 7 4	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median	0.559 0.365 <b>0.024</b> 0.732 0.787 0.292 <b>0.036</b>		1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.06) 1.082 (0.970 to 1.20) 1.038 (1.002 to 1.07)
	7 7 7 7 7 4 4	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted	0.559 0.365 <b>0.024</b> 0.732 0.787 0.292 <b>0.036</b> <b>0.010</b>		1.018 (0.980 to 1.057 1.032 (1.004 to 1.061 1.011 (0.953 to 1.073 1.008 (0.953 to 1.066
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7 7 4 4 4 4	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode Weighted mode	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198		1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.06) 1.082 (0.970 to 1.20) 1.038 (1.002 to 1.07) 1.039 (1.009 to 1.06) 1.037 (0.980 to 1.08)
	7 7 7 7 7 4 4 4 4 4	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median MR Egger MR Egger	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198		1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.06) 1.082 (0.970 to 1.06) 1.032 (1.002 to 1.07) 1.039 (1.009 to 1.06) 1.039 (0.989 to 1.08) 1.039 (0.989 to 1.38)
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7 7 7 4 4 4 4 4 4	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median MR Egger Weighted median	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.526 0.059		1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.07) 1.008 (0.953 to 1.06) 1.022 (0.970 to 1.20) 1.038 (1.002 to 1.07) 1.039 (1.009 to 1.06) 1.037 (0.989 to 1.08) 1.031 (0.983 to 1.08)
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7 7 4 4 4 4 4	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median MR Egger MR Egger	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198		1.018 (0.980 to 1.05 1.032 (1.004 to 1.08 1.011 (0.953 to 1.07 1.008 (0.953 to 1.07 1.032 (0.970 to 1.20 1.038 (1.002 to 1.07 1.039 (1.009 to 1.08 1.039 (0.993 to 1.08 1.081 (0.884 to 1.32 1.039 (0.999 to 1.08
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7 7 7 4 4 4 4 4 4	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median MR Egger Weighted median	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.526 0.059		1.018 (0.980 to 1.05' 1.032 (1.004 to 1.06' 1.011 (0.953 to 1.07' 1.008 (0.953 to 1.06') 1.082 (0.970 to 1.20' 1.038 (1.002 to 1.07' 1.039 (1.009 to 1.06') 1.037 (0.989 to 1.08' 1.039 (0.993 to 1.08') 1.031 (0.884 to 1.32' 1.039 (0.999 to 1.08') 1.039 (0.999 to 1.08')
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7 7 4 4 4 4 4 4 4 4	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode MR Egger Weighted median Inverse variance weighted MR Egger Weighted median Inverse variance weighted Simple mode	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.526 0.059		1.018 (0.980 to 1.05' 1.032 (1.004 to 1.06' 1.011 (0.953 to 1.07' 1.008 (0.953 to 1.06') 1.082 (0.970 to 1.20') 1.038 (1.002 to 1.07' 1.039 (1.009 to 1.06') 1.037 (0.988 to 1.08') 1.039 (0.993 to 1.08') 1.039 (0.993 to 1.08') 1.039 (0.999 to 1.08') 1.039 (1.097 to 1.07') 1.058 (0.991 to 1.12')
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)  Univariate microbial feature (asv: asv001) at the dorsal forearm (dry skin)	7 7 7 7 7 4 4 4 4 4 4 4 4 4 4	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted Simple mode	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.556 0.059 0.017 0.190	10 10 10 10 10 10 10 10 10 10 10 10 10 1	1.018 (0.980 to 1.05) 1.032 (1.004 to 1.06) 1.011 (0.953 to 1.07) 1.008 (0.953 to 1.06) 1.082 (0.970 to 1.20) 1.038 (1.002 to 1.07) 1.039 (1.009 to 1.06) 1.039 (1.009 to 1.06) 1.039 (0.993 to 1.08) 1.039 (0.999 to 1.08) 1.039 (0.999 to 1.08) 1.039 (0.999 to 1.08) 1.039 (0.999 to 1.08)
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	7 7 7 7 7 7 4 4 4 4 4 4 4 4 6	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted median Inverse variance weighted median Inverse variance weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted Simple mode MR Egger	0.559 0.365 0.024 0.732 0.737 0.292 0.036 0.010 0.226 0.198 0.526 0.059 0.017 0.148		1.018 (0.980 to 1.051 1.032 (1.004 to 1.061 1.011 (0.953 to 1.073 1.008 (0.953 to 1.076 1.082 (0.970 to 1.206 1.032 (1.070 to 1.064 1.039 (1.002 to 1.074 1.039 (1.099 to 1.068 1.039 (0.993 to 1.088 1.039 (0.999 to 1.081 1.039 (1.007 to 1.075 1.058 (0.991 to 1.125 1.055 (0.999 to 1.113
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)  Univariate microbial feature (asv: asv001) at the dorsal forearm (dry skin)	7 7 7 7 7 4 4 4 4 4 4 4 4 4 4	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted Simple mode	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.556 0.059 0.017 0.190	10 10 10 10 10 10 10 10 10 10 10 10 10 1	1.018 (0.980 to 1.051 1.032 (1.004 to 1.061 1.011 (0.953 to 1.073 1.008 (0.953 to 1.076 1.082 (0.970 to 1.206 1.032 (1.070 to 1.064 1.039 (1.002 to 1.074 1.039 (1.099 to 1.068 1.039 (0.993 to 1.088 1.039 (0.999 to 1.081 1.039 (1.007 to 1.075 1.058 (0.991 to 1.125 1.055 (0.999 to 1.113
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)  Univariate microbial feature (asv: asv001) at the dorsal forearm (dry skin)	7 7 7 7 7 7 4 4 4 4 4 4 4 4 6	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted median Inverse variance weighted median Inverse variance weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted Simple mode MR Egger	0.559 0.365 0.024 0.732 0.737 0.292 0.036 0.010 0.226 0.198 0.526 0.059 0.017 0.148		1.018 (0.980 to 1.057 1.032 (1.004 to 1.061 1.011 (0.953 to 1.073 1.082 (0.970 to 1.206 1.083 (1.002 to 1.074 1.039 (1.009 to 1.066 1.037 (0.989 to 1.088
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)  Univariate microbial feature (asv: asv001) at the dorsal forearm (dry skin)	7 7 7 7 7 7 4 4 4 4 4 4 4 4 6 6 6	Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted MR Egger Weighted mode MR Egger Weighted mode Weighted mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode Inverse variance weighted Inverse variance weighted	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.526 0.059 0.017 0.190 0.148 0.694 0.079 0.006		1.018 (0.980 to 1.057 1.032 (1.004 to 1.061 1.011 (0.953 to 1.065 1.082 (0.970 to 1.206 1.082 (0.970 to 1.206 1.083 (1.002 to 1.074 1.039 (1.009 to 1.065 1.037 (0.998 to 1.085 1.039 (0.993 to 1.087 1.039 (0.993 to 1.087 1.039 (0.999 to 1.081 1.039 (0.999 to 1.081 1.039 (0.999 to 1.081 1.055 (0.999 to 1.112 1.055 (0.999 to 1.113 0.967 (0.827 to 1.131 0.973 (0.944 to 1.005 0.968 (0.945 to 0.991
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)  Univariate microbial feature (asv: asv001) at the dorsal forearm (dry skin)	7 7 7 7 7 7 4 4 4 4 4 4 4 4 6 6	Weighted mode  MR Egger Weighted median Inverse variance weighted Simple mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted Simple mode  MR Egger Weighted median Inverse variance weighted Simple mode Weighted median Inverse variance weighted Simple mode Weighted median MR Egger Weighted median	0.559 0.365 0.024 0.732 0.787 0.292 0.036 0.010 0.226 0.198 0.526 0.059 0.017 0.148		1.018 (0.980 to 1.05: 1.032 (1.004 to 1.06: 1.011 (0.953 to 1.07: 1.008 (0.953 to 1.06: 1.082 (0.970 to 1.20: 1.038 (1.002 to 1.07: 1.039 (1.009 to 1.06: 1.037 (0.998 to 1.08: 1.039 (0.998 to 1.08: 1.039 (0.998 to 1.08: 1.039 (0.999 to 1.08: 1.039 (1.007 to 1.07: 1.058 (0.999 to 1.12: 1.056 (0.999 to 1.12: 1.056 (0.999 to 1.12: 1.056 (0.999 to 1.11: 0.967 (0.827 to 1.13:

Figure 2. Forest plot displaying the results of the Mendelian randomization analysis, highlighting the positive association between skin microbiota (exposure) and psoriasis (outcome).

features on psoriasis. The inverse variance weighted (IVW) method was used as the primary approach, with MR-Egger, weighted median, simple mode, and weighted mode as supplementary methods. Results were visualized using scatter plots. Sensitivity analyses were conducted to assess the robustness of the results. Cochran's *Q* test and the *I*<sup>2</sup> statistic were used to detect heterogeneity among the IVs. The MR-Egger intercept test was performed to evaluate the presence of horizontal pleiotropy.<sup>[21]</sup> MR-PRESSO was further applied to examine potential horizontal pleiotropy.<sup>[22]</sup> Additionally, leave-one-out sensitivity analysis was conducted to determine whether individual SNPs influenced the causal estimates. The Mendelian randomization analysis process is shown in Figure 1.

#### 3. Results

## 3.1. Forward 2-sample Mendelian randomization study

Mendelian randomization analysis revealed significant associations between several microbial features and psoriasis. Specifically, certain microbial features were identified as potential risk factors for psoriasis (Figs. 2 and 3). In the sebaceous skin of the forehead, the odds ratio (OR) for the family Neisseriaceae was 1.036 (95% confidence interval [CI]: 1.010-1.062, P = .0054). In the dry skin of the dorsal forearm, the OR for ASV011 was 1.024 (95% CI: 1.000-1.048, P = .0490). In the moist skin of the antecubital fossa, the OR for the order Clostridiales and the family Clostridiales were both 1.016 (95% CI: 1.000–1.032, P = .0449). Additionally, the OR for the genus Streptococcus in the antecubital fossa was 1.126 (95% CI: 1.019 - 1.244, P = .0196), for the family Flavobacteriaceae in the dorsal forearm was 1.031 (95% CI: 1.003-1.059, P = .0301), for ASV002 in the antecubital fossa was 1.032 (95% CI: 1.004–1.061, P = .0235), for the family Neisseriaceae in the dorsal forearm was 1.039 (95%

CI: 1.009-1.069, P = .0095), and for ASV001 in the dorsal forearm was 1.039 (95% CI: 1.007-1.073, P = .0165; Figs. 2 and 3)

Conversely, some microbial features were identified as potential protective factors against psoriasis (Figs. 2 and 3). In the dry skin of the dorsal forearm, the OR for ASV016 was 0.972 (95% CI: 0.949-0.994, P=.0136), for ASV053 was 0.973 (95% CI: 0.954-0.992, P=.0054), for ASV063 was 0.984 (95% CI: 0.969-0.999, P=.0341), and for ASV070 was 0.974 (95% CI: 0.950-0.999, P=.0438). Additionally, the OR for ASV070 in the dorsal forearm was 0.968 (95% CI: 0.945-0.991, P=.0065; Figs. 2 and 3).

## 3.2. Reverse 2-sample Mendelian randomization study

Reverse Mendelian randomization analysis assessed the impact of psoriasis as an exposure on the skin microbiome. The results revealed significant associations between psoriasis and the skin microbiome in different skin regions.

In the forearm (dry skin) region, psoriasis was identified as a significant risk factor (Fig. 4). Specifically, the OR for 'asv002' and 'genus: Haemophilus' were 1.266 (95% CI: 1.061-1.510, P=.027) and 1.364 (95% CI: 1.065-1.746, P=.013), respectively, indicating a strong association with psoriasis. Additionally, the OR for 'genus: Bacteroides' was 1.259 (95% CI: 1.000-1.584, P=.049), also showing a significant association. In the forehead (sebaceous skin) region, the OR for 'asv004' was 1.281 (95% CI: 1.058-1.549, P=.011), indicating its role as a risk factor for psoriasis (Fig. 4).

Conversely, in the forearm (dry skin) region, psoriasis showed a protective effect on certain microbial features (Fig. 4). The OR for 'asv012' was 0.714 (95% CI: 0.556–0.915, P = .007), for 'asv076' was 0.742 (95% CI: 0.559–0.990, P = .045), for 'family: Flavobacteriaceae' was 0.774 (95% CI: 0.591–0.998, P = .048), and for 'phylum: Bacteroidetes' was 0.799 (95% CI:

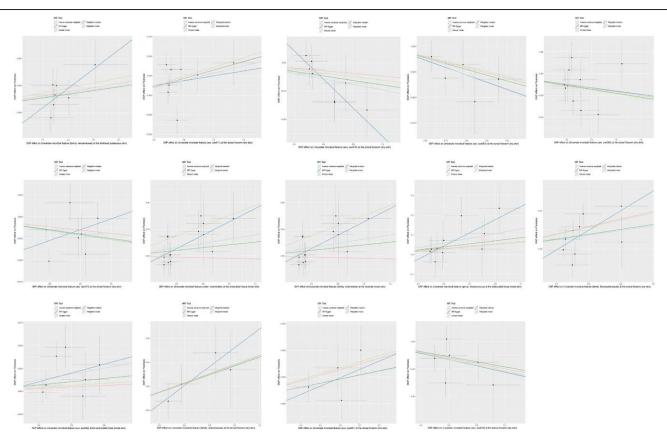


Figure 3. Scatter plot presenting the results of the positive Mendelian randomization analysis for psoriasis (exposure) and skin microbiota (outcome).

0.657-0.971, P = .024). These results suggest that these microbial features have a protective effect under the influence of psoriasis (Fig. 4).

We found that 'asv002' in the antecubital fossa (moist skin), 'Neisseriaceae' in the dorsal forearm (dry skin), and 'Flavobacteriaceae' in the dorsal forearm (dry skin) had bidirectional effects with psoriasis, while the remaining were

unidirectional causal effects. Overall, this study explored the complex relationship between psoriasis and the microbiome of different skin regions, revealing the potential role of exposure-microbiome interactions in skin diseases. These findings provide important evidence for further research into the pathogenesis of psoriasis and the role of the microbiome in skin diseases.

outcome	nsnp	method	pval	OR(95% CI)
Univariate microbial feature (asv: asv013) at the antecubital fossa (moist skin)	105	MR Egger	0.450	→ 1.163 (0.787 to 1.718
	105	Weighted median	0.383	→ 1.182 (0.812 to 1.721
	105	Inverse variance weighted	0.044	1.260 (1.007 to 1.576
	105	Simple mode	0.900	→ 0.950 (0.427 to 2.112
	105	Weighted mode	0.502	1.132 (0.789 to 1.623
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	105	MR Egger	0.003	→ 1.603 (1.179 to 2.180
	105	Weighted median	<0.001	→ 1.660 (1.237 to 2.226
	105	Inverse variance weighted	0.009	1.266 (1.062 to 1.510
	105	Simple mode	0.754	→ 1.119 (0.556 to 2.252
		Weighted mode		→ 1.540 (1.157 to 2.049
Helicalete released of free control (ACO) at the control black control (ACO)	105		0.004	
Univariate microbial feature (asv: asv012) at the antecubital fossa (moist skin)	105	MR Egger	0.079	0.669 (0.429 to 1.043
	105	Weighted median	0.070	0.673 (0.438 to 1.034
	105	Inverse variance weighted	0.008	0.714 (0.557 to 0.915
	105	Simple mode	0.396	0.692 (0.296 to 1.615
	105	Weighted mode	0.042	0.675 (0.465 to 0.981
Univariate microbial feature (order: bacteroidales) at the dorsal forearm (dry skin)	105	MR Egger	0.044	→ 1.479 (1.015 to 2.153
	105	Weighted median	0.482	1.129 (0.805 to 1.583
	105	Inverse variance weighted	0.049	1.259 (1.001 to 1.584
			0.373	→ 1.558 (0.590 to 4.110
	105	Simple mode		
	105	Weighted mode	0.218	→ 1.242 (0.882 to 1.748
Univariate microbial feature (asv: asv004) at the forehead (sebaceous skin)	105	MR Egger	0.315	1.182 (0.854 to 1.637
	105	Weighted median	0.589	1.094 (0.790 to 1.515
	105	Inverse variance weighted	0.011	1.281 (1.058 to 1.550
	105	Simple mode	0.693	→ 1.164 (0.549 to 2.47
	105	Weighted mode	0.538	1.102 (0.809 to 1.502
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	105	MR Egger	0.058	→ 1.433 (0.993 to 2.070
Companiate interestal reature (raining, neroscillatede) at the torsal lorealiti (try shift)				
	105	Weighted median	0.031	→ 1.432 (1.034 to 1.983
	105	Inverse variance weighted	0.027	1.278 (1.028 to 1.590
	105	Simple mode	0.373	0.688 (0.304 to 1.560
	105	Weighted mode	0.038	→ 1.393 (1.023 to 1.896
Univariate microbial feature (genus: haemophilus) at the dorsal forearm (dry skin)	105	MR Egger	0.103	→ 1.418 (0.935 to 2.149
•	105	Weighted median	0.035	→ 1.526 (1.031 to 2.260
	105	Inverse variance weighted	0.014	→ 1.364 (1.065 to 1.746
	105	Simple mode	0.141	→ 2.055 (0.794 to 5.318
	105	Weighted mode	0.019	→ 1.547 (1.080 to 2.215
Univariate microbial feature (genus: bacteroides) at the dorsal forearm (dry skin)	105	MR Egger	0.044	→ 1.479 (1.015 to 2.153
	105	Weighted median	0.508	1.129 (0.788 to 1.616
	105	Inverse variance weighted	0.049	1.259 (1.001 to 1.584
	105	Simple mode	0.374	→ 1.558 (0.588 to 4.124
	105	Weighted mode	0.190	→ 1.242 (0.900 to 1.713
Univariate microbial feature (genus: chryseobacterium) at the dorsal forearm (dry skin)	105	MR Egger	0.329	0.823 (0.557 to 1.218
Onivariate microbial leature (genus. Cili yseobacterium) at the dorsal forearm (dry skin)				
	105	Weighted median	0.305	0.820 (0.562 to 1.19)
	105	Inverse variance weighted	0.007	0.731 (0.581 to 0.919
	105	Simple mode	0.450	→ 0.716 (0.302 to 1.69)
	105	Weighted mode	0.188	0.780 (0.540 to 1.126
Univariate microbial feature (asv: asv076) at the dorsal forearm (dry skin)	105	MR Egger	0.166	0.710 (0.440 to 1.148
	105	Weighted median	0.051 ←	0.645 (0.415 to 1.00)
	105	Inverse variance weighted	0.039	0.742 (0.560 to 0.98
	105	Simple mode	0.592	→ 0.736 (0.241 to 2.25)
			,	
	105	Weighted mode	0.051 ←	0.653 (0.428 to 0.99)
Univariate microbial feature (family: flavobacteriaceae) at the dorsal forearm (dry skin)	105	MR Egger	0.862	0.969 (0.682 to 1.37)
	105	Weighted median	0.948	1.012 (0.708 to 1.44)
	105	Inverse variance weighted	0.015	0.774 (0.630 to 0.95
	105	Simple mode	0.014 ↔	0.361 (0.162 to 0.80)
	105	Weighted mode	0.775	0.952 (0.680 to 1.334
Univariate microhial feature (seu: seu/010) at the automitital feece (moiet skin)	105		0.063 ←	
Univariate microbial feature (asv: asv019) at the antecubital fossa (moist skin)		MR Egger		0.634 (0.394 to 1.02)
	105	Weighted median	0.029 ←	0.591 (0.368 to 0.94)
	105	Inverse variance weighted	0.023	0.732 (0.559 to 0.958
	105	Simple mode	0.215	0.505 (0.173 to 1.476
	105	Weighted mode	0.011 ←	0.566 (0.369 to 0.869
Univariate microbial feature (genus: anaerococcus) at the dorsal forearm (dry skin)	105	MR Egger	0.068	0.687 (0.462 to 1.023
S Zamato mioropiai roataro (gonao. antor 1000000) at the dorsal infeatili (dry skill)				
	105	Weighted median	0.004 ←	0.581 (0.402 to 0.840
	105	Inverse variance weighted	0.047	0.795 (0.634 to 0.99)
	105	Simple mode	0.821	→ 0.896 (0.348 to 2.30)
	105	Weighted mode	0.010 ←	0.614 (0.426 to 0.88
Univariate microbial feature (asv: asv007) at the dorsal forearm (dry skin)	105	MR Egger	0.103	0.646 (0.383 to 1.08)
	105	Weighted median	0.010 ←	0.522 (0.320 to 0.85
(-)		Inverse variance weighted		
		•	0.024	0.714 (0.532 to 0.95)
,	105		0.837	→ 0.890 (0.294 to 2.69
,	105 105	Simple mode	0.007	
,		Simple mode Weighted mode	0.013 ←	0.568 (0.367 to 0.88
Univariate microbial feature (phylum: bacteroidetes) at the dorsal forearm (dry skin)	105			
	105 105 105	Weighted mode MR Egger	0.013 ←→ 0.499 ←→	0.891 (0.638 to 1.243
	105 105 105 105	Weighted mode MR Egger Weighted median	0.013 ← 0.499 ← 0.701 ←	0.891 (0.638 to 1.243 0.938 (0.677 to 1.300
	105 105 105 105 105	Weighted mode  MR Egger  Weighted median  Inverse variance weighted	0.013 ← 0.499 ← 0.701 ← 0.024 ←	0.891 (0.638 to 1.243 0.938 (0.677 to 1.300 0.799 (0.657 to 0.973
	105 105 105 105	Weighted mode MR Egger Weighted median	0.013 ← 0.499 ← 0.701 ←	0.568 (0.367 to 0.881 0.891 (0.638 to 1.243 0.938 (0.677 to 1.300 0.799 (0.657 to 0.971 0.851 (0.446 to 1.623 0.899 (0.673 to 1.202

Figure 4. Forest plot of the reverse Mendelian randomization analysis, showing the relationship between psoriasis (exposure) and skin microbiota (outcome).

Table 1

Heterogeneity and pleiotropy results of dual sample positive analysis of skin microbiota and psoriasis.

Exposure	Method	Heterogeneity		Pleiotropy	
		Q	<i>Q</i> _pval	Intercept	P
Univariate microbial feature (family: neisseriaceae) at the forehead (sebaceous skin)	MR Egger	3.007	0.699	-0.067	.327
	Inverse variance weighted PRESSO	4.184	0.652		.687
Univariate microbial feature (asv: asv011) at the dorsal forearm (dry skin)	MR Egger	13.876	0.031	0.006	.863
	Inverse variance weighted	13.951	0.052	0.000	
The border and the fact was (see an Od O) at the above I for some (dec. 11)	PRESSO MR Egger	1.779	0.939	0.073	.074 .085
Univariate microbial feature (asv: asv016) at the dorsal forearm (dry skin)	Inverse variance weighted PRESSO	6.02	0.537	0.073	
Univariate microbial feature (asv: asv053) at the dorsal forearm (dry skin)	MR Egger	1.278	0.734	0.001	.553 .975
Univariate microbia reature (asv. asv003) at the dorsal forearm (dry shiri)	Inverse variance weighted PRESSO	1.28	0.865	0.001	.89
University microbial feature (acv. acv/062) at the dereal forearm (dry ckin)	MR Egger	10.14	0.255	-0.001	.09
Univariate microbial feature (asv: asv063) at the dorsal forearm (dry skin)	Inverse variance weighted	10.14	0.233	-0.001	.902
	PRESSO	10.141	0.559		.349
Univariate microbial feature (asv: asv070) at the dorsal forearm (dry skin)	MR Egger	7.68	0.175	-0.065	.253
	Inverse variance weighted	10.242	0.115	0.000	.200
	PRESSO				.156
Univariate microbial feature (order: clostridiales) at the antecubital fossa (moist skin)	MR Egger	6.685	0.878	-0.022	.184
, , ,	Inverse variance weighted PRESSO	8.673	0.797		.805
Univariate microbial feature (family: clostridiales) at the incertae (moist skin)	MR Egger	6.685	0.878	-0.022	.184
	Inverse variance weighted PRESSO	8.673	0.797		.81
Univariate microbial feature (genus: streptococcus) at the antecubital fossa (moist skin)	MR Egger	3.097	0.928	-0.124	.221
	Inverse variance weighted PRESSO	4.858	0.847		.853
Univariate microbial feature (family: flavobacteriaceae) at the dorsal forearm (dry skin)	MR Egger	11.815	0.107	-0.053	.277
	Inverse variance weighted PRESSO	14.161	0.078		.087
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	MR Egger	5.975	0.309	-0.009	.838
	Inverse variance weighted PRESSO	6.03	0.42		.44
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	MR Egger	0.425	0.809	-0.027	.529
	Inverse variance weighted	0.994	0.803	0.027	.020
	PRESSO				
Univariate microbial feature (asv: asv001) at the dorsal forearm (dry skin)	MR Egger	2.496	0.287	-0.022	.734
	Inverse variance weighted PRESSO	2.686	0.443		404
The contains an invalid for the contains and the devol for a superior (dur1.5)	MR Egger	5.69	0.223	0.001	.494 .992
Univariate microbial feature (asv: asv070) at the dorsal forearm (dry skin)	Inverse variance weighted	5.691	0.223	0.001	.992
	PRESSO	3.031	0.550		.372

MR = Mendelian randomization, PRESSO = Pleiotropy Residual Sum and Outlier.

### 3.3. Heterogeneity and pleiotropy tests

The complete results of heterogeneity and pleiotropy tests for forward and reverse MR analyses are presented in Tables 1 and 2. We performed Cochran's Q test for the associations between 150 skin microbiome traits and psoriasis, with most P values >.05, indicating the absence of heterogeneity. Importantly, all P values for the MR-Egger intercepts were >.05, excluding bias due to horizontal pleiotropy. Additionally, the MR-PRESSO global test also indicated that the MR analysis results were not influenced by horizontal pleiotropy (P > .05). The results of the leave-one-out analysis are presented in Figure 5.

## 4. Discussion

This study represents one of the most comprehensive Mendelian randomization (MR) investigations to date, evaluating the causal relationship between the skin microbiome and psoriasis. Through forward and reverse 2-sample MR analyses, we uncovered significant associations between psoriasis and the skin microbiome. The forward MR analysis identified certain microbial features as potential risk factors for psoriasis, while

others demonstrated protective effects. These findings suggest that the skin microbiome may play a crucial role in the onset and progression of psoriasis.

In the forward analysis, several microbial features were significantly associated with psoriasis in different skin regions (such as the forehead, forearm, and antecubital fossa). Specifically, microbial features such as the family Neisseriaceae, ASV011, the order Clostridiales, the genus Streptococcus, and the family Flavobacteriaceae showed higher odds ratios (OR) in psoriasis patients compared to healthy individuals. Conversely, microbial features like ASV016, ASV053, ASV063, and ASV070 exhibited lower ORs in psoriasis patients, indicating their potential protective role.

There are limited studies directly investigating the relationship between the genus Neisseria and psoriasis. However, some research has indicated an increased representation of Neisseria in the skin microbiome of psoriasis patients. Fyhrquist et all<sup>[23]</sup> found an increase in Neisseria and Streptococcus in psoriasis-affected skin compared to healthy skin. Kayıran et all<sup>[24]</sup> also reported an increased presence of Neisseria and Streptococcus in the scalps of psoriasis patients. Similarly, our study identified Neisseria as a strong risk factor in sebaceous skin of the forehead (P = .0054), suggesting that Neisseria may influence the skin's microenvironment and

Table 2

Heterogeneity and pleiotropy results of dual sample reverse analysis of skin microbiota and psoriasis.

Outcome	Method	Heterogeneity		Pleiotropy	
		Q	<i>Q</i> _pval	Intercept	P
Univariate microbial feature (asv: asv013) at the antecubital fossa (moist skin)	MR Egger	97.5633	0.6327	0.0105	.6245
	Inverse variance weighted PRESSO	97.8043	0.6525		.699
Univariate microbial feature (asv: asv002) at the antecubital fossa (moist skin)	MR Egger	81.094	0.9455	-0.0307	.0694
	Inverse variance weighted PRESSO	84.4601	0.9198		.896
Univariate microbial feature (asv: asv012) at the antecubital fossa (moist skin)	MR Egger	117.1862	0.1605	0.0083	.73
	Inverse variance weighted PRESSO	117.3224	0.1755		.194
Univariate microbial feature (order: bacteroidales) at the dorsal forearm (dry skin)	MR Egger	112.3232	0.2492	-0.0226	.2928
	Inverse variance weighted PRESSO	113.5425	0.2456		.26
Univariate microbial feature (asv: asv004) at the forehead (sebaceous skin)	MR Egger	99.9475	0.5668	0.0106	.5541
	Inverse variance weighted PRESSO	100.2998	0.5844		.575
Univariate microbial feature (family: neisseriaceae) at the dorsal forearm (dry skin)	MR Egger	128.5928	0.0446	-0.0156	.4494
	Inverse variance weighted	129.3126	0.0469		
	PRESSO	100 7775	0.0004	0.0050	.055
Univariate microbial feature (genus: haemophilus) at the dorsal forearm (dry skin)	MR Egger Inverse variance weighted	108.7775 108.8327	0.3294 0.3534	-0.0053	.8196
	PRESSO	100.0321	0.5554		.377
Univariate microbial feature (genus: bacteroides) at the dorsal forearm (dry skin)	MR Egger	112.3232	0.2492	-0.0226	.2928
	Inverse variance weighted	113.5425	0.2456		
	PRESSO				.257
Univariate microbial feature (genus: chryseobacterium) at the dorsal forearm (dry skin)	MR Egger	76.349	0.9772	-0.0158	.4649
	Inverse variance weighted PRESSO	76.8871	0.9786		.981
Univariate microbial feature (asv: asv076) at the dorsal forearm (dry skin)	MR Egger	108.304	0.341	0.0059	.8246
onivariate microbial reactive (asv. asvovo) at the dorsal forearm (ary skin)	Inverse variance weighted	108.3559	0.3654	0.0033	.0240
	PRESSO				.4
Univariate microbial feature (family: flavobacteriaceae) at the dorsal forearm (dry skin)	MR Egger	74.6637	0.984	-0.0299	.1255
	Inverse variance weighted	77.0492	0.9779		
	PRESSO	00 0005	0.0040	0.0104	.973
Univariate microbial feature (asv: asv019) at the antecubital fossa (moist skin)	MR Egger Inverse variance weighted	96.3865 96.9017	0.6643 0.6763	0.0184	.4745
	PRESSO	90.9017	0.0703		.675
Univariate microbial feature (genus: anaerococcus) at the dorsal forearm (dry skin)	MR Egger	98.1419	0.6169	0.0187	.3854
	Inverse variance weighted	98.9017	0.6229		
	PRESS0				.554
Univariate microbial feature (asv: asv007) at the dorsal forearm (dry skin)	MR Egger	106.1021	0.3973	0.0127	.6497
	Inverse variance weighted	106.3158	0.4186		400
The contains recovered from the charge hardward datas) at the days of ferrors (days 15)	PRESSO MR Egger	90.8322	0.7986	-0.0145	.403 .4318
Univariate microbial feature (phylum: bacteroidetes) at the dorsal forearm (dry skin)	Inverse variance weighted	90.8322 91.4551	0.7986	-0.0143	.4318
	PRESSO	J1.7001	0.0000		.826

MR = Mendelian randomization, PRESSO = Pleiotropy Residual Sum and Outlier.

contribute to psoriasis pathogenesis through interactions with sebaceous gland secretions or local immune responses.<sup>[25]</sup>

The antecubital fossa is characterized by skin folds that trap sweat and sebum, creating a moist and oily environment conducive to the growth of Streptococcus. [26,27] Streptococcus may impact skin health by secreting toxins and other metabolites. [28] Psoriasis patients often have compromised skin barrier function, which can be exacerbated by the proliferation of Staphylococcus aureus in psoriatic lesions. This pathogen produces toxins that further damage the skin barrier. Rachakonda et al<sup>[11]</sup> demonstrated a significant association between Streptococcus infection and psoriasis, with Streptococcus infections frequently triggering acute psoriasis flares. [11] The scratching induced by psoriasis-associated itching can further damage the skin, allowing bacteria (both commensals and pathogens) to penetrate deeper layers or even the bloodstream. [29]

There is currently limited research directly addressing the relationship between Clostridium species in moist skin and psoriasis, with most studies focusing on the gut microbiome. While Clostridium in the gut produces short-chain fatty acids that might influence systemic immune responses and potentially protect skin health, our findings suggest Clostridium as a risk factor for psoriasis. [30] Further research is needed to clarify this relationship and explore the role of Clostridium in the skin microbiome.

These results support previous research linking the skin microbiome to psoriasis. Given the protective and harmful roles of these microbial features in psoriasis, future studies could explore therapies that supplement beneficial microbes or inhibit harmful ones. For instance, targeting areas with high sebum production and skin folds in psoriasis patients, along with monitoring the health of the microbiome, might be beneficial. Probiotic therapies or targeted antimicrobial treatments (e.g., against Neisseria, Streptococcus, and Clostridium) could represent new therapeutic strategies. Researching key microbial features and their interactions with the skin barrier could lead to personalized treatments based on the specific microbiome characteristics of psoriasis patients.

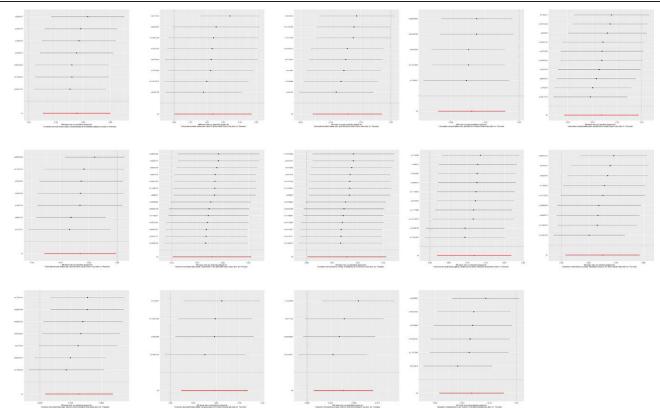


Figure 5. Leave-one-out analysis demonstrating the robustness of the results.

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