

# Metagenomics Analysis of Altered Gut Microbiome in Psoriasis and the Mediation Analysis: A Case-Control Study

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**Purpose:** Psoriasis is an inflammatory disease linked to gut microbiome dysbiosis. However, the mechanisms underlying gut microbiome changes caused by dietary habits in psoriasis remain unclear.

**Patients and Methods:** We performed a case-control study including 64 psoriasis patients and 64 age-, sex-, and body mass index (BMI)-matched controls. Stool samples were collected for metagenomics sequencing. The differential abundance analysis was performed to identify differentially abundant taxa between psoriasis and control groups. The dietary intake frequency information of each included subject was obtained through face-to-face interviews. Mediation analysis was used to identify potential mediators of the gut microbiome alterations in psoriasis.

**Results:** The gut microbiome of psoriasis patients was significantly altered when compared to controls. *Anaerostipes Hadrus*, *Blautia Wexlerae*, and the other six species may be beneficial to psoriasis. However, *Prevotella Copri* and *Eggerthellaceae* could be pathogenic bacteria. The study also identified correlations between specific dietary habits and psoriasis, with the largest correlation observed between poultry consumption and psoriasis (OR=0.735, P=0.001), followed by red meat (OR=0.784, P=0.007) and fresh vegetables (OR=0.794, P=0.028). Mediation analysis revealed that *Anaerostipes hadrus*, *Dorea longicatena*, and *Eggerthella lenta* mediated the association between poultry and psoriasis.

**Conclusion:** The characteristics of intestinal flora in psoriasis patients were significantly different from controls. Intestinal flora mediated the association between diet and psoriasis to some extent. This study provides new insights for adjuvant treatments of psoriasis through dietary and intestinal microbiota interventions.

**Keywords:** psoriasis, gut microbiome, metagenomics, diet, mediator

## Introduction

Psoriasis is a common immune-related inflammatory skin disease that affects over 100 million people worldwide.<sup>1,2</sup> It is of great significance to explore the risk factors of psoriasis and the possible prevention methods. While metabolic disorders and systemic inflammation have been suggested as possible triggers for psoriasis in recent years, the underlying cause remains unknown. The gut microbiota, which provided endogenous benefits and maintained immune homeostasis, has recently been recognized as the trigger of a variety of immune dysregulation and immune-related diseases.<sup>3,4</sup> Given

that psoriasis is often associated with comorbidities across metabolic and autoimmune diseases, investigating the potential link between changes in the gut microbiome and the development of psoriasis is a promising area of study.

Previous studies have attempted to characterize the intestinal microbiota of psoriasis patients using 16s RNA analysis.<sup>5</sup> For instance, one study found that the abundance of the bacterial phylum Firmicutes was significantly higher in psoriasis patients compared to healthy controls, while the abundance of Bacteroidetes was lower.<sup>6</sup> And another study found that psoriasis patients had a lower abundance of *Faecalibacterium*, a species that has been shown to have anti-inflammatory effects.<sup>7</sup> These findings suggest that psoriasis patients may have a distinct gut microbiota composition that is associated with the disease. However, the specific microbial species that contribute to psoriasis pathogenesis remain unclear and controversial, and all these studies have been limited by small sample sizes and limited research methods. Moreover, these studies have not taken into account the impact of diet habits on the endogenous environment and gut microbiota. Given the known link between diet and microbiota composition, it is crucial to examine the associations between diet, gut microbiota, and psoriasis. This approach will provide a more comprehensive understanding of the role of gut microbiota in psoriasis pathogenesis and offer new avenues for potential preventive or therapeutic interventions. To investigate the link between gut microbiome composition, dietary patterns, and psoriasis, we performed metagenomic sequencing to compare the gut microbiome of individuals with and without psoriasis. Our study aims to identify specific microbial species that are associated with psoriasis and explore the potential interactions between these microbes and dietary patterns. By analyzing the metagenomic data and dietary information, we hope to provide new evidence for the adjuvant treatment of psoriasis through dietary and intestinal microbiota interventions. Our study aimed to help identify specific dietary recommendations or probiotic treatments that could be used with conventional psoriasis therapies to improve patient outcomes.

## Materials and Methods

### Study Design and Participants

This study recruited participants from Changsha, Hunan Province, including patients diagnosed with psoriasis and normal controls aged between 18 to 60 years. The psoriasis patients were recruited from the Dermatology Department of Xiangya Hospital, while the control group was comprised of participants from the Hunan Civil Servant Cohort. We ensured an even distribution of sex, age, and body mass index (BMI) by stratified random sampling from the cohort participants. The psoriasis patients met the diagnostic criteria established by the International Classification of Diseases (ICD) and were not undergoing any systemic or topical therapy at the time of enrollment. Exclusion criteria for both groups included any history of antibiotic or probiotic use within the previous 3 months, any chronic gastrointestinal disease, and any systemic disease or autoimmune disorders. The study was approved by the Research Ethical Committee of Xiangya Hospital, Central South University (Approval No. XYFY2019-KL103), and all participants provided written informed consent before participating in the studies.

### Inclusion and Exclusion Criteria

Inclusion criteria for psoriasis patients were as follows: 1) meeting the diagnostic criteria of psoriasis Vulgaris; 2) primary-care patients with no regular treatment for psoriasis and no other long-term medication experience; 3) no autoimmune diseases, gastrointestinal diseases, allergies, and other known diseases; 4) no administration of antibiotics, probiotics or prebiotics within 3 months before sample collection; 5) no intake of cheese, yoghurt or pickles within 3 days before sample collection; 6) living in Changsha in the past year before sample collection. For normal controls were as follows: 1) no psoriasis; 2) the same as the inclusion criteria for psoriasis patients.

Exclusion criteria for psoriasis patients and NCs were as follows: 1) accompanied by other subtypes of psoriasis, such as erythroderma psoriatic and pustular psoriasis; 2) unavailability to collect samples as required; 3) pregnancy or lactation.

### Diet Frequency Questionnaire

The dietary intake frequency information of each included subject was obtained through face-to-face interviews and inquiries. Dietary types are confirmed and adjusted appropriately according to a variety of commonly used dietary

questionnaires and the dietary habits of Chinese residents, mainly including red meat, poultry, fish, eggs, beans and dairy products, fresh vegetables, fresh fruits, nuts, processed meat, sweets, sugary juices, and carbonated drinks.

## Processing and Preservation of Faecal Samples

Faecal samples were processed and preserved according to the following requirements: 1) use a sterile cotton swab to scratch the surface of the stool within 3 minutes after defecation, and then use another sterile cotton swab to extend into the interior of the stool and rotate for 3 circles until there is a piece of faeces about the size of soybean on the surface of the cotton swab; 2) put the cotton swab with faeces into the collection tube containing DNA preservation solution, and shake the cotton swab gently to make the faeces sample evenly dispersed in the preservation solution; 3) put the sample collection tube into the refrigerator at - 80°C for storage.

## DNA Extraction and PCR Amplification

Faecal genomic DNA was extracted according to the instructions of the MasterPure Nucleic Acid Extraction Kit (Epicentre, UK). Add 300 µL lysate and 1 µL protease K to the samples, scroll for 10 minutes, 65 °C and incubate for 15 minutes. Add 5 µg Ribonucleic Acid (RNA) to mix, incubate for 30 minutes at 37 °C, place on ice for 3–5 minutes. And then add 150 µL Mpc protein precipitator, swirl vigorously for 10s, centrifuge 10000 g 4 °C for 10 minutes to precipitate protein. After centrifugation, take the supernatant, add 500 µL isopropyl alcohol, turn and mix 30–40 times, centrifuge 4 °C for 10 min to precipitate DNA. Wash it twice with 70% ethanol, and dissolve the DNA precipitate in 15 µL sterile water.<sup>8</sup>

## Library Generation and Sequencing

A starting amount of 100 ng DNA was taken and broken into 300–400 bp fragments using Bioruptor non-contact Ultrasound fragmentation (Belgium) according to the ND604-VahTS Universal DNA Library Prep Kit. DNA sequencing libraries were constructed using HiSeq PE Cluster Kit V4 and HiSeq SBS Kit V4 250 cycle. The Kit (Illumina, USA) sequencing kit was used for 2×150 double-terminal metagenomic sequencing on HiSeq 2500 sequencing platform.

## Data Preparation

The image data obtained by metagenomic sequencing were processed into raw Fastq data by Casava (V1.8.2, Illumina, USA). The processing of raw data consisted of two main steps: 1) FastQC software was used for quality control analysis; Trimmomatic software was used to remove primers, connectors, and low-quality bases, and only the sequence data with reading length over 45 bp were retained; 2) given the overwhelming dominance of microorganisms in faecal samples, human host sequences were removed using the first step of the Csm analysis process by comparing sequence data to the standard Human reference genome (HG19) using Bwa and subtracting from the data using Samtools. Comparison sequences, where single-end sequences are compared to HG19 data, the other end sequences are also removed from the data. Pre-processed metagenomic sequencing data are then subjected to microbiome characterization analysis using MetaPhlAn 3.0 under its default parameters to obtain microbiome composition at all levels of accuracy in each sample microbiome.

## Statistical Analysis

The  $\alpha$  diversity was described by the Shannon index; and the  $\beta$  diversity was measured by the Bray-Curtis dissimilarity coefficient and analyzed by unrestricted and restricted ranking methods, respectively. Linear Discriminant Analysis is used to test for differences between groups using the Wilcoxon rank-sum test or Kruskal–Wallis rank-sum test (for numerical variables that do not conform to a normal distribution) or *t*-test (for numerical variables that conform to a normal distribution). Spearman correlation analysis was used to evaluate the correlation between intestinal microflora and factors like diet frequency. The receiver Operator Characteristic (ROC) curve was used to evaluate the potential diagnostic value of single bacteria species between groups. A P-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using the software R language (version 4.0.2).

# Results

## Characteristics of Participants

There were 64 patients with psoriasis vulgaris and 64 normal control subjects included in our study. The mean age of the patients with psoriasis vulgaris was  $38.14 \pm 10.79$  years, and 44 (68.7%) were male. No significant differences were observed in terms of age or gender between the two groups. The demographic characteristics of the patients with psoriasis vulgaris and the normal controls are presented in [Table 1](#).

## Analysis of the Diversity of Gut Microbiota

The  $\beta$  diversity ([Figure 1A](#)) and  $\alpha$  diversity ([Figure 1B](#)) of intestinal flora in the case group were significantly decreased. At the phylum level, the proportion of Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria was significantly different between the two groups ([Figure 1C](#)). At the family level, a total of 26 families were detected, among which Prevotellaceae was significantly enriched in the psoriasis group, while Eggerthellaceae was significantly enriched in the normal control group ([Figure 1D](#)). A total of 40 genera were detected at the genus level, among which 8 had significant differences between groups ([Figure 2A](#)). Only Prevotella was significantly enriched in the psoriasis group. All other genera showed significant enrichment in the normal control group. A total of 72 species were detected at the species level, among which 10 species had significant differences between groups ([Figure 2B](#)). Prevotella Copri and Parabacteroides Merdae were significantly enriched in the psoriasis group, while other species were significantly enriched in the normal control group. The systematic branches of the differential flora are shown in [Figure 2C](#). ROC curves were drawn for the 10 detected strains with inter-group differences ([Figure S1](#)). The results showed that Blautia Wexlerae and Prevotella Copri had the largest area under the curve, which reached 0.858 and 0.775, respectively.

## Diet Frequency Questionnaire

The results showed that the diet frequency of red meat, poultry, and fresh vegetables was different between the two groups ([Table S1](#)). The frequency of red meat, poultry, and fresh vegetables in patients with psoriasis was significantly less than that of the normal control population. A Logistic regression model was further established to evaluate the association between diet frequency with psoriasis ([Table S2](#)). After adjusting for gender, age, and BMI, a significant association between the dietary frequency of red meat, poultry, and fresh vegetables with psoriasis was observed. The largest correlation effect was observed between poultry and psoriasis (OR=0.735, 95% CI: 0.614–0.879, P=0.001), followed by red meat (OR=0.784, 95% CI: 0.658–0.935, P=0.007), and fresh vegetables (OR=0.794, 95% CI: 0.646–0.976, P=0.028).

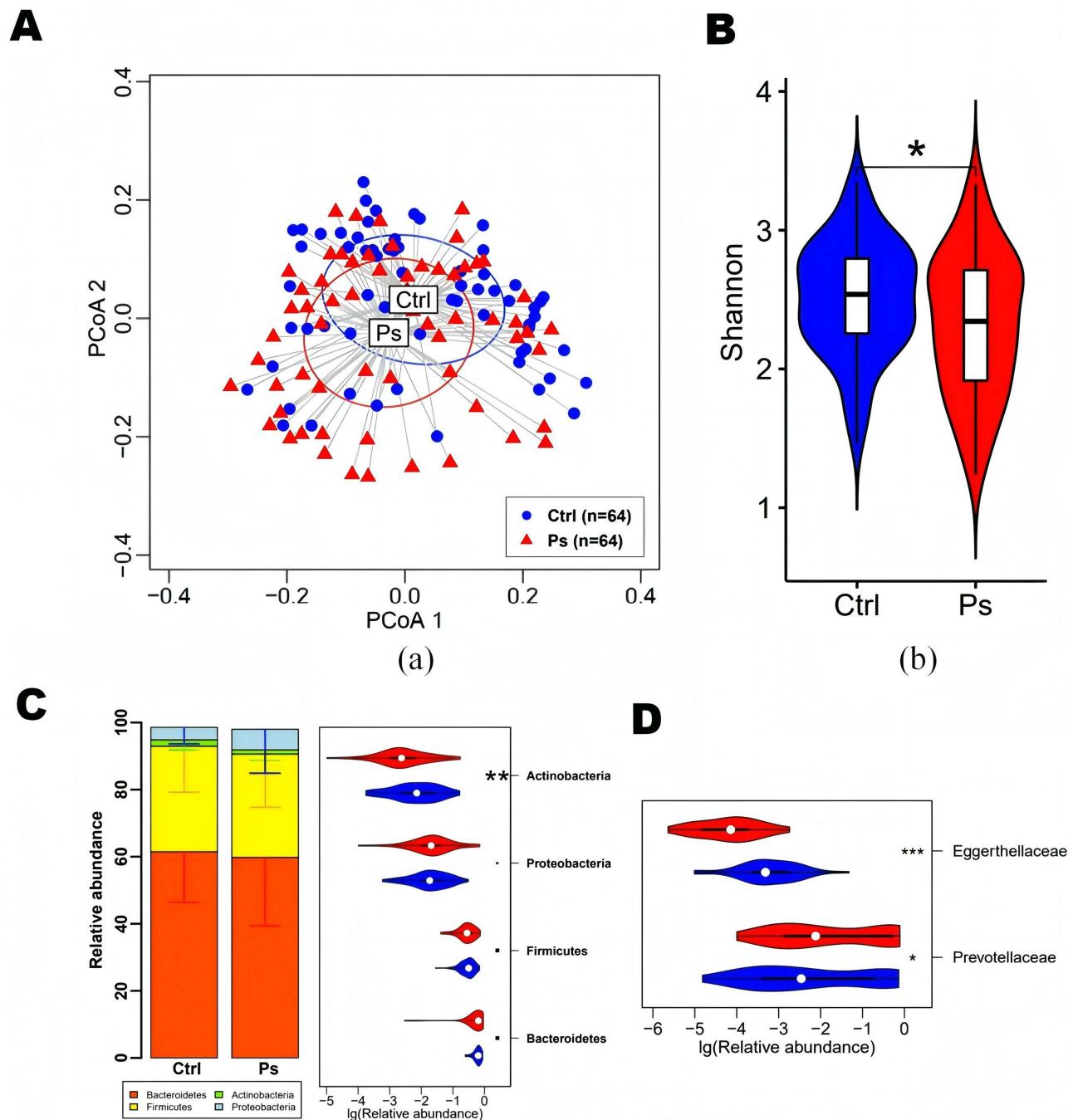
## Correlation Between Different Diet Frequency and Different Strains

The diet frequency of red meat was significantly correlated with the abundance of Anaerostipes hadrus (P=0.005), Blautia Wexlerae (P=0.026), Dorea Longicatena (P=0.031), and Eggerthella. The diet frequency of poultry was

**Table 1** Demographic Characteristics of the Patients With Psoriasis Vulgaris and the Healthy Controls

	Psoriasis Vulgaris (N=64)	Healthy Controls (N=64)	P
Gender, N (%)			1.000
Female	20 (31.3)	20 (31.3)	
Male	44 (68.7)	44 (68.7)	
Age (years), mean $\pm$ SD	38.14 $\pm$ 10.79	40.27 $\pm$ 7.52	0.199
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	25.97 $\pm$ 4.79	24.70 $\pm$ 3.73	0.105
Family history, N (%)	20 (31.3)	/	/
Onset age (years), mean $\pm$ SD	27.43 $\pm$ 10.44	/	/
Course (years), mean $\pm$ SD	10.60 $\pm$ 9.48	/	/
PASI, median(IQR)	12.90 (4.55,19.85)	/	/

**Abbreviations:** BMI, Body Mass Index; PASI, Psoriasis Area and Severity Index.



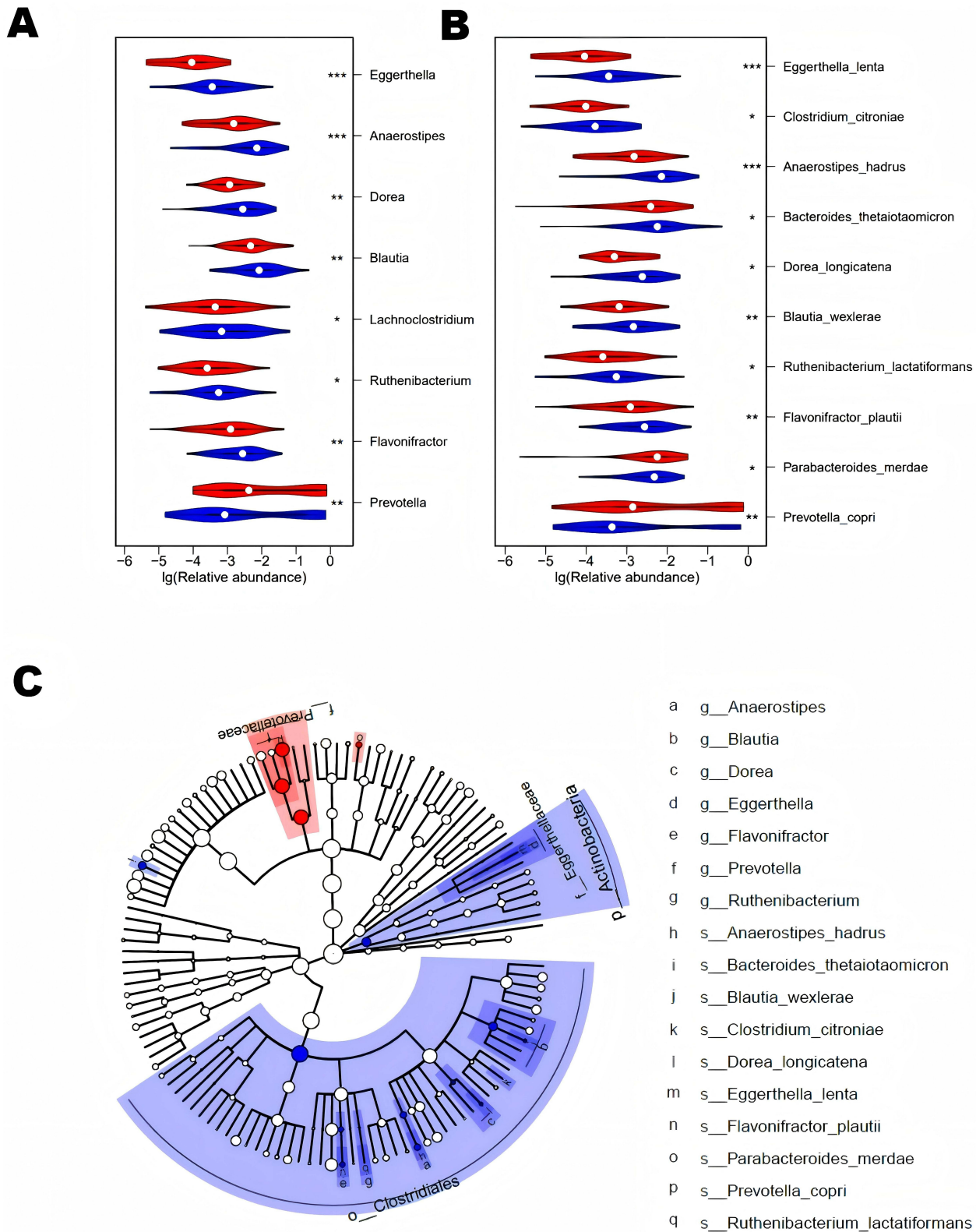
**Figure 1** Differences in gut microbiome between psoriasis and control group. **(A)**  $\beta$  diversity. **(B)**  $\alpha$  diversity. **(C)** Phylum level. **(D)** Family level. **Notes:** \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

significantly correlated with the abundance of *Anaerostipes hadrus* ( $P=0.041$ ), *Dorea Longicatena* ( $P=0.006$ ), and *Eggerthella lenta* ( $P=0.005$ ). And the abundance of *Blautia wexlerae* ( $P=0.056$ ) also showed a marginal correlation with poultry. The diet frequency of fresh vegetables also shows a trend with the abundance of some bacteria species such as *Clostridium citroniae* ( $P=0.067$ ), however, with no statistical significance (Table S3).

## Mediation Analysis

As shown in Table 2, *Anaerostipes hadrus* was observed to mediate a 22.4% effect between red meat with psoriasis ( $P<0.001$ ) and a 33.4% effect between poultry with psoriasis ( $P=0.040$ ). *Dorea longicatena* may mediate a 17.8% effect





**Figure 2** Differences in gut microbiome between psoriasis and control group. **(A)** Genus level. **(B)** Species level. **(C)** System branch.  
**Notes:** \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

**Table 2** Mediating Effects of Different Strains

	Mediators	Total Effect (95% CI)	Direct Effect (95% CI)	Mediating Effect <sup>a</sup> (95% CI)	%	P
Red meat→psoriasis	Anaerostipes hadrus	-0.069 (-0.092, -0.051)	-0.052 (-0.075, -0.023)	-0.017 (-0.038, -0.001)	22.4	<0.001
	Blautia wexlerae	-0.069 (-0.085, -0.053)	-0.062 (-0.084, -0.042)	-0.007 (-0.017, 0.001)	8.7	0.080
	Dorea longicatena	-0.069 (-0.088, -0.054)	-0.057 (-0.079, -0.039)	-0.012 (-0.021, -0.002)	17.8	0.040
	Eggerthella lenta	-0.058 (-0.083, -0.032)	-0.028 (-0.058, -0.012)	-0.030 (-0.050, -0.010)	54.3	<0.001
Poultry→psoriasis	Anaerostipes hadrus	-0.057 (-0.089, -0.010)	-0.039 (-0.068, -0.010)	-0.018 (-0.037, -0.001)	33.4	0.040
	Blautia wexlerae	-0.053 (-0.090, -0.022)	-0.044 (-0.078, -0.021)	-0.009 (-0.023, 0.002)	17.1	0.080
	Dorea longicatena	-0.060 (-0.092, 0.034)	-0.037 (-0.067, -0.003)	-0.023 (-0.039, -0.010)	36.2	<0.001
	Eggerthella lenta	-0.060 (-0.093, 0.011)	-0.014 (-0.041, 0.002)	-0.047 (-0.080, -0.001)	79.7	0.040

Notes: <sup>a</sup>Adjusted for sex, age, and BMI.

between red meat with psoriasis ( $P=0.040$ ) and a 36.2% effect between poultry with psoriasis ( $P<0.001$ ). *Eggerthella lenta* may mediate a 54.3% effect between red meat with psoriasis ( $P<0.001$ ) and a 79.7% effect between poultry and psoriasis ( $P=0.040$ ). And *Blautia wexlerae* was found to have a marginal mediating effect on the association between red meat with psoriasis ( $P=0.080$ ) and between poultry with psoriasis ( $P=0.080$ ).

## Discussion

In this study, we explored the characteristics of intestinal flora in patients with psoriasis by metagenomic sequencing. And the mediating effect model was established to explore the relationship between diet, microbiota, and psoriasis. The results showed that eight species, including *Anaerostipes Hadrus* and *Blautia Wexlerae*, may be beneficial to psoriasis. However, *Prevotella Copri* and *Eggerthellaceae* could be the pathogenic bacteria of psoriasis. At the same time, mediation analysis showed that some intestinal microbiota could serve as mediating factors between diet and psoriasis. To the best of our knowledge, this is the first study to report intestinal microbiota-specific markers for psoriasis based on metagenomic results.

The study's findings demonstrate that the abundance of *Prevotella copri* in the intestinal flora of psoriasis patients is significantly increased. Previous research has suggested that *Prevotella copri* is associated with a range of metabolic and autoimmune disorders, including rheumatoid arthritis.<sup>9,10</sup> Studies have also linked this species to an increased risk of insulin resistance and glucose intolerance.<sup>11</sup> Research on the mechanisms underlying *Prevotella copri*'s effects has revealed that it plays a role in carbohydrate catabolism and can alter glucose homeostasis by modulating bile acid metabolism and the Farnesoid X Receptor signalling pathway.<sup>12</sup> Furthermore, the impact of *Prevotella copri* on the gut microbiome appears to be strongly influenced by diet, and its abundance is positively correlated with improved glucose and insulin tolerance in individuals who consume a high-fiber diet.<sup>13</sup> The results of this study suggest that *Prevotella copri* may serve as a characteristic marker of intestinal flora in psoriasis patients, and its increased abundance may contribute to the initiation and exacerbation of psoriasis. However, the specific mechanisms by which *Prevotella copri* may drive psoriasis-related inflammation remain unclear and require further investigation.

Furthermore, the study revealed several species with a significant decrease in relative abundance in the intestinal flora of psoriasis patients. *Anaerostipes Hadrus* was found to have the most significant decrease, and this species is known for its beneficial role in maintaining intestinal mucosal immune system homeostasis. Studies on the mechanism of *Anaerostipes hadrus* have shown that the gene of this strain contains a region that encodes the complex inositol catabolic butyrate biosynthesis pathway, which is associated with a lower risk of host metabolic diseases.<sup>14</sup> Another species with a significant decrease in relative abundance was *Blautia wexlerae*, which is related to the production of short-chain fatty acids (SCFAs) and belongs to the same order of *Clostridium* as *Anaerostipes hadrus*. Previous studies have linked *Blautia wexlerae* with weight control.<sup>15</sup> Notably, of the eight species that showed a significant decrease in relative abundance, six were from *Clostridium*, which is associated with SCFAs production. These SCFA-producing species participate in maintaining the integrity of the intestinal barrier through their metabolites and have anti-inflammatory and immunomodulatory properties. They are considered to have inhibitory effects on the occurrence and development of tumors and

other chronic diseases.<sup>16,17</sup> In addition, the IL-10 cytokine family was linked to psoriasis.<sup>18–20</sup> SCFAs have been reported to enhance the expression of IL-10 by modulating B cells and M2 macrophages to mitigate skin inflammation.<sup>21</sup> Therefore, it is suggested that the decreased abundance of these SCFA-producing species and their products in the gut microbiota may play a crucial role in triggering psoriasis and its flares.

The results showed that some species may have a mediating effect on the relationship between different dietary frequencies and psoriasis, and the mediating effect was mainly mediated by SCFA-producing strains. The established studies have shown that diet may change the type of SCFAs produced by gut microbiota. For example, the concentration of SCFAs in the gut is lower under the Western dietary pattern.<sup>22</sup> On the contrary, healthy foods like white meat and dietary fibre may shift the gut microbiota toward increased production of SCFAs like butyrate.<sup>23,24</sup> A previous study to assess the effects of dietary white meat on intestinal microbiota and its metabolites in rats suggested that the white meat-based diet-mediated changes in the enrichment of beneficial bacteria and SCFAs.<sup>23</sup> Dietary fibre was also reported beneficially reshaped gut microbial ecology and improved dysbiosis, promoting the expansion of SCFA-producing bacteria of the genera and, increased faecal and systemic SCFA concentrations.<sup>24,25</sup> The increased production of SCFAs could up-regulate the expression of Adenosine Monophosphate Activated Protein Kinase (AMPK), which improves the integrity of the intestinal barrier, thereby affecting the body's metabolism and other functions.<sup>26</sup> Therefore, intestinal microbiota may be greatly influenced by various dietary factors, and participate in the occurrence and development mechanism of many diseases including psoriasis through the effects of bioactive compounds such as SCFAs and their downstream related pathways. Recently, there has been a growing body of research supports the bidirectional correlation between the gut microbiome and skin conditions. The host immune system coordinates the balance between the gut and skin through the gut-skin axis, and the interactions between the microbiome and the host immune system are important for maintaining skin homeostasis.<sup>27–30</sup> However, the key factors in the diet-microbiota-metabolite association network that contribute to the pathogenesis of psoriasis are still unknown, and further research is needed to determine the specific substances or pathways involved. By elucidating these pathways, it may be possible to develop more targeted dietary interventions for the prevention and treatment of psoriasis.

While our study provides insights into the association between gut microbiota, dietary habits, and psoriasis, it has some limitations that must be acknowledged. Firstly, the study design was cross-sectional, which does not allow for the establishment of causality. Future longitudinal studies or randomized controlled trials are necessary to verify the potential causal relationships between gut microbiota, dietary habits, and psoriasis. Secondly, the study population was restricted to a small geographical area in China, and caution should be taken when generalizing the findings to other populations with different characteristics. Thirdly, the results need to be replicated in other cohorts to ensure their robustness and generalizability. Due to the heterogeneity of the gut microbiome in different geographical locations, changes in specific bacterial species may not be replicable in other populations. Further studies are therefore required to validate our findings.

Despite these limitations, our study has several notable strengths. It is the first study to investigate the association between gut microbiota, dietary habits, and psoriasis by integrating metagenomics analysis and dietary surveys. Additionally, we carefully matched the study participants based on age, gender, and BMI, which minimized the confounding effects of these variables on gut microbiota and dietary habits. This approach enhances the internal validity of the study and strengthens the observed associations between gut microbiota, dietary habits, and psoriasis. Overall, our findings suggest that gut microbiota and dietary habits may be critical factors in the pathogenesis of psoriasis, and further studies are necessary to establish the causal relationships between these factors.

## Conclusion

This study indicated significant correlations between specific dietary habits and psoriasis, particularly with poultry consumption. Additionally, our mediation analysis highlights the role of specific microbes—*Anaerostipes hadrus*, *Dorea longicatena*, and *Eggerthella lenta*—as key mediators in the relationship between poultry consumption and psoriasis. These insights not only enhance our understanding of how diet modulates the gut microbiome in psoriasis but also encourage doctors to advise patients on making dietary modifications could lead to better management of psoriasis.



## Abbreviations

AMPK, Activated Protein Kinase; BMI, body mass index; CFAs, short-chain fatty acids; ICD, International Classification of Diseases; RNA, Ribonucleic Acid; ROC, receiver operating characteristic.

## Data Sharing Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

## Ethics Statement

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of Xiangya Hospital, Central South University (Approval No. 201709993) and complies with the Declaration of Helsinki. The patients/participants provided written informed consent to participate in this study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflict of interest.

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