

The Causal Effect Between Human Microbiota and Scabies: A Study from the Genetic Perspective

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Background: Previous studies have indicated that human flora may affect the development of scabies, however, no studies have proven a causal relationship between human flora and scabies, which would be detrimental to future in-depth studies on human flora and scabies.

Methods: Mendelian randomization (MR) was used to analyze the causal effect between human microbiota and scabies, with data on intestinal flora and skin flora from two large published studies and data on scabies from the FinnGen database. Five MR analysis methods were used to increase the reliability of the results, and sensitivity analyses were conducted to increase the robustness of the results.

Results: Our results suggest that 13 intestinal flora as well as 7 skin flora can have a causal effect on scabies.

Conclusion: Overall, our results demonstrate a causal relationship between intestinal and skin flora and scabies and are consistent with previous observational findings. This will contribute to the future development of probiotic agents for the prevention or treatment of scabies.

Keywords: gut microbiota, skin microbiota, scabies, FinnGen, Mendelian randomization

Introduction

Scabies is a globally prevalent skin condition usually thought to be caused by an infection with a mite called *Sarcoptes scabiei*, with itchy skin (worse at night) being the main clinical manifestation.¹ It is now suggested that the scabies mite may affect the skin barrier function by the following mechanism: the mite produces large quantities of saliva when digging holes in the skin, which stimulates the body to develop an immune and inflammatory response, compromising the skin integrity and possibly promoting secondary bacterial infections.^{2,3} Although scabies can be contracted through contact with contaminated items such as the clothing of a person with scabies, direct skin contact is still the primary route of mite infection.⁴ It has been reported that patients with poor hygiene, use of immunosuppressive medications (such as steroid hormone use, immunosuppression), chronic diseases (such as hypertension, and diabetes), or AIDS are more likely to suffer from scabies.⁵ Since physical contact is unavoidable in communal living areas, immune-compromised populations are more susceptible to mite attacks, and how to target susceptible populations for effective protection is a major public health challenge.⁶

With the in-depth study of human microecology in recent years, people have gradually realized the role played by microorganisms in the human body. Microorganisms are distributed in various parts of the body, such as the skin and intestines, and they interact with each other and play a very important role in maintaining the homeostasis of the internal environment of the human body.⁷⁻¹⁰ The human flora plays a crucial role in immunity regulation. It has been reported that intestinal flora can enhance the body's immunity by maintaining the integrity of the intestinal mucosa and signaling

pathways of the host, and influence the progression of diseases such as irritable bowel syndrome and inflammatory bowel disease.^{11–13} In addition, the skin flora also plays an unimportant role in maintaining the skin barrier against external pathogens.¹⁴ Several studies have been carried out to demonstrate the importance of the relationship between the human flora and skin diseases (such as psoriasis, and atopic dermatitis).^{15,16} However, there is a lack of studies on the association between scabies and gut and skin flora, and no study has demonstrated a causal effect between scabies and gut or skin flora.

Mendelian randomization (MR) is a research tool to explain the causal relationship between disease and exposure from a genetic point of view, using genetic information about exposure, such as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs), which are derived from published articles on human genetics research. According to Mendel's laws of inheritance, parental alleles segregate randomly when gametes are formed and each gamete carries one allele, a process similar to randomized grouping in a randomized controlled trial that ensures that the distribution of genetic variation in a population is random. Because genetic variants are randomly assigned before the onset of disease, confounding factors are avoided, providing strong evidence to explain the causal relationship between exposure and outcome.¹⁷ This study aimed to utilize MR to clarify the causal relationship between the skin, intestinal flora, and scabies. It provides a theoretical reference for future studies related to scabies control.

Material and Methods

Data Sources

In this study, all genetic data were obtained from the European population. Scabies data were obtained from the FinnGen database, which combines genetic data with health record data and is designed to study genetic variants associated with the disease.¹⁸ The total number of cases in the scabies cohort was 411,729, comprising a total of 1244 cases and 410,485 controls.

Data on intestinal flora were obtained from a study involving 5959 individuals.¹⁹ The data included 473 flora-related data. Data for skin flora were obtained from a study involving 597 individuals. Data for this study were obtained from the PopGen database and the Cooperative Health Research in the Region Augsburg (KORA) platform, with the PopGen cohort comprising 324 individuals and the KORA FF4 cohort comprising a total of 273 individuals, involving a total of 150 flora-related data.²⁰

IVs Selection

The main purpose of using IVs in MR analyses is to address endogeneity. That is, when exposure factors are associated with potential confounders, traditional observational research methods are unable to estimate the causal relationship between exposure factors and outcomes accurately. IVs provide a way to assess the causal relationship between exposure factors and outcomes by using genetic variants strongly associated with exposure factors as instrumental variables. In this study, SNPs were used as IVs in MR analyses. MR analyses were based on three main principles: (1) there is a strong correlation between genes and exposures (correlation assumption). (2) SNPs are not related to confounders (independence assumption). (3) SNPs affect outcomes only through exposures (exclusivity assumption).²¹ To fulfill these three core assumptions, choosing the right IVs is critical. Firstly, to fulfill the correlation assumption, we selected SNPs that were strongly correlated with intestinal and skin flora, respectively, and used these SNPs as IVs. At the beginning, we set the threshold for the P-value to 5×10^{-8} , but this would result in too few SNPs to allow further MR analysis. We therefore set the threshold for the P value to 1×10^{-5} .²² In addition, to further ensure that there was a strong correlation between IVs and exposure, we retained only those IVs with an F statistic greater than 10 to prevent MR results from being affected by weak IVs.²³

Subsequently, since genetic variants that are located too close to each other in the genome are usually more inclined to be co-inherited to offspring, this may lead to a weakening of the effect of IVs, also known as the phenomenon of Linkage Disequilibrium (LD).²⁴ Therefore, we removed SNPs in the presence of LD ($R^2 < 0.01$ and clumping distance = 10,000 kb).

MR Analysis

This study was statistically analyzed using R software (version 4.2.1), and R packages such as “TwoSampleMR” and “MendelianRandomization” were used. We performed MR analysis using skin and intestinal flora as exposures and scabies as an outcome. To increase the accuracy of MR results, we used five methods to perform MR analysis (including Inverse variance weighted (IVW), MR-Egger, Weighted median, Simple mode, and Weighted mode), of which we mainly used the IVW method because it was considered the most reliable.²⁵

Subsequently, we performed sensitivity analyses to ensure that the exclusivity assumption was valid. First, Cochran’s Q statistic was employed in this study to evaluate the presence of heterogeneity, which was considered to exist if $P < 0.05$. Subsequently, the MR-Egger intercept test, as well as the Mendelian Randomized Polytypic Residuals and Outliers (MR-PRESSO) test, were used to detect polytropy, which was considered to exist if $P < 0.05$. Subsequently, a “leave-one-out” analysis was performed to ensure that there were no SNPs that did not overly influence the overall MR effect.

Reverse MR Analysis

To clarify whether scabies have a causal effect on intestinal and skin flora, we performed reverse MR analysis, designating scabies as the exposure and intestinal and skin flora as the outcome. Due to the limitation of the number of SNPs, we similarly set the threshold of P-value to 1×10^{-5} when screening for SNPs associated with scabies, and these SNPs were similarly required to have F-statistic values greater than 10, as well as the absence of an LD effect.

Results

The Causal Effect of Intestinal Flora on Scabies

In this study, all analyzed SNPs were strongly correlated with exposure ($P < 1 \times 10^{-5}$), with F values > 10 and no LD effect.

We performed MR analyses of intestinal flora as exposure and scabies as outcome, and identified a total of 13 flora that were causally associated with scabies. IVW results suggested that family. *Barnesiellaceae* (OR (95% CI) = 0.741 (0.557–0.987), $p = 0.040$), genus. *Barnesiella* (OR (95% CI) = 0.745 (0.594–0.933), $p = 0.010$), species. *blautia* sp001304935 (OR (95% CI) = 0.611 (0.380–0.982), $p = 0.042$), family. *Fusobacteriaceae* (OR (95% CI) = 0.370 (0.189–0.722), $p = 0.004$), genus. *Lactobacillus* B (OR (95% CI) = 0.740 (0.557–0.983), $p = 0.038$), species. *Prevotella* sp002933775 (OR (95% CI) = 0.632 (0.432–0.923), $p = 0.017$), genus. *Olsenella* C (OR (95% CI) = 0.518 (0.300–0.895), $p = 0.018$), species. *Staphylococcus aureus* (OR (95% CI) = 0.537 (0.291–0.991), $p = 0.047$) was able to reduce the risk of scabies, species. *CAG-177* sp002451755 (OR (95% CI) = 1.357 (1.040–1.769), $p = 0.024$), genus. *CAG-475* (OR (95% CI) = 1.329 (1.022–1.729), $p = 0.034$), species. *Eubacterium_F* sp000434115 (OR (95% CI) = 1.250 (1.007–1.550), $p = 0.043$), species. *Negativibacillus massiliensis* (OR (95% CI) = 2.230 (1.344–3.670), $p = 0.002$), genus. *UBA1409* (OR (95% CI) = 1.562 (1.009–2.418), $p = 0.046$) increased the risk of scabies. Meanwhile, we plotted the corresponding forest plot (Figure 1) as well as the scatterplot (Figure 2). It is noteworthy that on the scatterplot, all five statistical methods showed a consistent direction, which increased the reliability of the findings.

The results of the sensitivity analysis indicated no heterogeneity or pleiotropy, and the leave-one-out method analysis suggested that there were no SNPs that had an excessive effect on the total effect (Figure S1). Specific MR analysis results as well as sensitivity results are detailed in [Supplementary Table 1](#).

The Causal Effect of Scabies on Intestinal Flora

Subsequently, we conducted a reverse MR analysis using scabies as exposure and gut flora as outcome, and the results suggested that scabies was not reverse causally associated with the 13 flora mentioned above, and that it had a causal effect on 14 gut flora. The IVW results suggested that scabies had a causal effect on species. *Alistipes* (OR (95% CI) = 0.956 (0.917–0.997), $p = 0.034$), species. *Blautia* A sp900066355 (OR (95% CI) = 0.972 (0.947–0.998), $p = 0.034$), species. *Blautia* A sp900066355 (OR (95% CI) = 0.972 (0.947–0.998), $p = 0.037$), species. *Coprobacillus cateniformis* (OR (95% CI) = 0.968 (0.938–0.998), $p = 0.037$), genus. *Coprobacillus* (OR (95% CI) = 0.963 (0.931–0.996), $p = 0.030$), species. *Eisenbergiella* sp900066775 (OR (95% CI) = 0.956 (0.925–0.989), $p = 0.008$), species. *QALR01* sp003150035 (OR (95% CI) = 0.974

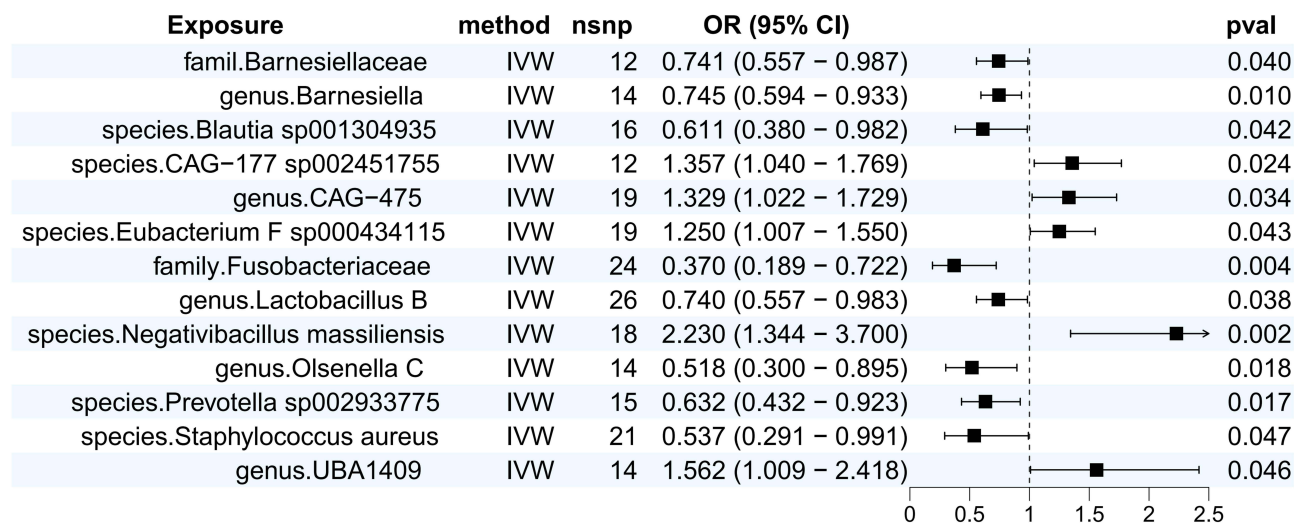


Figure 1 Forest plot of the results of MR Analysis of gut microbiota and scabies.

Abbreviations: IVW, inverse variance weighted; nsnp, number of single nucleotide polymorphism; OR, odds ratio; CI: confidence interval.

(0.949–0.999), $p = 0.038$), species.RUG420 sp900317985 (OR (95% CI) = 0.984 (0.970–0.999), $p = 0.034$), family. Thioalkalivibrionaceae (OR (95% CI) = 0.980 (0.967–0.993), $p = 0.003$) produce an CAG-273 sp003507395 (OR (95% CI) = 1.073 (1.021–0.998), $p = 1.129$), genus. Enterococcus (OR (95% CI) = 1.019 (1.004–1.035), $p = 0.013$), family. Fervidobacteriaceae (OR (95% CI) = 1.021 (1.007–1.036), $p = 0.004$), genus. Gillisia (OR (95% CI) = 1.019 (1.001–1.037), $p = 0.041$), species. Kandleria vitulina (OR (95% CI) = 1.038 (1.009–1.068), $p = 0.009$), species. UBA5394 sp002409725 (OR (95% CI) = 1.024 (1.000–1.049), $p = 0.049$) produced a promoting effect. The sensitivity analysis results suggested there was no heterogeneity or pleiotropy, and the leave-one-out results suggested the absence of SNPs that disproportionately affected the results. Specific MR analysis results as well as sensitivity results are detailed in [Supplementary Table 2](#).

The Causal Effect of Skin Flora on Scabies

We performed MR analysis for the KORA FF4 cohort as well as the PopGen cohort, respectively. In the KORA FF4 cohort, five skin flora had a causal effect on scabies. IVW results showed that genus. Paracoccus (OR (95% CI) = 1.065 (1.004–1.129), $p = 0.036$), ASV004 (OR (95% CI) = 1.063 (1.004–1.126), $p = 0.036$), class. Betaproteobacteria (OR (95% CI) = 1.088 (1.006–1.177), $p = 0.034$), family. Rhodobacteraceae (OR (95% CI) = 1.065 (1.004–1.129), $p = 0.036$) were positively associated with the risk of scabies, and ASV053 (OR (95% CI) = 0.934 (0.883–0.989), $p = 0.019$) was negatively associated with the risk of scabies.

In the PopGen cohort, 2 skin flora had a causal effect on scabies, with IVW results suggesting that ASV008 (OR (95% CI) = 1.084 (1.008–1.166), $p = 0.031$), ASV005 (OR (95% CI) = 1.067 (1.002–1.137), $p = 0.044$) was positively associated with the risk of developing scabies.

We then plotted a forest plot ([Figure 3](#)) and a scatterplot ([Figure 4](#)) of the MR results, with all five statistics having the same orientation in the scatterplot. The sensitivity analysis results suggested there was no heterogeneity or pleiotropy. Specific results of the MR analyses and sensitivity analyses are shown in [Supplementary Table 3](#). The leave-one-out results did not show any SNPs that had an excessive effect on the total ([Figure S2](#)).

The Causal Effect of Scabies on Skin Flora

Reverse MR results suggested that scabies was not reverse causally associated with the seven skin flora of the appeal. In the KORA FF4 cohort, scabies inhibited ASV026 (OR (95% CI) = 0.602 (0.408–0.889), $p = 0.011$).

In the PopGen cohort, scabies had an inhibitory effect on family. Clostridiales (OR (95% CI) = 0.663 (0.452–0.974), $p = 0.036$), genus. Streptococcus (OR (95% CI) = 0.647 (0.442–0.948), $p = 0.026$), ASV007 (OR (95% CI) = 0.550

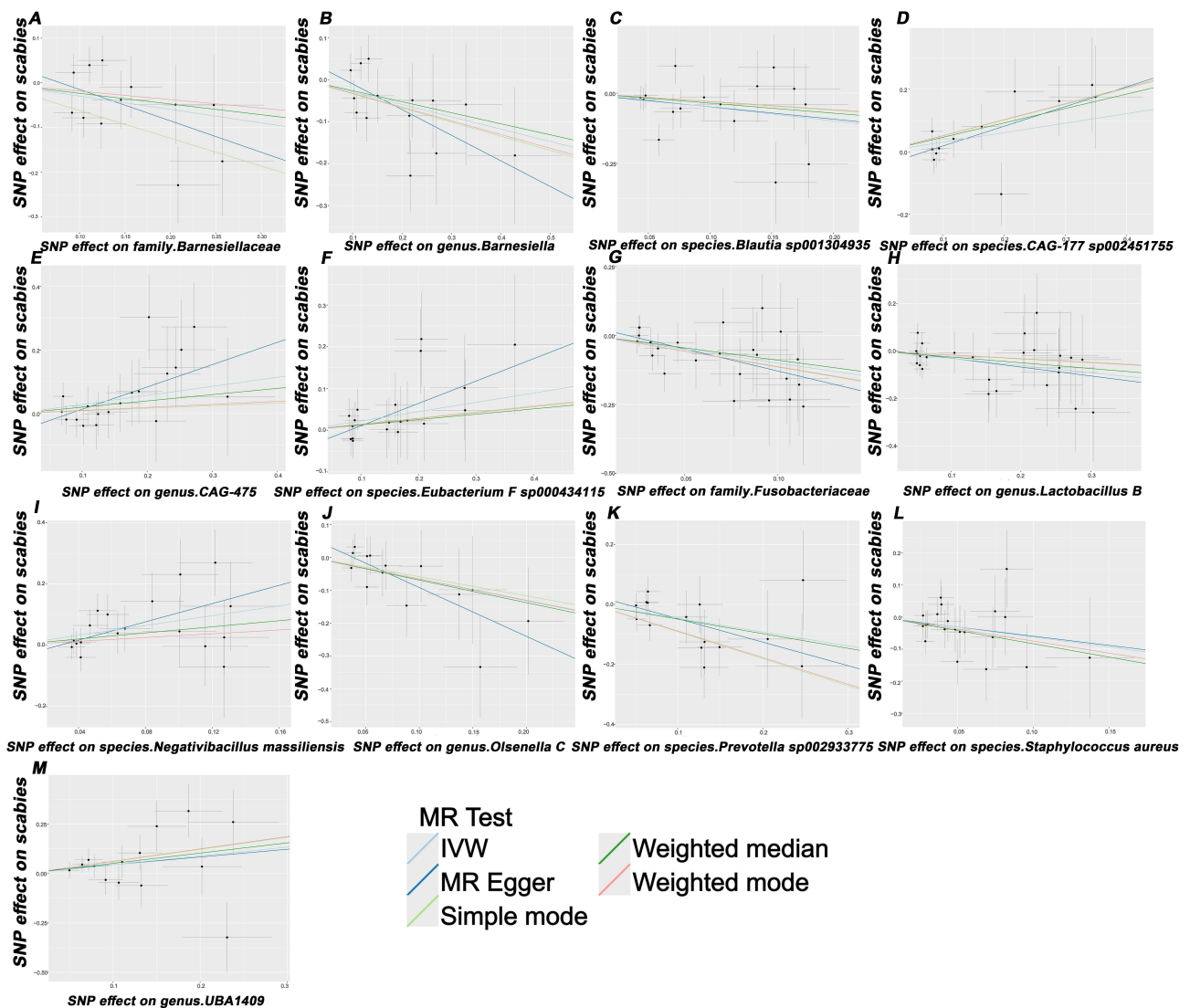


Figure 2 Scatterplot of the causal effect of (A) family Barnesiellaceae, (B) genus Barnesiella, (C) species *Blautia* sp001304935, (D) species CAG-177 sp002451755, (E) genus CAG-475, (F) species *Eubacterium* F sp000434115, (G) family Fusobacteriaceae, (H) genus *Lactobacillus* B, (I) species *Negativibacillus massiliensis*, (J) genus *Olsenella* C, (K) species *Prevotella* sp002933775, (L) species *Staphylococcus aureus*, and (M) genus *UBA1409* on scabies risk. Each black dot represents a SNP, with the effect of the SNP on exposure plotted on the x-axis and the effect on outcome plotted on the y-axis. These dots are displayed on a scatterplot, where the slope of each line indicates causality. If the slope is positive, it indicates a positive causal relationship between exposure and outcome.

Abbreviations: IVW, inverse variance weighted; SNP, single nucleotide polymorphism.

(0.315–0.959), $p = 0.035$), ASV035 (OR (95% CI) = 0.619 (0.402–0.954), $p = 0.030$), and ASV045 (OR (95% CI) = 1.712 (1.077–2.719), $p = 0.023$), ASV057 (OR (95% CI) = 1.906 (1.159–3.135), $p = 0.011$) and growth-promoting effect.

Sensitivity analysis results suggested no heterogeneity or pleiotropy. Besides, the leave-one-out results did not show SNPs that had an excessive effect on the total effect. The specific results of the MR analysis as well as the sensitivity analysis are shown in [Supplementary Table 4](#).

Discussion

In this study, we identified a total of 13 intestinal flora and 7 skin flora that exert a causal effect on scabies. Seven of the gut flora and one of the skin flora had a protective effect, and six of the gut flora and six of the skin flora increased the risk of developing scabies.

The gut microbiome refers to the microbial communities present in the human intestine, including bacteria, fungi, viruses, and archaea. Its composition is primarily influenced by environmental factors, particularly diet, while genetic

KORA FF4:

Exposure	method	nsnp	OR (95% CI)	pval
genus.Paracoccus	IVW	8	1.065 (1.004 – 1.129)	0.036
ASV004	IVW	11	1.063 (1.004 – 1.126)	0.036
ASV053	IVW	5	0.934 (0.883 – 0.989)	0.019
class.Betaproteobacteria	IVW	6	1.088 (1.006 – 1.177)	0.034
family.Rhodobacteraceae	IVW	8	1.065 (1.004 – 1.129)	0.036

PopGen:

Exposure	method	nsnp	OR (95% CI)	pval
ASV008	IVW	3	1.084 (1.008 – 1.166)	0.031
ASV004	IVW	11	1.067 (1.002 – 1.137)	0.044

Figure 3 Forest plot of the results of MR Analysis of skin microbiota and scabies.

Abbreviations: IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; nsnp, number of single nucleotide polymorphism.

factors play a relatively minor role.²⁶ Gut microbes are responsible for processing and digesting nutrients and significantly impact overall health by regulating the immune system.^{27,28} Recently, the “gut-skin axis” theory has gained attention, revealing a close relationship between gut health and skin health. Gut microbiota and their metabolites can affect skin conditions through various pathways.²⁹

The skin, the largest organ of the human body, constantly interacts with the external environment and employs various defense mechanisms to protect the host from infections.³⁰ The skin microbiome, which includes bacteria, fungi, and viruses, plays an essential role in immune regulation, inflammatory responses, protective functions, and nutrient metabolism. Under normal conditions, the skin microbiome establishes a symbiotic relationship with host tissues through both innate and adaptive immune systems. However, an imbalance in the skin microbiome can compromise the skin barrier, increasing susceptibility to external pathogens such as scabies mites.³¹

It is noteworthy that, although previous studies have established a correlation between gut and skin microbiota and conditions such as psoriasis and atopic dermatitis, this research is the initial one to report a causal connection between gut and skin microbiota and scabies. Most prior studies have primarily focused on the diagnosis and pharmacological treatment of scabies. This study offers valuable insights into the potential role of probiotics in adjunctive therapy.

In the gut microbiome, the abundance of the Barnesiellaceae family has been found to be reduced in patients with Behçet’s disease. One possible reason for this is that Barnesiellaceae may exert anti-inflammatory effects by lowering TNF- α levels.³² And individuals with scabies often exhibit elevated TNF- α levels,³³ which may explain why our results indicate a negative correlation between Barnesiellaceae and the risk of scabies.

The *Lactobacillus* genus is a common probiotic in the digestive tract, playing an indispensable role in regulating immune responses and suppressing inflammation. Additionally, *Lactobacillus* directly combats skin pathogens by producing antimicrobial metabolites that influence the metabolism of these pathogens. It has also been reported that *Lactobacillus* can be formulated into oral probiotics, demonstrating effectiveness in the prevention and treatment of skin conditions such as atopic dermatitis.^{34–36}

Our results align with previous studies. The genus *Eubacterium* has been extensively researched and is believed to be associated with the development of skin diseases such as psoriasis and atopic dermatitis.³⁷ In an animal study, researchers found that the levels of *Fusobacteriaceae* were lower than normal in dogs with dust mite-induced atopic dermatitis.³⁸ Similarly, a reduced abundance of *Fusobacteriaceae* has been observed in patients with immune disorders like Crohn’s

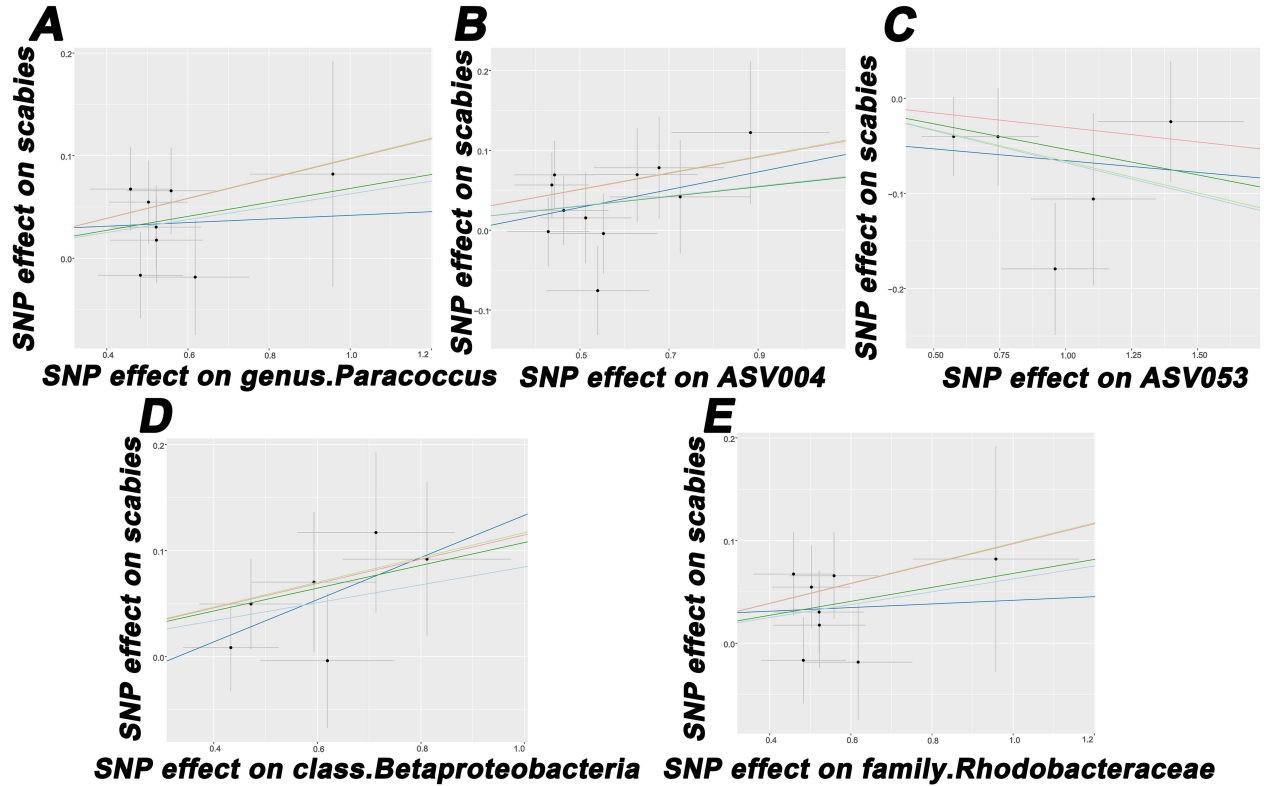
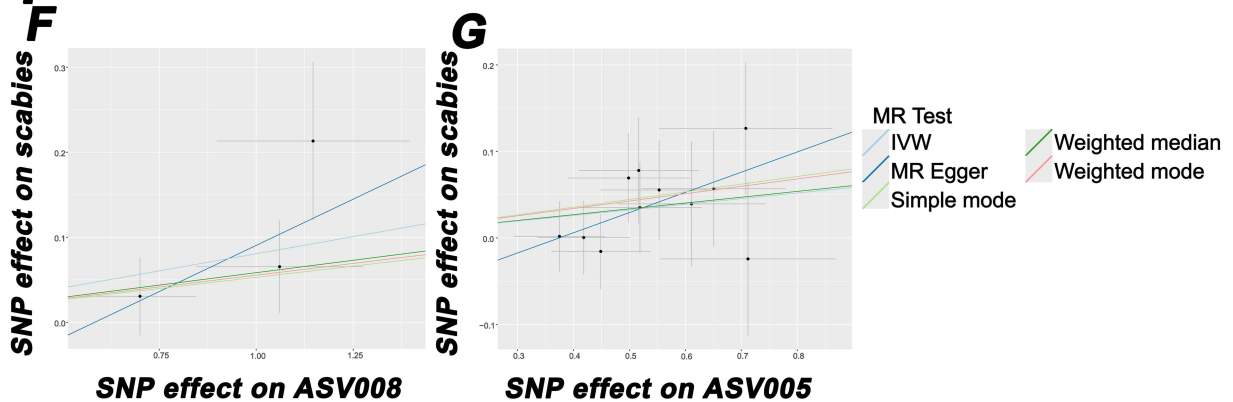
KORA FF4:**PopGen:**

Figure 4 Scatterplot of the causal effect of (A) genus *Paracoccus*, (B) ASV004, (C) ASV053, (D) class *Betaproteobacteria*, (E) family *Rhodobacteraceae*, (F) ASV008, and (G) ASV005 on scabies risk. Each black dot represents a SNP, with the effect of the SNP on exposure plotted on the x-axis and the effect on outcome plotted on the y-axis. These dots are displayed on a scatterplot, where the slope of each line indicates causality. If the slope is positive, it indicates a positive causal relationship between exposure and outcome.

Abbreviations: IVW, inverse variance weighted; SNP, single nucleotide polymorphism; IVW, inverse variance weighted; SNP, single nucleotide polymorphism.

disease.³⁹ Although the specific mechanisms remain unclear, there may be a connection to the body's immune response, warranting further investigation to clarify these mechanisms.

Our results suggest that the genus *Paracoccus* may promote the occurrence of scabies within the skin microbiome. Previous studies have established a strong association between *Paracoccus* and skin diseases. Research has consistently shown a high abundance of *Paracoccus* near skin pustules, in patients with Darier disease (a genetic skin disorder), and individuals with atopic dermatitis.^{40–42} Overall, *Paracoccus* may increase host susceptibility to pathogens and negatively impact the maintenance of the skin mucosal barrier.

However, most current studies are observational and do not establish a causal relationship between gut and skin microbiota and skin diseases such as scabies. This research offers a significant advantage by analyzing genetic factors, thereby eliminating confounding influences and demonstrating the causal effect of microbiota on scabies. Additionally, this study conducts a multi-site microbiota analysis rather than focusing solely on gut or skin microbiota, which will enhance our understanding of the relationship between the overall human microbiota and disease.

This study has some limitations. First, due to insufficient genetic data, we only analyzed the microbiomes of the skin and gut. It is important to acknowledge that microbiomes in different parts of the body interact and influence one another, highlighting the need for future analyses of additional body sites. Second, our sample population consisted solely of individuals of European descent, which may limit the applicability of our findings to other ethnic groups. Third, the number of SNPs analyzed was limited, leading us to set the P-value threshold for selected SNPs at 1×10^{-5} , which is higher than the conventional threshold of 5×10^{-8} . This may affect the strength of the association between the selected SNPs and exposure.

Conclusion

In summary, this study identifies the gut and skin microbiota that are causally linked to scabies, which will aid in the future development of probiotic formulations to support scabies treatment. Additionally, it paves the way for further research into the interactions between human microbiota and scabies, clarifying how human microbiota influences the onset and progression of the condition.

Data Sharing Statement

Data on scabies are available in the Finnish database (https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_AB1_SCABIES.gz), and data on intestinal flora and skin flora are available in the GWAS catalog (<https://www.ebi.ac.uk/gwas/>).

Ethics Statements

According to Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will it touch sensitive personal privacy or trade secrets, so the ethical review can be exempted. In addition, the database used in this study was publicly available and legally available.

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Disclosure

The authors report no conflicts of interest in this work.

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