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ORIGINAL RESEARCH

Exploring the Bidirectional Effects of Gut Microbiota and Short-Chain Fatty Acids on Urticaria Subtypes Through Mendelian Randomization and Mediation Analysis

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Background: Emerging evidence links gut microbiota and their by-products, notably short-chain fatty acids (SCFAs), to urticaria. This study employs multiple Mendelian Randomization (MR) analyses to unravel the complex interactions among gut microbiota, SCFAs, and different subtypes of urticaria, aiming to elucidate the underlying mechanisms and enhance future clinical research.

Methods: We analyzed published genome-wide association study (GWAS) summary statistics to identify associations between gut microbiota and three common subtypes of urticaria: spontaneous, dermatographic, and temperature-triggered. Initial two-sample and reverse MR analyses explored the causality in these relationships. Subsequent multivariate MR analyses investigated the role of SCFAs in modulating these interactions, with multiple sensitivity analyses to ensure robustness.

Findings: Specific taxa were differently associated with various urticaria subtypes. From microbiota to urticaria: one taxon was negatively associated with dermatographic urticaria; seven taxa were negatively associated and four positively associated with temperature-triggered urticaria; four taxa were negatively associated and six positively associated with spontaneous urticaria. Conversely, from urticaria to microbiota: five taxa were negatively associated with dermatographic urticaria; four were negatively and two positively associated with temperature-triggered urticaria; and two were negatively associated with spontaneous urticaria. These associations were observed at a nominal significance level ($P < 0.05$). After applying Bonferroni correction for multiple testing, these associations did not reach statistical significance. The observed trends, however, provide insights into potential microbiota-urticaria interactions. Multivariate MR analyses elucidated the role of SCFAs, particularly acetate, which plays a crucial role in modulating immune response. Adjusting for acetate revealed direct effects of Actinobacteria, Bifidobacteriales, and Bifidobacteriaceae on spontaneous urticaria, with corresponding mediation effects of −22%, −24.9%, and −24.9% respectively. Similarly, adjustments for Alcaligenaceae and Betaproteobacteria indicated significant negative effects of acetate on dermatographic and spontaneous urticaria, with mediation effects of −21.7% and −23.7%, respectively.

Conclusion: This study confirms the interconnected roles of gut microbiota, SCFAs, and urticaria. It highlights SCFAs' potential mediating role in influencing urticaria through microbiota, providing insights for future therapeutic strategies.

Keywords: urticaria, short-chain fatty acids, gut microbiota, gut-skin axis, Mendelian randomization

Background

Urticaria is a widespread and debilitating dermatological condition affecting approximately 20% of individuals during their lifetime.[1,2] This disorder is categorized into two principal types: spontaneous urticaria, occurring without any external trigger, and inducible urticaria, which is triggered by external stimuli such as temperature fluctuations and

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physical stress.[3] Urticaria significantly impacts patients' quality of life and imposes substantial economic burdens.[2–4] Despite advancements in understanding some underlying mechanisms of urticaria, including autoimmunity,[5] inflammation,[6] and coagulation,[7] a clear and comprehensive understanding of the exact pathophysiology remains elusive,[8] particularly given the diversity of urticaria subtypes.

Recently, the role of gut microbiota and their metabolites in urticaria has garnered increased focus.[9] Evidence from animal models[10] and observational studies[8] underscores the gut microbiota's role in urticaria progression via numerous signaling pathways, indicating a potential causal relationship between gut microbiota and urticaria. However, related reports reveal inconsistencies in the association trends between gut microbiota and urticaria.[9] These variations may stem from study design limitations, including the confounding effects of urticaria subtypes and antibiotic use among participants.

Among these metabolites, short-chain fatty acids (SCFAs) have emerged as particularly significant. SCFAs, predominantly comprising acetate, propionate, and butyrate, are produced through the fermentation of dietary fiber by gut microbiota.[11,12] These compounds are critical for maintaining intestinal homeostasis, regulating immune balance, and alleviating inflammatory responses.[10,13,14] SCFAs exert their anti-inflammatory effects through multiple mechanisms, including interactions with specific membrane receptors, inhibition of histone deacetylases, and modulation of metabolic pathways.[14] Notably, SCFAs serve as crucial communication mediators between the host and microbes, not only diminishing inflammation but also inhibiting IgE and non-IgE mediated mast cell activation,[10] thereby offering promising treatment directions for urticaria.

This underscores the necessity for further investigations into the gut microbiota-urticaria relationship. While randomized controlled trials (RCTs) are the benchmark for establishing causality, their application in microbiota research faces challenges due to the complex influence of environmental factors like diet, lifestyle, and broader environmental exposures. The dynamic nature of these factors complicates the study, potentially impacting the accuracy and reproducibility of research findings.[15] The Mendelian randomization[16] (MR) method, by utilizing genetic variations as instrumental variables (IVs), effectively overcomes many limitations of traditional observational study designs and thus provides more reliable evidence of causal inference. This study aims to reveal the causal relationship between specific gut microbiota and different urticaria subtypes through bidirectional MR analysis. Furthermore, it incorporates a two-step MR and multivariable MR (MVMR) analysis to explore the role of SCFAs in mediating the impact of gut microbiota on urticaria. This research not only offers a new perspective for understanding the complex pathogenesis of urticaria but also establishes a theoretical foundation for developing more targeted treatment approaches.

Methods

Study Overview

Genetic variants in this study were obtained from existing, publicly published GWAS studies that had received ethical approval and informed consent. Genetic variants for gut microbiota, urticaria and SCFAs were from MiBioGen consortium,[17] GWAS Catalog(https://www.ebi.ac.uk/gwas/) and IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/). Detailed information on the study population, study design and genetic data can be found in the above original studies (listed in Table 1). GWAS sample populations included in this study were mainly European and largely independent of each other. The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian randomization (STROBE-MR) guidelines[18](STROBE-MR checklist in Supplementary Material 1). Our MR study was performed in three steps. First, we used a two-sample MR design to explore whether there was a bidirectional cause-effect between gut microbiota and urticaria. Then, we evaluated the effect of gut microbiota on SCFAs and SCFAs on urticaria with univariable MR(two-step MR analysis). Last, a multivariate MR model was used to assess the direct effect. The product of the coefficients method was applied to calculate the mediating effect.[19] In addition, we explored the mediating effect of gut flora between SCFAs and urticaria, analyzing the same steps as above. The conception of the study design is shown in Figure 1.

Table 1 The Details of the Study Design and Data Sources

Trait		Sample Size	Population	Data Source (PMID)	Description
Gut microbiota	Phylum Class Order Family Genus	18340	European (16 cohorts, N = 13,266) Middle-Eastern (1 cohort, N = 481) East Asian (1 cohort, N = 811) American Hispanic/Latin (1 cohort N = 1097) African American (1 cohort, N = 114) Multi-ancestry (4 cohorts, N = 2571)	MiBioGen consortium www.mibiogen.org (PMID:33462485)	The abundance of the gut microbiome (measured by 16SrRNA) Only the taxa present in more than 10% of the samples were included
Urticaria	Inducible urticaria Spontaneous urticaria	951 3269	European	IEU OpenGWAS project https://gwas.mrcieu.ac.uk/ NA	Dermatographic urticaria Temperature-triggered Urticaria (Urticaria due to cold and heat) Other and unspecified urticaria
SCFAs	Acetate Propionate Butyrate Isovalerate	115050 7738 291	European (UK) European (Netherlands) European (NR)	GWAS Catalog https://www.ebi.ac.uk/gwas/ (PMID:35213538) GWAS Catalog https://www.ebi.ac.uk/gwas/ (PMID:35115690) GWAS Catalog https://www.ebi.ac.uk/gwas/ (PMID:33437055)	Short-chain fatty acid (acetate measurement) Short chain fatty acid (gut microbiome measurement) Short-chain fatty acid (metabolite measurement)

Data Sources

The IVs, typically single-nucleotide polymorphisms (SNPs) for gut microbiota were obtained from a meta-analysis conducted by the the MiBioGen consortium, which included twenty-four cohorts with a total of 18340 participants.[17] This study included 211 taxa, including 9 phyla, 16 classes, 20 orders, 35 families and 131 genera. To avoid sample overlap in the MR analysis, we used the dataset excluding the MiBioGen consortium sample. GWAS summary statistics for urticaria were obtained from the IEU OpenGWAS project. Our study focused on three common subtypes of urticaria: spontaneous urticaria and two types of inducible urticaria (dermatographic urticaria and temperature-triggered urticaria). The phenotypes adopted in our study included spontaneous urticaria (3269 cases and 212464 controls), dermatographic urticaria (844 cases and 212464 controls), and temperature-triggered urticaria due to cold and heat (107 cases and 212464 controls).

GWAS Catalog was searched for the data of SCFAs. Acetate-related SNPs were acquired from a GWAS summary association data from 115050 individuals with European ancestry.[20] Propionate-related SNPs came from a study of 7738 participants from the Dutch.[21] Butyrate-related and isovalerate-related SNPs were obtained from a metabolome-wide association study from 291 cases of European.[22]

Instrumental Variable (IV)

The criteria for selecting IVs were as follows: (1) the IVs should be associated with the exposure. SNPs from gut microbiota with a threshold of 1×10^{-5} for p-value were selected as potential IVs;[23] (2) the IVs can only affect the outcome through exposure. 1000 Genomes project European samples data were used as the reference panel to calculate the linkage disequilibrium (LD) between the SNPs, and $r^2<0.1$ (clumping window size=500 kb) was set to avoid LD,[24] and (3) the IVs should be independent of confounders of the exposure-outcome association. SCFAs were performed in multivariate MR analysis since they were reported to be associated with the pathogenesis of urticaria.[10]

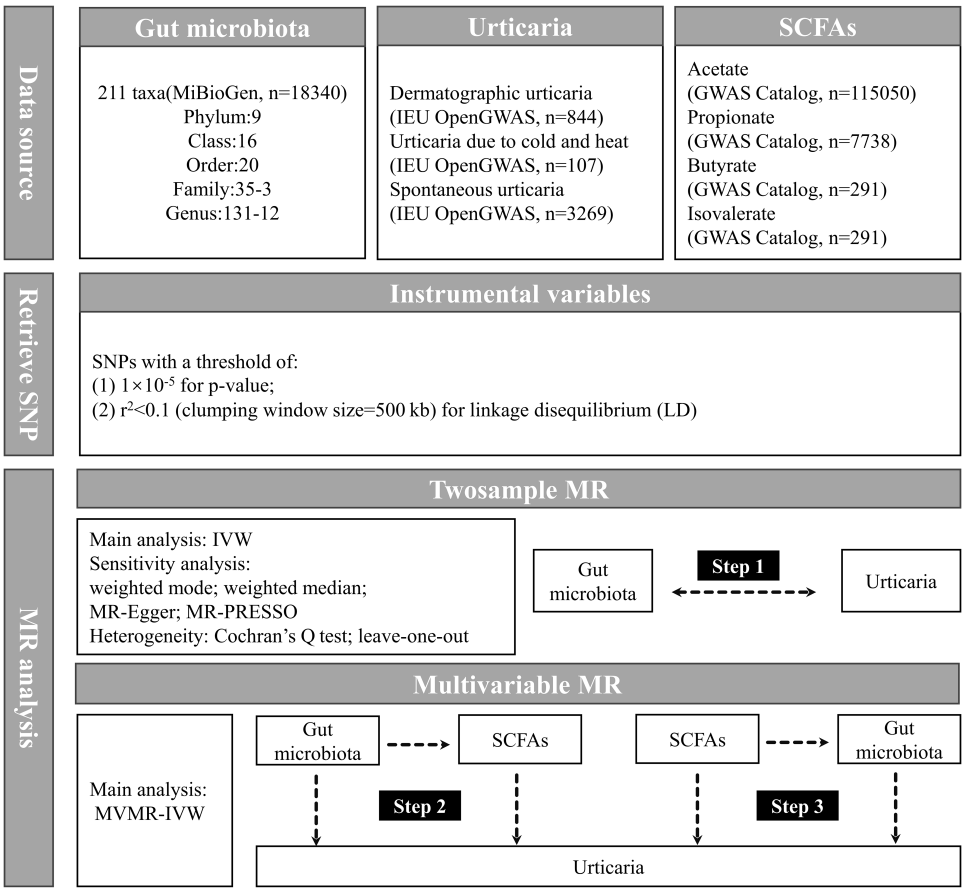

Figure 1 The schematic representation of the study design.
Abbreviations: SCFAs, short-chain fatty acids; snp, single-nucleotide polymorphisms; MR, Mendelian Randomization; IVW, Inverse variance weighted; MVMR, Multivariable Mendelian Randomization.

Statistical Analysis

The two-sample MR study was incorporated to evaluate the causality between gut microbiota taxa and urticaria phenotypes. Five methods were used to estimate causal effects: the inverse-variance weighted (IVW)[16] (MR method), weighted mode method[25] (sensitivity analysis), weighted median method[26] (sensitivity analysis), MR-Egger regression[27] (sensitivity analysis), and MR-PRESSO[28] (sensitivity analysis). The primary analysis was IVW analysis, and the association between gut microbiota and urticaria was determined by the IVW analysis when the results were inconsistent between primary and sensitivity analyses. In addition, IVW tested heterogeneity using Cochran's Q statistic. If the *P*-value of the *Q* statistic is less than 0.05, it indicates heterogeneity. To identify potential heterogeneous SNPs, the "leave-one-out" analysis was performed by omitting each instrumental SNP in turn. The weighted median method and weighted mode method combined the median and mode MR Estimates to evaluate bias, respectively. In MR-Egger regression analysis, the intercept was estimated as an indicator of average pleiotropic bias, which could test the independence assumption. MR-PRESSO was used to evaluate horizontal pleiotropy and it also corrected for horizontal pleiotropy by removing outliers. Multiple-testing significance thresholds[29] ($P < 0.05/n$) were used at each feature level (where n is the effective number of independent bacterial taxa on the corresponding taxonomic level).

We also performed a reverse MR analysis and a two-step MR analysis using a two-sample MR study. The methods used were consistent with the forward MR. Furthermore, as an attempt to uncover the direct effect that could arise from gut microbiota to urticaria, multivariable MR analyses including MVMR-IVW were performed. The parameter setting was the same as for two-sample MR.

All statistical analyses were performed using R software (version 4.3.2). R packages included TwosampleMR (version 0.5.6)[30] and MR-PRESSO (version 1.0).[28]

Results

Causal Effect of Gut Microbiota on Urticaria

Since 3 unknown families and 12 unknown genera existed in the 211 taxa of the original study, the remaining 196 taxa were included in the present study for analysis. Multiple-testing correction was taken into account by setting significance thresholds as follows: phylum p = 5.56×10^{-3} (0.05/9), class p = 3.13×10^{-3} (0.05/16), order p = 2.50×10^{-3} (0.05/20), family p = 1.56×10^{-3} (0.05/32), genus p = 4.20×10^{-4} (0.05/119). The results of the IVW test showed that 22 taxa reached statistical significance (Table S1 and Figure 2).

Inducible Urticaria

Dermatographic Urticaria

The IVW analysis showed the abundance of family.Alcaligenaceae.(*OR* = 0.55, *95%Cl* = 0.32–0.94, *P* = 0.029) were negatively associated with Dermatographic urticaria. However, the results did not reach the threshold for multiple corrections.

Temperature-Triggered Urticaria

The abundance of order.Burkholderiales. (*OR*= 0.16, *95%Cl*=0.03–0.82, *P*=0.027), genus.Desulfovibrio.(*OR*=0.30, *95%*

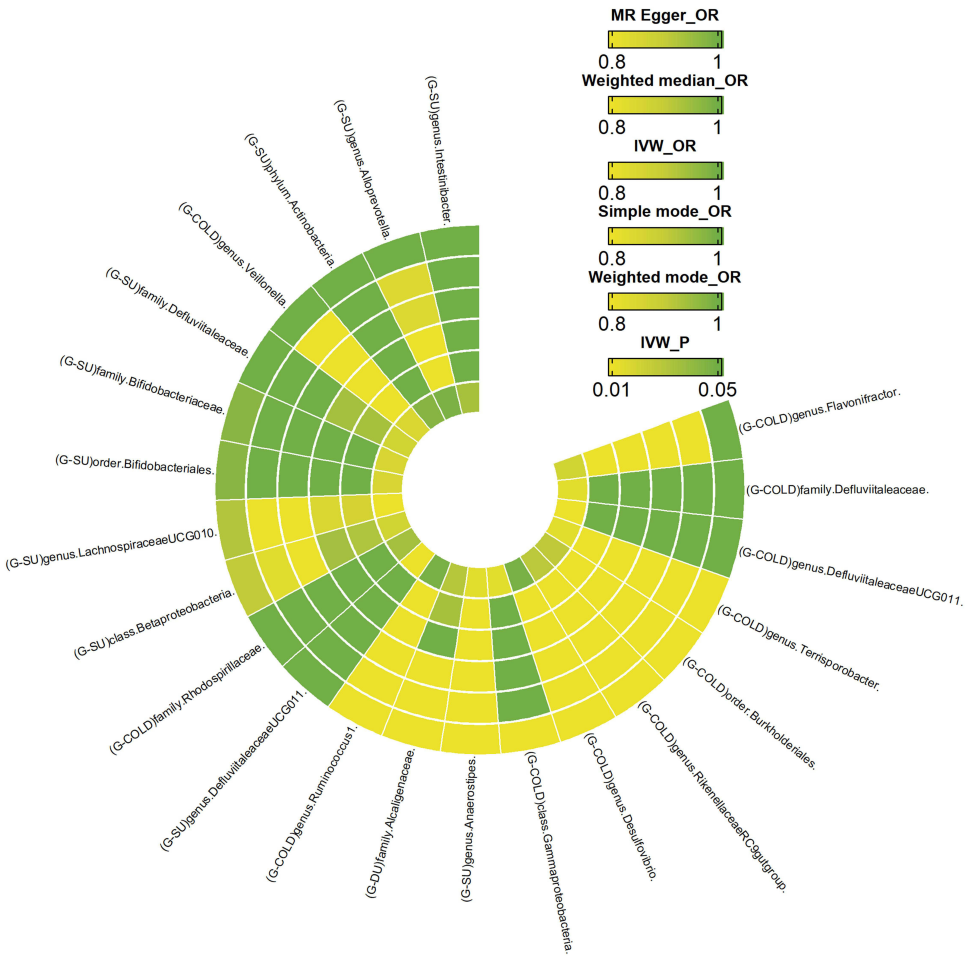

Figure 2 Circo heatmap of significant MR results (gut microbiota to urticaria phenotypes).
Abbreviations: G, gut microbiota; SU, Spontaneous urticaria; CLOD, Temperature-Triggered Urticaria (Urticaria due to cold and heat); DU, Dermatographic urticaria.

Cl=0.09–0.99, *P*=0.048), genus.Flavonifractor.(*OR*=0.12, *95%Cl*=0.02–0.72, *P*=0.02), genus.RikenellaceaeRC9 gutgroup.(*OR*=0.48, *95%Cl*=0.24–0.92, *P*=0.028), genus.Ruminococcus1.(*OR*=0.23, *95%Cl*=0.05–0.99, *P*=0.048), genus.Terrisporobacter.(*OR*=0.14, *95%Cl*=0.03–0.66, *P*=0.013) and genus.Veillonella.(*OR*=0.14, *95%Cl*=0.03–0.71, *P*=0.017) were negatively associated with it, while the abundance of class.Gammaproteobacteria.(*OR*=14.74, *95%Cl*=1.75–124.20, *P*=0.013), family.Defluviitaleaceae.(*OR*=4.00, *95%Cl*=1.34–11.99, *P*=0.013), family.Rhodospirillaceae.(*OR*=2.72, *95% Cl*=1.07–6.91, *P*=0.035) and genus.DefluviitaleaceaeUCG011.(*OR*=5.92, *95%Cl*=1.76–19.91, *P*=0.0041) were positive with it. These results did not retain their statistical significance after multiple testing adjustments.

Spontaneous Urticaria

When considering spontaneous urticaria, the result showed the abundance of class.Betaproteobacteria.(*OR*=0.71, *95% Cl*=0.53–0.95, *P*=0.02), genus.Alloprevotella.(*OR*=0.84, *95%Cl*=0.71–1.00, *P* =0.047), genus.Anaerostipes.(*OR*= 0.69, *95%Cl*=0.51–0.92, *P* =0.013), and genus.LachnospiraceaeUCG010.(*OR*= 0.67, *95%Cl*=0.51–0.89, *P* =0.0052) were negatively associated with it, while the abundance of phylum.Actinobacteria.(*OR*=1.24, *95%Cl*=1.01–1.54, *P*=0.044), order.Bifidobacteriales.(*OR*=1.23, *95%Cl*=1.04–1.46, *P*=0.0018), family.Bifidobacteriaceae.(*OR*=1.23, *95%Cl*=1.04–1.46, *P*=0.0018), family.Defluviitaleaceae.(*OR*=1.31, *95%Cl*=1.04–1.65, *P*=0.02), genus.DefluviitaleaceaeUCG011.(*OR*=1.45, *95%Cl*=1.15–1.84, *P*=0.0017), and genus.Intestinibacter.(*OR*= 1.25, *95%Cl*=1.02–1.54, *P*=0.034) were positive with it. After adjustment for multiple-testing, these results were not statistically significant.

Horizontal Pleiotropy and Sensitivity Analysis

The sensitivity analyses showed there was no potential horizontal pleiotropy (all *P* for Egger intercept > 0.05, Table S1; all *P* for PRESSO global test > 0.05, Table S2). Heterogeneity was not found among SNPs (all *P* for *Cochran's Q* > 0.05, Table S2; the results were robust after leave-one-out, Appendix 1).

Causal Effect of Urticaria on Gut Microbiota

Inducible Urticaria

Dermatographic Urticaria

The results of IVW analyses showed that Dermatographic urticaria had a causal contribution to a decreased abundance of phylum.Tenericutes.(*OR*=0.96, *95%Cl*=0.93–1.00, *P*=0.037), class.Alphaproteobacteria.(*OR*=0.95, *95%Cl*=0.92–0.99, *P*=0.013), class.Mollicutes. (*OR*=0.96, *95%Cl*=0.93–1.00, *P*=0.037), genus.Coprococcus1.(*OR*=0.97, *95%Cl*=0.94–1.00, *P*=0.032), and genus.Marvinbryantia(*OR*=0.96, *95%Cl*=0.93–0.99, *P*=0.018). These results were not statistically significant according to the multiple testing threshold.

Temperature-Triggered Urticaria

Temperature-triggered urticaria was causally related to a higher abundance of family.Ruminococcaceae.(*OR*=0.99, *95% Cl*=0.98–1.00, *P*=0.042) and genus.Eisenbergiella.(*OR*=0.97, *95%Cl*=0.94–1.00, *P*=0.028), but a lower abundance of class Deltaproteobacteria.(*OR*=1.02, *95%Cl*=1.00–1.03, *P*=0.017), order.Desulfovibrionales.(*OR*=1.02, *95%Cl*=1.00–1.03, *P*=0.02), family.Desulfovibrionaceae.(*OR*=1.02, *95%Cl*=1.00–1.03, *P*=0.017), and genus.Desulfovibrio.(*OR*=1.03, *95%Cl*=1.01–1.05, *P*=0.0018). Based on the multiple testing, the results did not maintain their statistical significance.

Spontaneous Urticaria

Spontaneous urticaria had a causal contribution to a decreased abundance of family. Family XI.(*OR*=0.85, *95%Cl*=0.75–0.97, *P*=0.019) and genus.Prevotella9. (*OR*=0.91, *95%Cl*=0.86–0.97, *P*=0.0051). After adjusting for multiple tests, these results were not significant.

Horizontal Pleiotropy and Sensitivity Analysis

Neither horizontal pleiotropy nor heterogeneity was detected (all *P* for Egger intercept > 0.05, Table S3; all *P* for PRESSO global test > 0.05, Table S4; and all *P* for *Cochran's Q* > 0.05, Table S4; the results were robust after leave-one-out, Appendix 2). Detailed significant results for the causal relationship from urticaria to gut microbial taxa are shown in Table S3 and Figure 3.

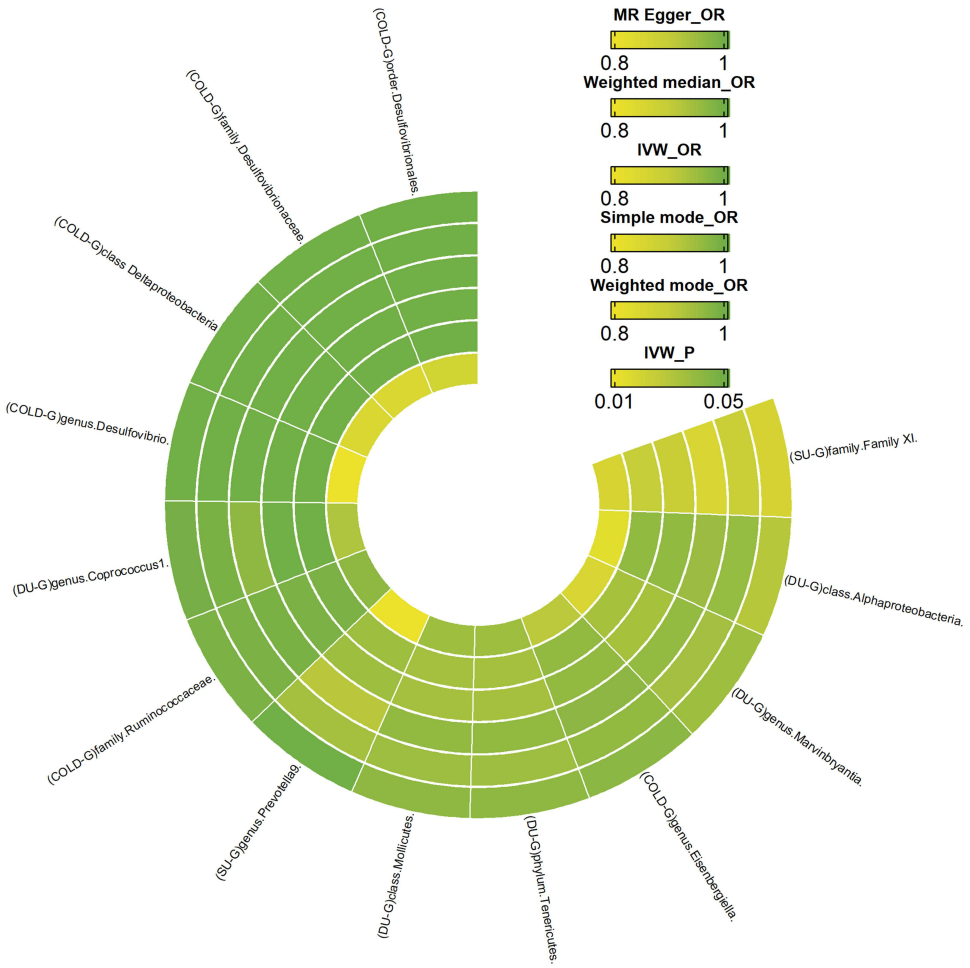

Figure 3 Circo heatmap of significant MR results (urticaria to gut microbiota phenotypes).
Abbreviations: G, gut microbiota; SU, Spontaneous urticaria; CLOD, Temperature-Triggered Urticaria (Urticaria due to cold and heat); DU, Dermatographic urticaria.

The Results of the Two-Step MR Analysis

Causal Effect of SCFAs on Urticaria

There were only acetate had a causal effect on dermatographic urticaria(*OR*=0.64, *95%CI*=0.49–0.84, *P*=0.036) and spontaneous urticaria(*OR*=0.85, *95%CI*=0.75–0.97, *P*=0.001). No causal effect of other SCFAs and urticaria. (Table S5)

Causal Effect of Gut Microbiota on SCFAs

The results of IVW analyses showed that in spontaneous urticaria the abundance of phylum.Actinobacteria. (*OR* = 1.05, *95%CI* =1.00–1.10, *P* = 0.0477), order.Bifidobacteriales. (*OR* = 1.07, *95%CI* = 1.02–1.12, *P* = 0.0069), and family. Bifidobacteriaceae. (*OR* = 1.07, *95%CI* = 1.02–1.12, *P* = 0.0069) were positively associated with acetate. (Table S6)

Causal Effect of SCFAs on Gut Microbiota

Acetate had a causal contribution to a decreased abundance of family. Alcaligenaceae. (*OR*=0.77, *95%CI*=0.66–0.91, *P*=0.0023) and class.Betaproteobacteria. (*OR*=0.78, *95%CI*=0.67–0.93, *P*=0.0037). (Table S6)

Neither horizontal pleiotropy nor heterogeneity was detected (all *P* for Egger intercept > 0.05, Tables S5 and S6; all *P* for PRESSO global test > 0.05, Tables S7 and S8; and all *P* for *Cochran's Q* > 0.05, Tables S7 and S8).

The Results of MVMR Analyses and Mediating Effect

When adjusting the acetate using MVMR-IVW, we found a direct effect between phylum. Actinobacteria. and spontaneous urticaria was 0.2617744(*P*=0.0007), between order.Bifidobacteriales. and spontaneous urticaria was 0.2256752

(*P*=0.0006), and between family.Bifidobacteriaceae. and spontaneous urticaria was 0.2256752(*P*=0.0006). The percentage of mediating effects of acetate for the process mentioned above were −22%, −24.9% and −24.9%, respectively.

When adjusting the family.Alcaligenaceae. using MVMR-IVW, we found the direct effect between acetate. and dermatographic urticaria was −0.8538835 (*P*= 0.0071), and the percentage of mediating effects was −21.7%. Besides, after adjusting the class.Betaproteobacteria. using MVMR-IVW, the direct effect between acetate. and spontaneous urticaria was −0.4353336(*P*= 0.0013) and the percentage of mediating effects was −23.7%. (Table S9) The summary of the key findings is shown in Figure 4.

Discussion

Main Findings

This study highlights the potentially critical role of gut microbes in the pathogenesis of urticaria, particularly the influence of metabolites SCFAs, an area that continues to gain attention in recent research. Utilizing large-scale genome-wide association study (GWAS) data, we applied Mendelian randomization (MR) analysis to unveil fresh insights into the association between the gut microbiota, SCFAs, and urticaria. Specifically, we identified 12 taxa that appear to play a protective role against the development of urticaria, suggesting they may act as protective factors against urticaria risk, while another 10 taxa were identified as potential risk factors. Bidirectional MR analysis further revealed a negative correlation between different urticaria subtypes and nine taxa, whereas a positive correlation with another four taxa. Although these associations did not reach statistical significance after stringent multiple testing correction, these microbial markers still offer new perspectives for further exploring the pathophysiological mechanisms and therapeutic strategies for urticaria. Additionally, this study highlights the importance of SCFAs (especially acetate) in regulating the composition of the gut microbiome and their potential role in the prevention and treatment of urticaria. This research establishes a solid foundation for future research on the interaction between gut microbiota and skin diseases, paving the way for the development of more personalized and targeted therapeutic approaches.

Comparison with Existing Evidence

In alignment with the existing literature, this study enriches the understanding of the role of the gut microbiota in the pathogenesis of urticaria. For example, Lu et al[31] found a significantly higher abundance of Actinobacteria in patients with chronic urticaria (CU) compared to healthy individuals, while Zhu et al[10] observed a dominance of Lachnospiraceae in healthy subjects. Specifically, for CU patients resistant to H1-antihistamines, Song et al[32] noted a significant decrease in the abundance of Anaerostipes. Liu et al[8] compared chronic spontaneous urticaria (CSU) patients (especially those

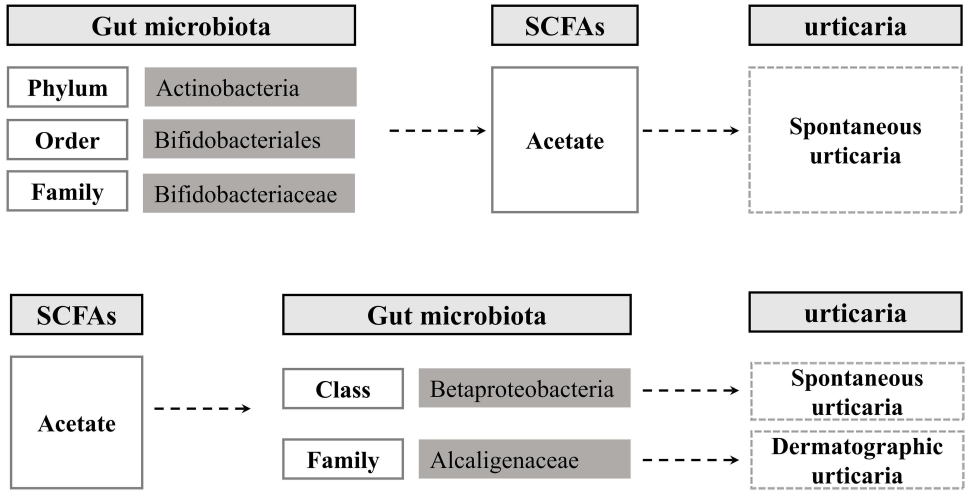

Figure 4 The schematic representation of the summary of the key findings.
Abbreviation: SCFAs, short-chain fatty acids.

with dermographism) with healthy subjects and found a significant increase in the abundance of Gammaproteobacteria in CSU patients, whereas the abundance of Alphaproteobacteria and Rikenellaceae was significantly reduced. Furthermore, Wang et al[33] in a comparative study found a lower abundance of Ruminococcaceae in CSU patients. Notably, although studies on Coprococcus1 and Marvinbryantia—both members of the Lachnospiraceae family—are scarce, Liu et al[34] found a lower expression of Lachnospiraceae in CSU patients unresponsive to antihistamines. This finding suggests a direct link between the composition of certain gut microbiota communities and the clinical outcomes of CU, highlighting the potential for targeted microbiome interventions in managing this condition.

However, there are some inconsistencies between our results and existing evidence due to the complexity of the gut microbiota. For example, Previous research indicates that healthy individuals possess a higher abundance of Bifidobacteriales compared to CU patients.[33] Another study showed that Veillonella levels are significantly elevated in CU patients relative to healthy individuals.[31] Additionally, lower levels of Deltaproteobacteria and Desulfovibrionales have been observed in CSU patients with dermographism.[8] These discrepancies may be attributed to variations in the sample size across studies, participants' racial backgrounds, dietary habits, and age disparities.[35] Given the complex physiological and pathological processes between the gut microbiota and urticaria, which may also be modulated by gut metabolites, further investigation into the impact of the gut microbiome on urticaria development is a vital area for future research.

Gut metabolites are one of the key mediators of the interplay between the gut microbiota and the host, exerting profound effects on host health. Any quantitative or qualitative changes in gut metabolites can trigger inflammatory or allergic reactions.[36] SCFAs, including acetate, propionate, and butyrate, are produced predominantly by gut microbiota via dietary fiber fermentation.[37] These SCFAs are crucial in managing inflammatory skin conditions such as urticaria, through acting on specific membrane receptors, inhibiting histone deacetylases (HDAC), and participating in various metabolic pathways.[14] Recent studies have highlighted[33] significant differences in the expression of gut metabolites between urticaria patients and healthy individuals, with a reduction in SCFA levels seemingly exacerbating urticaria reactions.

Cross-Talk Between Gut Microbiota and SCFAs in Urticaria

In this study, we investigated simultaneously the role of gut microbiota and SCFAs in the pathogenesis of urticaria. Through two rounds of mediation analysis, we identified acetate as a key intermediary factor linking the complex interactions between the gut microbiota and urticaria. In the first round of mediation analysis, the gut microbiota was considered as the exposure factor, SCFAs as the mediating factor, and urticaria as the outcome. The findings reveal that acetate serves a negative regulatory function within the pathway through which three specific gut microbiota positively influence urticaria effectively diminishing their potential to exacerbate the condition. This seemingly paradoxical result highlights the intricate regulatory dynamics present within the gut ecosystem. The gut microbiota produces effects beyond the function of its specific metabolites (eg, acetate) on its own. The gut microbiota may also participate in the development of urticaria through other pathways, such as affecting gut barrier function or modulating immunity or functioning through other metabolites such as unsaturated fatty acids.[38] This combined effect could obscure acetate's independent negative impact, resulting in an overall positive correlation between gut microbiota and urticaria. Although direct studies exploring the impact of acetate on urticaria are still scarce, existing research in psoriasis mouse models has found a negative correlation between acetate levels and IL-23/IL-27, and that supplementing acetate could alleviate symptoms of skin inflammation.[39] Moreover, acetate may directly act on skin cells to exert protective effects on the skin barrier.[40] This evidence further supports that acetate could influence urticaria through multiple mechanisms. Even if the gut microbiota may increase the risk of urticaria, its metabolic product acetate could reduce this risk by inhibiting inflammation.

In the second mediation analysis, we reversed this process to examine SCFAs as the exposure factor, the gut microbiota as the mediating factor, and urticaria as the outcome. The results revealed that acetate has a negative effect on urticaria. Interestingly, when considered as the exposure factor, acetate also had a negative effect on microbial communities viewed as protective factors against urticaria. The traditional view is that the gut microbiota alleviates inflammatory skin diseases through metabolites such as acetate,[14] but it ignores the bidirectional nature of interactions in organisms. Additionally, the effect of acetate on the microbiota may be concentration-dependent.[41] Given the varied concentrations of SCFAs and differences in host health status, these compounds could have bidirectional effects.[42] These findings highlight the complexity of interactions within the gut environment. On one hand, alterations in the gut microbiota play a crucial role in impacting the

host's health and susceptibility to diseases. On the other hand, SCFAs, especially acetate, might offer potential protective effects against urticaria by altering the gut microbiota and directly modulating the host's immune response.[14] These observations underscore the interconnected role of the gut microbial community and its metabolites in host pathophysiology, establishing a complex network of interactions that significantly affect host health. Thus, in developing interventions aimed at the gut microbiome, it's crucial to account for these multifaceted interactions to fully leverage the gut microbiota's capacity for preventing and managing inflammatory skin conditions.

Building upon the observed cross-talk between gut microbiota and SCFAs in urticaria, it is important to expand on the immune significance of SCFAs, particularly acetate. Recent research demonstrates that acetate influences T cell differentiation,[43] modulates cytokine production,[44] and can modulate the immune response of dendritic cells, macrophages and Treg cells.[45] These immunomodulatory effects of SCFAs extend beyond the gut and can impact various systemic conditions, including skin disorders. In our study, acetate's effects were particularly prominent, while other SCFAs showed no significant association. This finding underscores the specific importance of acetate in modulating the gut-skin axis in the context of urticaria. While our results highlight acetate's role, it's important to note that the broader family of SCFAs may still have potential effects that warrant further investigation. These findings highlight acetate's distinctive role in the gut-skin axis of urticaria, while suggesting the need for further investigation into other SCFAs, collectively pointing towards microbiome modulation as a potential therapeutic avenue.

Strength and Limitations

This study introduces unique contributions to the field of Mendelian randomization analyses on urticaria and gut microbiota. As summarized in Table 2, our research presents several key findings and comparisons with previous studies. Earlier research[35]

Table 2 Review Table

Purpose
This study aims to reveal the causal links between SCFAs produced by gut microbiota and different urticaria subtypes through bidirectional MR analysis. Furthermore, it incorporates two-step multivariable MR analysis to explore the role of SCFAs in the gut microbiota's influence on urticaria.
Data Sources
Genetic variants in this study were obtained from existing, publicly available GWAS studies that had received ethical approval and informed consent. Genetic variants for gut microbiota, urticaria, and SCFAs were sourced from the MiBioGen consortium, GWAS Catalog (https://www.ebi.ac.uk/gwas/), and IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/).
Summary points
This study confirms the interconnected roles of gut microbiota, SCFAs, and urticaria. It highlights SCFAs' potential mediating role in influencing urticaria through microbiota, providing insights for future therapeutic strategies. 1. There is a reciprocal causal relationship between gut microbiota and urticaria. Specifically, we identified 12 taxa that act as possible protective factors against urticaria risk, while another 10 taxa were identified as potential risk factors. We found a negative correlation between different urticaria subtypes and nine taxa, whereas a positive correlation was observed with another four taxa. 2. SCFAs (especially acetate) are key mediators linking the complex interactions between the gut microbiota and urticaria.
Limitations
1. Our findings were primarily applicable to European populations due to the limited data sources. 2. The results were no longer statistically significant after stringent Bonferroni correction, which should be interpreted with caution. 3. There may be other known or unknown factors affecting the composition of the gut microbiota and the risk of urticaria that were not accounted for in this study.
Implications
Using Mendelian randomization as a tool, the present study provides favorable evidence for the expansion of the gut-skin axis theory. We found that the gut microbiota and SCFAs do not seem to be involved in the pathogenesis of urticaria through a single pathway (gut microbiota-metabolites-urticaria) alone. The gut microbiota-SCFAs-urticaria pathway may represent an additional interaction among these three elements, which warrants further exploration in future studies.

explored the bidirectional causal relationships between the gut microbiota and urticaria (mainly allergic types) through two-sample MR analysis. Different from previous studies, this study is the first to consider the heterogeneity of different subtypes of urticaria, especially the three common clinical subtypes: spontaneous type, dermatographic (scarification type), and temperature-triggered. This study not only provides new evidence for understanding the complex connection between gut microbiota and urticaria, but also establishes a new theoretical foundation for studying the pathogenic mechanisms and treatment strategies of specific subtypes. Moreover, this study broadens the scope of research into the causal relationship between the gut microbiota and urticaria, with a particular focus on the potential role of the gut metabolite—SCFAs—in influencing urticaria development. This finding not only challenges the current understanding of the relationship between the gut microbiome and host health but also provides theoretical support for developing urticaria treatment strategies based on regulating the gut microbiome.

Although this study provides new insights into the relationship between gut microbiota and urticaria, several limitations must be acknowledged: 1. The reliance on GWAS data predominantly from European populations limits the applicability of our findings across diverse ethnic groups. 2. Although we identified several gut microbiota with nominal significance to urticaria, these did not achieve statistical significance after Bonferroni adjustment. Nonetheless, the potential roles of these gut microbiota remain noteworthy, as they may reveal key bacterial components with potential value in influencing urticaria episodes and treatment prognosis. 3. There may be other known or unknown factors affecting the composition of the gut microbiota and the risk of urticaria, adding complexity to interpreting the study results. Future research, incorporating more extensive datasets with additional participants and single nucleotide polymorphisms (SNPs) of gut microbiota, is needed to further validate these preliminary associations.

Conclusion

Through two-sample Mendelian randomization, this study has enhanced our understanding of the causal relationship between gut microbiota and three prevalent urticaria subtypes. It delves into the interactions between SCFAs, the gut microbiota, and urticaria, via two rounds of mediation analysis. This approach sheds light on the potential mechanisms of the gut-skin axis in disease manifestation. Our findings highlight the critical role of SCFAs, particularly acetate, in mediating the interactions between gut microbiota and urticaria risk. Despite limitations, these results lay an important foundation for developing new preventive and therapeutic strategies aimed at adjusting the balance of the gut microbiome to improve skin health. Future research is needed to further explore the complexity of these interactions.

Ethics Statement

This study is exempt from ethical review as per Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings (National Science and Technology Ethics Committee, China). The exemption is based on the use of non-harmful, non-sensitive data from open, legal databases.

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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 report no conflicts of interest in this work.

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