

# Exploring Causal Relationships Between Gut Microbiota, Inflammatory Cytokines, and Inflammatory Dermatoses: A Mendelian Randomization Study

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**Background:** Some studies have established a link between gut microbiota, inflammatory proteins, and inflammatory dermatoses. However, the mediating role of inflammatory proteins in the gut-skin axis remains unclear.

**Methods:** Data on inflammatory proteins and gut microbiota were drawn from the GWAS catalog and MiBioGen consortium, with inflammatory skin disease data provided by the FinnGen consortium. Using genome-wide association studies (GWAS), we performed linkage disequilibrium score regression (LDSC) to assess genetic correlations and conducted a two-step Mendelian Randomization (MR) analysis to investigate circulating inflammatory proteins as potential mediators between gut microbiota and inflammatory dermatoses.

**Results:** MR analysis identified 38 gut microbiota and 23 inflammatory proteins associated with inflammatory skin diseases. After false discovery rate (FDR) correction, four gut microbiota taxa—*Eubacterium fissicatena*, *Bacteroidaceae*, *Allisonella*, and *Bacteroides*, remained statistically significant (OR = 1.32, 95% CI: 1.16–1.50, *adjusted P* = 0.007; OR = 2.25, 95% CI: 1.48–3.42, *adjusted P* = 0.026; OR = 1.42, 95% CI: 1.18–1.70, *adjusted P* = 0.014; OR = 2.25, 95% CI: 1.48–3.42, *adjusted P* = 0.013), with only IL-18R1 significantly associated with eczema (OR = 1.05, 95% CI: 1.03–1.08, *adjusted P* = 0.017). Further mediation analysis showed that IL-15RA mediated 11% of the pathway between *Veillonellaceae* and eczema, while FGF19 mediated 6% of the pathway between genus *Lachnospiraceae*UCG001 and psoriatic arthritis.

**Conclusion:** These findings provide potential targets for therapeutic interventions in inflammatory skin diseases.

**Keywords:** gut microbiota, inflammatory dermatoses, Mendelian randomization, inflammatory proteins, genetic correlation

## Introduction

Inflammatory skin diseases encompass a broad spectrum of dermatological conditions, primarily characterized by skin inflammation that manifests as redness, swelling, pain, and itching. These conditions may arise from dysregulated immune responses, genetic predispositions, environmental triggers, infections, or allergic reactions.<sup>1</sup> Furthermore, patients with moderate to severe psoriasis are reported to have an increased risk of developing metabolic syndrome and atherosclerotic cardiovascular disease.<sup>2,3</sup>

The gut-skin axis, proposed in recent years, has highlighted the relationship between gut microbiota and skin disorders.<sup>4</sup> Clinical studies have demonstrated a decreased *Firmicutes*/*Bacteroidetes* ratio in patients with acne, characterized by a lower abundance of *Firmicutes* and a higher abundance of *Bacteroidetes* compared to healthy controls.<sup>4,5</sup> Similarly, patients with psoriatic arthritis show reduced levels of *Akkermansia* and *Ruminococcus*.<sup>6,7</sup> Additionally, a lower abundance of *Ruminococcaceae* has been observed in patients with eczema and acne.<sup>5,8</sup> These discoveries all suggest a potential causal relationship between gut microbiota and inflammatory skin diseases.

Pathological activation of the immune system results in the accumulation of immune cells and the release of inflammatory proteins, such as interleukins, chemokines, and growth factors. These processes can activate specific inflammatory pathways, leading to the development of inflammatory skin disorders. For instance, the TNF- $\alpha$ /IL-23/IL-17 pathway plays a central role in maintaining psoriasis, while an imbalance in TH2 responses is key to the pathogenesis of atopic dermatitis (AD), alongside contributions from Th22, Th17/IL-23, and Th1-regulated pathways.<sup>9</sup> Among these inflammatory mediators, IL-18 promotes Th1-mediated responses, with elevated IL-18R expression detected in the lesioned skin of patients with psoriasis, eczema, and AD.<sup>10</sup> Similarly, high expression of FGF19 has been observed in the lesioned skin of psoriasis patients, suggesting its role in disease progression.<sup>11</sup> IL-15RA, essential for T-cell regulation, is significantly upregulated in patients with rheumatoid arthritis (RA), highlighting its broader involvement in inflammatory pathways.<sup>12</sup> Additionally, increased serum levels of CCL-4 have been reported in patients with AD and psoriasis compared to healthy individuals.<sup>13</sup> Given the critical role of these inflammatory pathways, targeting cytokines such as IL-18, FGF19, IL-15RA, and chemokines like CCL-4 has become a promising therapeutic strategy.

Extensive research has shown that the gut microbiota plays a crucial role in regulating the inflammatory response. Imbalance in gut microbiota leads to overgrowth and release of bacterial products like lipopolysaccharides and peptidoglycans, causing inflammation.<sup>14</sup> Recent research has shown a correlation between gut microbiota and IL-2R, which plays a contributory role in the inflammation of psoriasis.<sup>9</sup> Additionally, *Fusicatenibacter* can induce IL-10 in intestinal mucosa to exert anti-inflammatory effects, potentially modulating systemic inflammation.<sup>15</sup> Conversely, a reduced abundance of *Fusicatenibacter* has been reported in rheumatoid arthritis, suggesting there was an association between gut microbiota, cytokines, and inflammatory diseases.<sup>16</sup> However, due to the observational studies being easily affected by some confounding bias, such as sample size of patients, environment, and age, the conclusions have varied in different studies. For instance, one study showed lower microbial diversity in psoriasis patients, while another showed no significant difference.<sup>17</sup> Additionally, it is difficult to infer causality between gut microbiota/inflammatory proteins and inflammatory dermatoses from observational studies. Furthermore, it is not clear whether inflammatory proteins act as mediators in the pathway from gut microbiota to inflammatory skin diseases.

GWAS has identified numerous human genetic variants linked to various diseases by examining correlations between millions of genetic variations and disease outcomes. By using genetic variations as instrumental variables (IVs), MR infers causal relationships between exposures and outcomes.<sup>18</sup> Moreover, bidirectional MR effectively mitigates confounding biases in traditional epidemiological studies and ascertains directional causality between interconnected phenotypes. This study employs MR analysis to investigate whether specific inflammatory proteins, particularly IL-15RA and IL-18R1, mediate the connection between gut microbiota and inflammatory dermatoses. The findings aim to provide a foundation for developing future treatment strategies targeting both gut microbiota and inflammatory pathways.

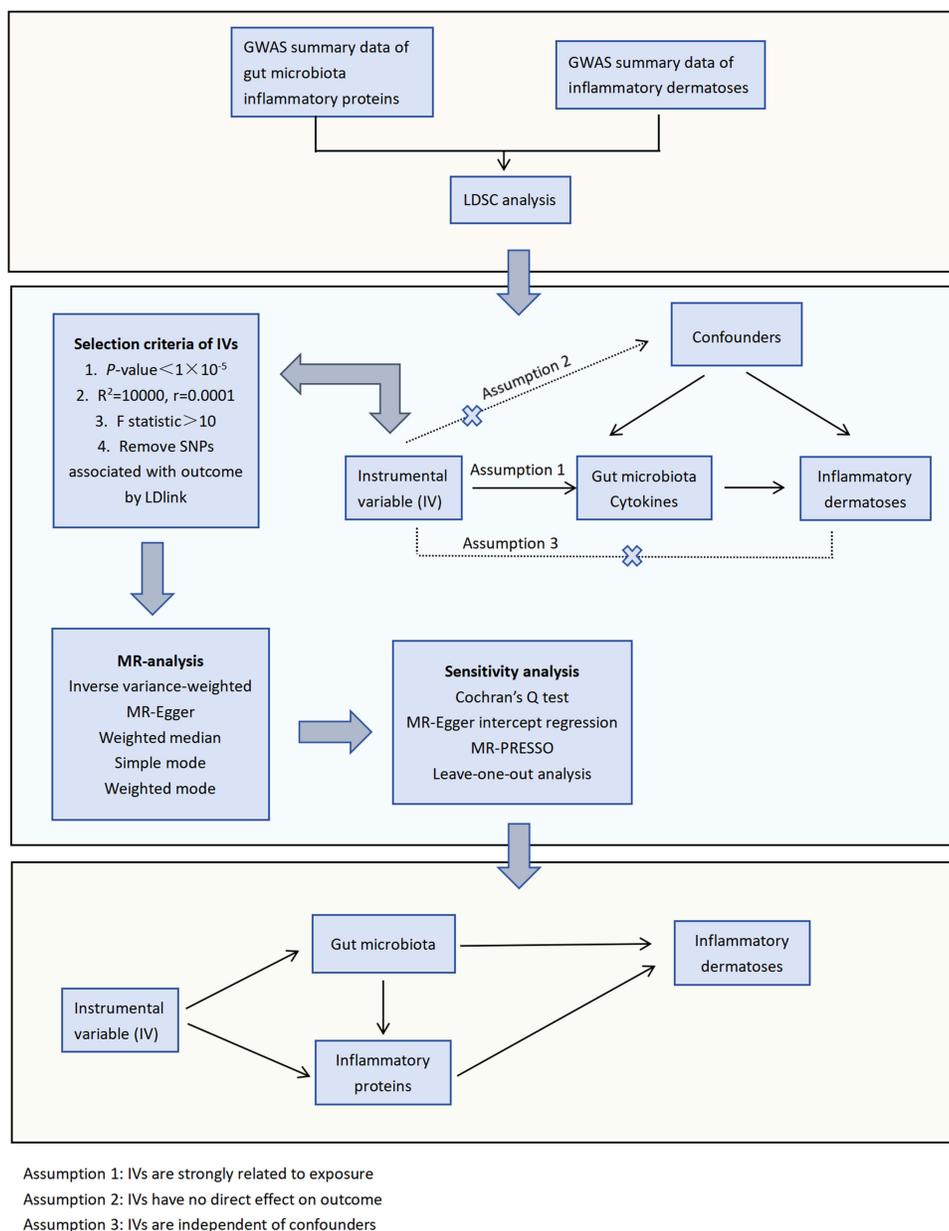
## Methods

### Study Design

Based on GWAS summary data, we conducted a two-step MR-analysis in order to examine the role of circulating inflammatory proteins as potential mediators in the association between intestinal microbiota and six inflammatory skin diseases including acne, allergic contact dermatitis, eczema, psoriasis vulgaris, psoriatic arthritis and seborrheic dermatitis. Moreover, we employed LDSC and reverse two-sample MR to figure out the genetic correlation and reverse causal link between the gut microbiota and inflammatory proteins in relation to inflammatory diseases. More details are shown in [Figure 1](#). Our study followed the STROBE-MR reporting guidelines and no ethical approval was required.<sup>19</sup>

### Data Source

GWAS summary data for gut microbiota was obtained from the MiBioGen consortium, which encompassed 18,340 participants across 24 cohorts from 11 countries. It is worth noting that the majority of participants (N=13,266) had European ancestry. The MiBioGen research team conducted 16s ribosomal RNA gene sequencing for all participants to identify and categorize the gut microbiota into five distinct categories: phylum, class, order, family, and genus.<sup>20</sup> Inflammatory proteins came from a recent study and was measured using the Olink Target Inflammation panel, composed



**Figure 1** Study design.

**Abbreviations:** LDSC, linkage disequilibrium score regression; SNP, single nucleotide polymorphisms; MR, Mendelian randomization.

of 91 inflammatory proteins,<sup>21</sup> and genome-wide genetic data from 11 cohorts consisting of 293,646 individuals (6509 cases and 287,137 controls) who were all European.

The GWAS summary statistics for psoriatic arthritis were sourced from the IEU Open GWAS project (GWAS ID: ieu-b-5116, n case = 5065, n control = 21,286; <https://gwas.mrcieu.ac.uk/>).<sup>22</sup> As for other inflammatory diseases, they could all be obtained in the FinnGen consortium ([https://www.finnngen.fi/en/access\\_results](https://www.finnngen.fi/en/access_results)), in which participants were screened according to International Classification of Diseases diagnosis codes. We obtained GWAS summary data in the FinnGen biobank for psoriasis vulgaris, which included 5,018 cases and 330,975 controls, while we also drew on GWAS summary data for acne, which involved 2313 cases and 328,747 controls. In addition, we extracted GWAS summary data for seborrheic dermatitis (n case = 2949, n control = 367,046), allergic contact dermatitis (n case = 3846, n control = 306,909), and eczema (n case = 30,359, n control = 278,795) in the FinnGen consortium. More details are shown in [Table S1](#).

## Instrumental Variables (IVs)

In our study, we used specific criteria to select IVs for MR analysis with single nucleotide polymorphisms (SNPs). (1) Correlation with exposure: SNPs had to show a significant correlation with gut microbiota, with a *p-value* less than  $5 \times 10^{-8}$ . Due to limited SNPs meeting this, a *p-value* threshold of  $1 \times 10^{-5}$  was used for gut microbiota and  $5 \times 10^{-6}$  for inflammatory proteins.<sup>23,24</sup> (2) Linkage disequilibrium (LD) removal: a clumping procedure was performed to remove LD, using an  $R^2$  threshold of 0.001 and a window size of 10,000 kb. (3) Robustness assessment: the association between IVs and exposures was evaluated using the F statistic, calculated as  $F = \beta^2/se^2$ . SNPs with an F value below 10 were excluded to minimize biases. (4) Association with outcome check: SNPs selected were examined in LDlink to identify any associations with the outcome. SNPs related to the outcome were excluded to avoid potential pleiotropy. These criteria were implemented to ensure the reliability of our MR analysis.

## Statistical Analysis

### Genetic Correlation Analysis

Conducting genetic correlation analysis through LDSC solely based on aggregated summary statistics from GWAS, incorporating all SNPs in the analysis, enables us to mitigate any bias from sample overlap. In univariate LDSC, performing regression analysis between the chi-square statistics of GWAS and LD scores enables the estimation of SNP-based liability-scale heritability ( $h^2$ ) of data in every GWAS summary.<sup>25</sup> By conducting regression analysis between the product of z-scores from two studies and LD scores, the genetic covariance can be calculated. Genetic correlation ( $r_g$ ) can be obtained by standardizing the genetic covariance using SNP-heritability.<sup>26</sup> In addition, in accordance with HapMap3 ref, SNPs meeting the following criteria were selectively eliminated from the GWAS summary data. The criteria were: (1) variants was not SNPs like indel, (2) SNPs were repeating and ambiguous (3) if providing MAF, SNPs with  $MAF < 0.01$  would be excluded.<sup>27</sup>

### Mendelian Randomization Analysis

#### Primary Analysis

To investigate the causal link between gut microbiota/inflammatory proteins and inflammatory skin diseases, we primarily employed the inverse variance weight (IVW) method, supplemented by MR-Egger, weighted median, simple mode, and weighted mode methods.<sup>28</sup> In MR studies, the IVW method is the main tool for estimating causal effects, providing higher statistical power for hypothesis testing. It integrates Wald estimates for each SNP through a meta-analytic approach to evaluate the effects of gut microbiota and inflammatory proteins on inflammatory diseases. During regression analysis, the intercept term is omitted, and the inverse variance ( $se^2$ ) of the outcome serves as a weighting factor. Results are unbiased in the absence of horizontal heterogeneity.<sup>29</sup> MR-Egger regression operates on the premise that the instrumental variable's strength is not influenced by direct effects. It identifies and adjusts for causal relationships between IVs and outcomes. If the intercept is close to zero, indicating no horizontal pleiotropy, MR-Egger findings closely match those from IVW.<sup>30</sup> Furthermore, we conducted reverse two-sample MR analysis to figure out the causal relationship from inflammatory diseases to gut microbiota and inflammatory proteins. It is noteworthy that the three categories of gut microbial taxa (the *Verrucomicrobiae* class, the *Verrucomicrobiales* order, and the *Verrucomicrobiae* family) are identical. Consequently, we have chosen to retain only the results pertaining to the *Verrucomicrobiae* family.

#### Mediation Analysis

After carrying out MR analysis from gut microbiota and inflammatory proteins to inflammatory diseases, we further explored the causal relationship of gut microbiota to inflammatory proteins that exerted large significant differences with inflammatory diseases. In the presence of a significant difference between gut microbiota and inflammatory proteins, MVMR analysis was conducted to investigate whether inflammatory proteins act as mediators in the path from gut microbiota to inflammatory diseases. It is worth noting that in two-sample MR analysis, the impact of gut microbiota on inflammatory diseases was characterized as the "total effect" ( $\beta_1$ ), whereas in MVMR, it is referred to as the "direct effect" ( $\beta_2$ ). In addition, the effect of inflammatory proteins on inflammatory diseases in MVMR analysis was defined as  $\beta_3$ , while the influence exerted by gut microbiota on inflammatory proteins in two-sample MR analysis was labeled as

$\beta_4$ . The mediating effect could be calculated as  $\beta_3*\beta_4$ , and the mediated ratio could be quantified by  $(\beta_3*\beta_4)/\beta_1$ .<sup>31</sup> Confidence intervals (95% CI) and odds ratios were estimated by the delta method. In addition, the Sobel test was utilized to assess the significance of mediator.

### Sensitivity Analysis

Cochran's Q test was utilized to evaluate the presence of heterogeneity among IVW IVs. Heterogeneity is considered to be present if the *p-value* is below 0.05. In addition, the random-effects IVW model is employed in the presence of heterogeneity ( $P < 0.05$ ), while the fixed-effects IVW model is used when there is no heterogeneity ( $P > 0.05$ )<sup>32</sup>. To identify the presence of pleiotropy among SNPs, we employed the MR-Egger intercept with a *p-value* below 0.05 as an indicator of noteworthy pleiotropic effects.<sup>30</sup> By employing the MR pleiotropy residual sum and outlier (MR-PRESSO) methodology, we detected outliers and evaluated the robustness of our analysis to examine the existence of horizontal pleiotropy. Through the identification and removal of such outliers, we obtained refined estimates that accounted for their influence. Moreover, to ensure the reliability of our analysis, leave-one-out analysis was carried out.<sup>33</sup>

To enable our results to be more rigorous, differences were considered significant if the *p-value* was still less than 0.05 after conducting the Benjamin-Hochberg procedure (FDR) in LDSC and MR analysis. In addition, it was represented as a suggestive association when *p-values* were less than 0.05 and the FDR-corrected *p-value* was above 0.05.<sup>34</sup> The MR analysis performed in this study was executed utilizing the R software (version 4.2.3), employing the two-sample package (version 0.5.9), and MR-PRESSO (version 1) for the analysis.

## Results

### Genetic Correlation Analysis

LDSC regression analysis was utilized to elucidate the genetic correlations between 196 gut microbiota and inflammatory diseases, as well as between 91 inflammatory proteins and these diseases. Owing to the incomputable negative heritability in LDSC, only 135 gut microbiota and 87 inflammatory proteins were included in the LDSC analysis. Based on univariate LDSC the heritability ( $h^2$ ) of SNPs in 135 gut microbiota and 87 inflammatory proteins was estimated to range from 0.0006 to 0.21 in microbiota and 0.004 to 0.19 in inflammatory proteins (Tables S2 and S3). The results which were with significant difference between gut microbiota/inflammatory proteins and inflammatory diseases were shown in Table 1 and Table 2. It was worth noting that after conducting FDR correction, 4 cytokines still remained significantly associated with acne. DNER, IL-1 alpha, IL 20 and PD-L1 were all associated with higher risk of developing acne ( $r_g = 0.63$ ,  $P = 0.003$ , *adjusted P* = 0.034;  $r_g = 1.12$ ,  $P = 0.001$ , *adjusted P* = 0.033;  $r_g = 1.08$ ,  $P = 0.0001$ , *adjusted P* = 0.005;  $r_g = 0.66$ ,  $P = 0.002$ , *adjusted P* = 0.034).

**Table 1** Genetic Correlation Between Gut Microbiota and Inflammatory Dermatoses

Trait 2	Trait 1	$r_g$	$r_g$ se	pval	Adjusted P
Allergic contact dermatitis	Class Alphaproteobacteria	-0.894	0.420	0.033	0.561
	Class Bacteroidia	0.904	0.460	0.049	0.555
	Family Verrucomicrobiaceae	-0.677	0.315	0.031	0.849
	Genus Akkermansia	-0.674	0.312	0.031	1.000
	Genus Flavonifractor	0.633	0.319	0.047	0.634
	Genus Ruminococcaceae NK4A214 group	-1.215	0.525	0.021	1.000
	Order Bacteroidales	0.904	0.460	0.049	0.605
	Phylum Actinobacteria	-0.718	0.352	0.041	0.616
	Phylum Verrucomicrobia	-0.755	0.322	0.019	1.000
	Eczema	Class Gammaproteobacteria	-0.283	0.121	0.019
Class Mollicutes		0.833	0.395	0.035	0.523
Family Alcaligenaceae		0.642	0.320	0.045	0.552

(Continued)

**Table 1** (Continued).

Trait 2	Trait 1	r <sub>g</sub>	r <sub>g</sub> se	pval	Adjusted P
	Family Enterobacteriaceae	-0.430	0.188	0.022	0.596
	Genus Escherichia-Shigella	-0.679	0.273	0.013	0.576
	Genus LachnospiraceaeUCG004	0.379	0.169	0.025	0.484
	Genus Subdoligranulum	-0.503	0.195	0.010	0.676
	Order Enterobacteriales	-0.430	0.188	0.022	0.496
	Order MollicutesRF9	1.021	0.511	0.046	0.514
	Phylum Proteobacteria	-0.342	0.154	0.027	0.447
	Phylum Tenericutes	0.833	0.395	0.035	0.471
	Phylum Verrucomicrobia	-0.341	0.172	0.047	0.487
	Psoriasis vulgaris	Genus Eggerthella	0.475	0.214	0.026
Phylum Proteobacteria		0.397	0.202	0.049	1.000
Psoriatic arthritis	Family Christensenellaceae	-0.983	0.441	0.026	1.000
	Genus ChristensenellaceaeR.7 group	-1.023	0.387	0.008	0.554
	Genus Ruminiclostridium9	-0.979	0.318	0.002	0.282
Seborrheic dermatitis	Family Verrucomicrobiaceae	-1.017	0.335	0.002	0.081
	Genus Akkermansia	-1.005	0.333	0.003	0.069
	Genus LachnospiraceaeUCG010	0.892	0.435	0.040	0.776
	Phylum Verrucomicrobia	-1.139	0.331	0.001	0.077

**Notes:** r<sub>g</sub>, genetic correlation; r<sub>g</sub> se, standard error of genetic correlation; pval, p-value; adjusted P, p-value after false discovery rate (FDR) correction.

**Table 2** Genetic Correlation Between Inflammatory Proteins and Inflammatory Dermatoses

Trait 2	Trait 1	r <sub>g</sub>	r <sub>g</sub> se	pval	Adjusted P
Acne	4EBPI	0.512	0.259	0.048	0.174
	Beta-NGF	0.609	0.224	0.007	0.063
	CCL11	0.451	0.177	0.011	0.084
	CCL19	0.389	0.165	0.019	0.107
	CCL28	0.464	0.187	0.013	0.088
	CX3CLI	0.536	0.225	0.017	0.107
	CXCL10	0.389	0.195	0.045	0.171
	CXCL6	0.443	0.201	0.028	0.127
	DNER	0.632	0.211	0.003	0.034
	Fit3L	0.421	0.153	0.006	0.065
	IL-1alpha	1.125	0.346	0.001	0.033
	IL-20	1.087	0.282	0.0001	0.005
	LIF	0.969	0.475	0.042	0.164
	MCP-1	0.591	0.217	0.007	0.057
	MCP-4	0.338	0.166	0.041	0.171
	MIP-1alpha	0.471	0.209	0.024	0.117
	PD-L1	0.663	0.218	0.002	0.035
	TSLP	0.583	0.256	0.022	0.115
TWEAK	0.559	0.223	0.012	0.089	
VEGF A	0.866	0.370	0.019	0.106	

(Continued)

**Table 2** (Continued).

Trait 2	Trait 1	$r_g$	$r_g$ se	pval	Adjusted P
Allergic contact dermatitis	4EBP1	0.504	0.248	0.042	0.608
	CCL23	1.033	0.421	0.014	0.412
	CSF-1	0.494	0.249	0.047	0.515
	IL-2RB	0.702	0.297	0.018	0.391
	LAP TGF-beta-1	1.091	0.393	0.006	0.482
	MCP-1	0.532	0.266	0.046	0.567
	MCP-4	0.489	0.188	0.009	0.402
	MIP-1alpha	0.555	0.256	0.030	0.528
Eczema	FGF-19	0.251	0.127	0.047	1.000
	IFN-gamma	0.614	0.238	0.010	0.434
	IL-6	0.532	0.213	0.012	0.358
Psoriasis vulgaris	CCL19	0.285	0.110	0.010	0.865
	CCL9	0.306	0.123	0.013	0.546
	TNF	-1.065	0.499	0.033	0.953
	TWEAK	-0.277	0.135	0.041	0.888
Psoriatic arthritis	AXINI	-1.099	0.539	0.041	1.000
Seborrheic dermatitis	EN-RAGE	-0.481	0.238	0.043	1.000

**Abbreviations:** 4EBP1, Eukaryotic translation initiation factor 4E-binding protein 1; Beta-NGF, Beta-nerve growth factor; CCL, C-C motif chemokine; CX3CL1, Fractalkine; CXCL, C-X-C motif chemokine; DNER, Delta and Notch-like epidermal growth factor related receptor; Flt3L, Fms-related tyrosine kinase 3 ligand; IL, Interleukin; LIF, Leukemia inhibitory factor; MCP, Monocyte chemoattractant protein; MIP, Macrophage inflammatory protein; PD-L1, Programmed cell death 1 ligand 1; TSLP, Thymic stromal lymphopoietin; TWEAK, Tumor necrosis factor (Ligand) superfamily member 12; VEGF A, Vascular endothelial growth factor A; CSF-1, Macrophage colony-stimulating factor 1; IL-2RB, Interleukin-2 receptor subunit beta; LAP TGF-beta-1, Latency-associated peptide transforming growth factor beta 1; FGF, Fibroblast growth factor; IFN-gamma, Interferon gamma; TNF, Tumor necrosis factor; AXINI, Axin-1; EN-RAGE, Protein S100-A12.

## Mendelian Randomization

According to the criteria of screening, 2559 SNPs were selected as IVs for 196 gut microbiota and 1819 SNPs were chosen as IVs for inflammatory proteins. As shown in [Figures 2 and 3](#), we found that 11, 8, 3, 4, 8, and 5 gut microbiota had a significant causal effect on acne, allergic contact dermatitis, eczema, psoriasis, psoriatic arthritis, and seborrheic dermatitis, respectively, while 2, 5, 5, 6, 5, and 5 inflammatory proteins were associated with these conditions respectively. The results of the estimates of causal associations between 196 gut microbiota/inflammatory proteins and inflammatory diseases are presented in [Tables S3–S7](#). It is noteworthy that, following FDR correction, four gut microbiota remained statistically significant. In the MR analysis linking gut microbiota to psoriasis vulgaris, the genus *Eubacterium fissicatena* group remained significantly associated with an increased risk of developing psoriasis vulgaris (OR = 1.32, 95% CI: 1.16–1.50,  $P = 0.00004$ , *adjusted P* = 0.007). Additionally, family *Bacteroidaceae*, genus *Allisonella* and genus *Bacteroides* were identified as significant risk factors for acne (OR = 2.25, 95% CI: 1.48–3.42,  $P = 0.0001$ , *adjusted P* = 0.026; OR = 1.42, 95% CI: 1.18–1.70,  $P = 0.0002$ , *adjusted P* = 0.014; OR = 2.25, 95% CI: 1.48–3.42,  $P = 0.0001$ , *adjusted P* = 0.013). Moreover, IL-18R1 remained significantly related to eczema after FDR correction (OR = 1.05, 95% CI: 1.03–1.08,  $P = 0.0002$ , *adjusted P* = 0.017).

## Mediation Analysis

Following MR analysis of gut microbiota and inflammatory proteins to inflammatory diseases, we explored the causal relationships between gut microbiota and inflammatory proteins. These gut microbiota and inflammatory proteins put into

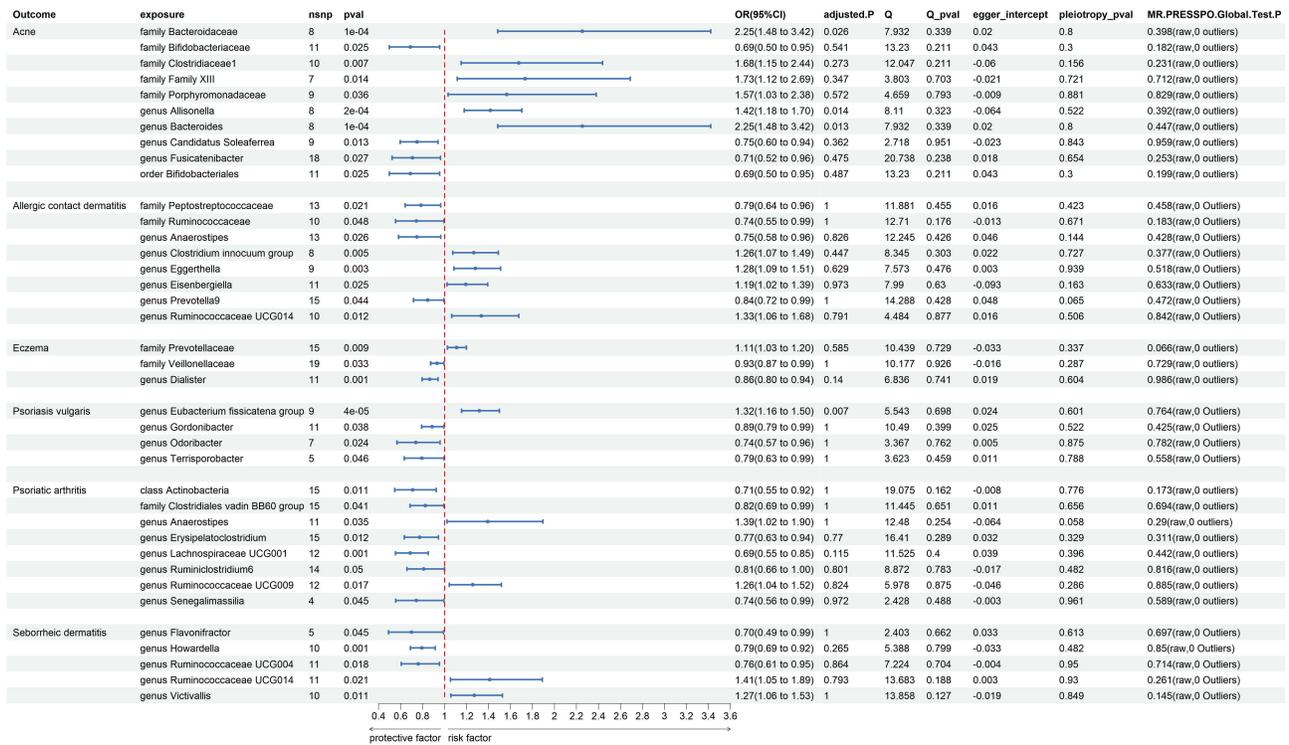


Figure 2 Forest plot of significant effects between gut microbiota and inflammatory dermatoses, using the IVW method.

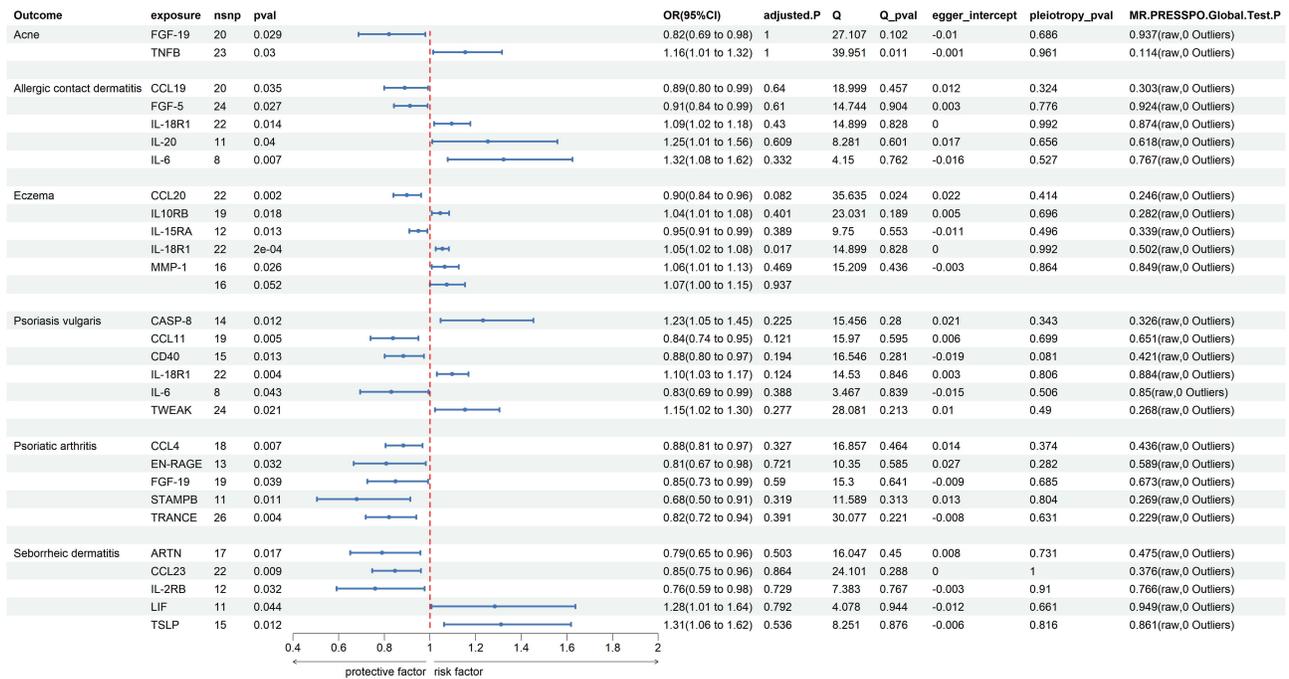
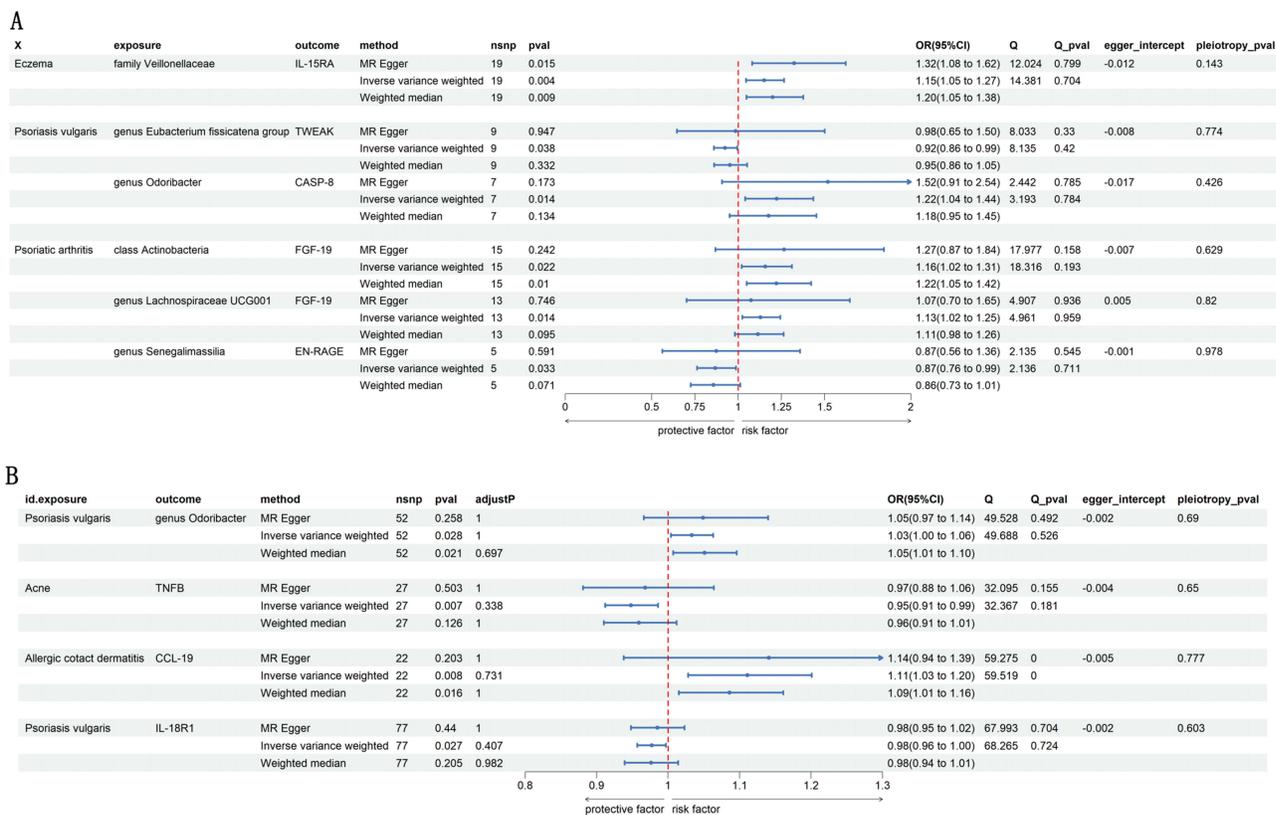


Figure 3 Forest plot of significant effect between inflammatory proteins and inflammatory dermatoses, using the IVW method.

**Abbreviations:** FGF, Fibroblast growth factor; TNFB, TNF-beta; CCL, C-C motif chemokine; IL-18R1, Interleukin-18 receptor 1; IL, Interleukin; IL10RB, Interleukin-10 receptor subunit beta; IL-15RA, Interleukin-15 receptor subunit alpha; MMP, Matrix metalloproteinase; CASP-8, Caspase 8; CD40, CD40L receptor; TWEAK, Tumor necrosis factor (Ligand) superfamily member 12; EN-RAGE, Protein S100-A12; STAMPB, STAM-binding protein; TRANCE, TNF-related activation cytokine; ARTN, Artemin; LIF, Leukemia inhibitory factor; TSLP, Thymic stromal lymphopoietin.



**Figure 4 (A)** forest plot of significant effect between gut microbiota and inflammatory proteins; **(B)** forest plot of bidirectional causality between gut microbiota/inflammatory proteins and inflammatory dermatoses.

this MR analysis were all associated with inflammatory diseases with significant differences respectively (Figure 4 and Table S8). Subsequently, we carried out MVMR analysis to figure out whether inflammatory proteins acted as mediators from gut microbiota to inflammatory skin diseases (Table 3). After entering IL-15RA into MVMR to assess the correlation of family *Veillonellaceae* to eczema, the correlation still remained statistically significant, and the mediating effect was calculated as  $-0.008$  (OR = 0.992, 95% CI: 0.984–0.998) while the mediating proportion was 11%. Similarly, entering FGF19 into MVMR analysis, for class *Actinobacteria* and genus *LachnospiraceaeUCG001* to psoriatic arthritis, still showed significant differences from FGF19 to psoriatic arthritis in two pathways, respectively, with a mediating effect of  $-0.026$  and  $-0.024$  (OR = 0.974, 95% CI: 0.934–1.001; OR = 0.976, 95% CI: 0.944–0.998). In addition, after conducting the Sobel test, only IL-15RA as a mediator from family *Veillonellaceae* for eczema, and FGF19 as a mediator from genus *LachnospiraceaeUCG001* for psoriatic arthritis remained statistically significant. For other inflammatory proteins, after MVMR analysis, no intermediary effect was shown.

**Table 3** Mediating Analysis From Gut Microbiota to Inflammatory Dermatoses

Mediator	Pathway	$\beta$ I	Mediating effect	Mediating proportion	Confidence intervals
IL-15RA	Family <i>Veillonellaceae</i> to eczema	-0.071	-0.008	11%	(0.984,0.998)
FGF19	Class <i>Actinobacteria</i> to psoriatic arthritis	-0.342	-0.026	8%	(0.934,1.001)
FGF19	Genus <i>LachnospiraceaeUCG001</i> to psoriatic arthritis	-0.375	-0.024	6%	(0.944,0.998)

**Notes:**  $\beta$ I: impact of gut microbiota on inflammatory diseases in two-sample MR analysis; IL-15RA, Interleukin-15 receptor subunit alpha; FGF, Fibroblast growth factor.

## Sensitivity Analysis

Heterogeneity existed between TNFB and acne ( $P = 0.041$ ) while heterogeneity was found between CCL20 and eczema through Cochran's Q test (Figure 4). Hence, a random-effects IVW model was applied when heterogeneity existed. Except for the results mentioned above, there was no heterogeneity found in the remaining results. According to MR-Egger intercept regression analysis and MR-PRESSO, there was no significant horizontal pleiotropy in our study (Tables S9–S11).

## Reverse Causality Analysis

In the reverse MR analysis, we selected inflammatory skin diseases as the exposure and 196 gut microbiota and 91 inflammatory proteins as the outcomes. As shown in Figure 4, we found a bidirectional relationship between the genus *Odoribacter* and psoriasis vulgaris (OR = 1.03, 95% CI: 1.00–1.06,  $P = 0.028$ ). Regarding inflammatory proteins, acne was associated with a decreased risk of TNFB (OR = 0.95, 95% CI: 0.91–0.99,  $P = 0.007$ ), while allergic contact dermatitis was linked to an increased risk of CCL-19 (OR = 1.11, 95% CI: 1.03–1.20,  $P = 0.008$ ). Additionally, psoriasis vulgaris was associated with a decreased risk of IL-18R1 (OR = 0.98, 95% CI: 0.96–1.00,  $P = 0.027$ ). Except for heterogeneity detected between TNFB and allergic contact dermatitis, no heterogeneity or horizontal pleiotropy was detected based on Cochran's Q test and MR-Egger. More details are shown in Tables S12–S15.

## Discussion

To our knowledge, this is the first study to use two-step MR analysis to explore whether inflammatory proteins mediate the pathway from gut microbiota to inflammatory dermatoses. Based on GWAS data, we identified suggestive associations and estimated genetic correlations between gut microbiota, inflammatory proteins, and inflammatory dermatoses. The lack of overlap between LDSC regression analysis and MR analysis indicates that the findings from MR analysis are independent of shared genetic components. Furthermore, MVMR analysis identified IL-15RA and FGF-19 as mediators. This study pioneers the causal investigation of how gut microbes and cytokines interact to influence inflammatory skin diseases, providing the first genetic-level evidence of cytokine mediation from gut microbiota to these conditions.

As part of the gut-skin axis, extensive research has highlighted the critical role of gut microbiota in skin disorders. Dysbiosis, or an imbalance in microbiota diversity, is considered one of the key underlying causes of inflammatory skin diseases. It enhances host susceptibility, disrupts mucosal immune tolerance, and directly influences neurotransmitter production or modulates neurotransmitter metabolism pathways, ultimately impacting skin health.<sup>35</sup> Although previous observational studies have noted significant differences in microbiota diversity in patients with skin disorders, causality remains unclear due to the limitations of observational research. In contrast, MR analysis, based on genetic variations, is less affected by confounding factors and allows for causal inferences between gut microbiota and inflammatory skin disorders.

Previous observational studies have suggested a reduced abundance of *Ruminococcaceae* in patients with eczema and acne,<sup>5,8</sup> indicating a potential association with disease pathogenesis. However, these studies could not establish causality. In contrast, our MR-based findings provide robust genetic evidence that *Ruminococcaceae* exerts a causal, protective effect against allergic contact dermatitis, psoriasis vulgaris, and seborrheic dermatitis. In addition to *Ruminococcaceae*, our study identifies several microbiota, such as *Lachnospiraceae*UCG001 and *Bifidobacterium*, as protective factors against inflammatory dermatoses. These protective microbes commonly produce short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which travel from the gut to the skin and can modulate local immune responses.<sup>36</sup> Thus, *Ruminococcaceae* may confer protection by modulating immune responses via SCFA production. SCFAs enhance innate immune cell function, potentially improving the skin's defense against inflammation. They also shape adaptive immunity by influencing T and B cell differentiation.<sup>36</sup> Accordingly, interventions that increase SCFA levels—either through microbiota manipulation or direct supplementation, may offer therapeutic potential. Another study linked *Veillonellaceae* enrichment with higher propionate levels in patients with Glycogen Storage Disease, suggesting that *Veillonellaceae* may regulate inflammation via SCFA modulation.<sup>37</sup> Consistent with these findings, we show that *Veillonellaceae* is associated with reduced eczema risk, reinforcing its potential anti-inflammatory role. Furthermore, our MR analysis reveals

that *Bifidobacterium* is associated with a reduced risk of acne. By enhancing tryptophan levels and its metabolites, *Bifidobacterium* may help maintain intestinal barrier integrity and alleviate acne-related inflammation.<sup>38</sup> These findings strengthen the hypothesis that *Bifidobacterium* plays a causal role in the prevention of inflammatory dermatoses.

Moreover, our study identifies several bacteria, including *Fusicatenibacter*, *Flavonifractor*, and *Odoribacter*, as potentially protective factors against inflammatory dermatoses, possibly through their interaction with circulating inflammatory cytokines. *Flavonifractor prausnitzii* is a well-known microbial marker for various inflammatory conditions, such as psoriasis and AD.<sup>39</sup> Elevated *Flavonifractor* abundance has been observed in moderate-severe AD and bullous pemphigoid, suggesting a pattern of involvement across different conditions.<sup>40,41</sup> Correlations between *Flavonifractor* and multiple inflammatory markers further implicate it in immune dysregulation. Additionally, *Fusicatenibacter* and *Odoribacter* have shown the ability to induce regulatory pathways such as IL-10 production and regulatory T cell enhancement that could help maintain immune balance.<sup>15,16,42</sup> These findings suggest that beyond traditionally studied taxa, a broader range of gut microbes may contribute to modulating immune responses in the skin. Our study also identified gut microbiota genera *Erysipelatoclostridium*, *Anaerostipes*, *Eggerthella*, and *Eisenbergiella* to be associated with inflammatory skin diseases. However, related research is limited and requires more exploration.

Our MR analysis reveals a causal relationship between IL-18R1 and the increased risk of allergic contact dermatitis, eczema, and psoriasis vulgaris, supporting prior findings. IL-18R is expressed on various immune cells such as Th1, NK, and mast cells, suggesting a broad immunomodulatory function.<sup>43</sup> Higher IL-18R expression in lesional skin compared to healthy skin may explain its role in driving these inflammatory processes.<sup>10</sup> Similarly, IL-6 shows a causal link with conditions such as allergic contact dermatitis and psoriasis vulgaris. IL-6, a pleiotropic cytokine, correlates with psoriasis severity, consistent with our causal inference. Moreover, IL-6-driven mononuclear cell infiltration likely sustains inflammation in contact dermatitis.<sup>44</sup>

Our MR analysis shows that FGF19 reduces the risk of acne and psoriatic arthritis, suggesting a protective effect. As a member of the fibroblast growth factor family, FGF19 influences immune responses and keratinocyte biology. Although its role in acne remains unclear, previous studies have reported elevated FGF19 expression in lesioned skin of psoriasis patients, suggesting that it may be involved in inflammation regulation.<sup>11</sup> Thus, FGF19 may maintain immune balance and keratinocyte homeostasis, potentially slowing disease progression. Our study also identified several chemokines, such as CCL-20, as protective factors for inflammation. However, given the limited research available, further studies are needed to investigate this relationship in greater detail.

Our study provides genetic evidence that IL-15RA and FGF19 act as mediators in the pathway from gut microbiota to inflammatory diseases. Specifically, IL-15RA mediated the effect of *Veillonellaceae* on eczema, while FGF19 mediated the association between *Actinobacteria*, *LachnospiraceaeUCG001*, and psoriatic arthritis. IL-15RA, a high-affinity  $\alpha$  chain that forms a trimeric receptor complex with IL-2R $\beta$  and IL-2R $\gamma$ , triggers downstream signaling pathways such as MAPKs and promotes the secretion of proinflammatory cytokines, including IL-6, IL-8, and TNF- $\alpha$ .<sup>12</sup> While previous studies have observed elevated IL-15RA expression in RA, its role in eczema has not been previously explored.<sup>12</sup> Notably, a mouse model has shown exacerbated allergic inflammation due to IL-15 deficiency, which may relate to eczema pathogenesis.<sup>45</sup> Identifying IL-15RA as a mediator offers new insight into eczema pathogenesis and suggests a potential therapeutic target. For psoriatic arthritis, FGF19 mediated the association between *Actinobacteria* and *LachnospiraceaeUCG001* with disease risk. Elevated FGF19 levels in psoriatic lesions suggest its involvement in keratinocyte regulation and inflammatory processes.<sup>11</sup> However, the mediating effect was relatively modest, implying that gut microbiota may regulate inflammatory skin disorders through additional pathways. These microbial taxa produce SCFAs, which reduce proinflammatory cytokines and influence circulating metabolites, thereby shaping immune responses in the skin. SCFAs, particularly butyrate, have been shown to control the differentiation and function of mucosal Tregs. Dysregulation of Treg cells or an imbalance in cytokines, particularly elevated pro-inflammatory cytokines like IL-6 and IL-17, can contribute to the onset and progression of inflammatory dermatosis.<sup>46</sup> These findings underscore the importance of gut microbiota and their metabolites in modulating immune responses in inflammatory dermatoses.

## Strengths and Limitations

Our research offers several key advantages. First, this is the first study to investigate the genetic correlation by LDSC analysis and causal relationship by MR analysis between gut microbiota, inflammatory proteins, and inflammatory dermatoses, such as acne, allergic contact dermatitis, eczema, psoriasis vulgaris, psoriatic arthritis and seborrheic dermatitis. We also figured out, through two-step MR, whether inflammatory proteins serve as mediators in the pathway from gut microbiota to inflammatory skin disorders, which provides genetic evidence for further treatment targeting gut microbiota or cytokines. In addition, our investigation was conducted based on robust methodology by leveraging GWAS and MR, which minimizes confounding biases relative to traditional studies. Furthermore, our research employs a comprehensive methodology to ensure result reliability. Sensitivity analyses were performed, utilizing Cochran's Q test to assess heterogeneity, MR-Egger intercept and MR-PRESSO to detect horizontal pleiotropy.

Despite its strengths, our research also has some limitations. First, since the GWAS data primarily originates from European populations, the findings may not be generalizable to other ethnicities. Secondly, although MR analysis helps infer causal relationships, it can not completely eliminate all confounding variables. While MR analysis serves as a hypothesis-driven approach, it necessitates experimental and clinical studies to confirm the causal relationship between gut microbiota/inflammatory proteins and inflammatory dermatoses. Additionally, this study relies on cross-sectional genetic data, which limits the ability to capture dynamic changes in gut microbiota or cytokine levels over time. Longitudinal studies are required to better understand the temporal interactions between these factors and their influence on the progression of inflammatory skin diseases. Finally, although we identified IL-15RA and FGF19 as mediators, their mediating proportions were relatively modest, suggesting that additional pathways or mechanisms may play significant roles in the gut-skin axis.

## Conclusion

As far as we know, this is the first study to examine whether inflammatory proteins mediate the pathway from gut microbiota to inflammatory dermatoses using a two-step MR analysis. Drawing from GWAS data, we identified IL-15RA and FGF19 as mediators, providing novel insights into the gut-skin axis and its potential therapeutic targets. Despite modest mediating effects, these findings highlight the complexity of the gut-skin axis and suggest additional unexplored pathways. Future research with diverse populations and longitudinal data is needed to validate and expand these results. This study provides a foundation for developing microbiota-based or cytokine-targeted therapies, offering new directions for treating inflammatory skin diseases.

## Data Sharing Statement

The genome-wide association study (GWAS) data for inflammatory proteins is accessible through the GWAS catalog, while gut microbiota data is available from the MiBioGen consortium. Information on inflammatory skin disorders can be obtained via the FinnGen consortium. Code used in the analysis are available at <https://github.com/>.

## Consent for Publication

Not required.

## Consent to Participate

Not required.

## Ethical Approval

According to Article 32 of the "Measures for the Ethical Review of Life Science and Medical Research Involving Humans" (National Health Commission [2023] No. 4), research using anonymized, publicly available data is exempt from ethical review, provided it does not involve sensitive personal information or individual-level interventions. This study exclusively utilizes anonymized public data, with no individual-level interventions, and complies with relevant

regulations. Therefore, it qualifies for exemption from ethical review. The data source and anonymization process have been clearly stated for transparency and compliance.

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## Disclosure

The authors have no conflicts of interest to declare in this work.

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