Received: 4 March 2024 | Revised: 5 July 2024 | Accepted: 9 July 2024

DOI: 10.1096/fba.2024-00037

REVIEW ARTICLE

FASEB BioAdvances WILEY

Gut microbiota and autoimmune diseases: Insights from Mendelian randomization

Fangxiang Mu | **Gusbakti Rusip** | **Florenly Florenly**

University Prima Indonesia, Medan, Sumatera Utara, Indonesia

Correspondence
Gusbakti Rusip, JI. Danau Singkarak No.3, University Prima Indonesia, Medan, Sumatera Utara 20118, Indonesia.
Email: gusrusip@gmail.com

Abstract

In recent years, the scientific community has shown interest in the role of gut microbiota in the development of autoimmune diseases (AID). Although observational studies have revealed significant associations between gut microbiota and AID like rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, these connections do not necessarily imply causality. Mendelian randomization (MR) approach has been extensively employed to investigate the causal relationship. Relevant MR study findings indicate that a reduction in beneficial microbial populations, particularly *Bifidobacterium* and *Lactobacillus*, and an increase in potential pathogenic microbes, is correlated with an elevated AID risk. Given the innovative potential of MR in unraveling the etiopathogenesis of AIDs, this article offers an overview of this methodological approach and its recent applications in AID research.

KEYWORDS

autoimmune diseases, gut microbiota, Mendelian randomization, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus

1 | INTRODUCTION

The human body hosts extensive symbiotic microbes, primarily bacteria, residing in varied niches including the gut, skin, vagina, and oral cavity.[1] These microbes present inter- and intra-individual variations in diversity and abundance across different organs.[2] Factors such as dietary habits, environmental exposures, and host genetics have been attributed to the broad microbial variance.[3] Notably, the microbiota and its metabolites may regulate the development and function of the host's immune system.[4] These microbiota also influence other physiological activities in mammals, including metabolism and behavior.[5,6] Recent scientific research suggests an important role of commensal bacteria in the pathogenesis of various diseases, particularly autoimmune diseases (AID).[7]

Mendelian randomization (MR) offers a new approach to analyze the intricate interactions between the gut microbiota and AID.[8,9] The aim of this review was to synthesize existing research and enhance our understanding of the microbiota's role in AID pathogenesis. We also aimed to evaluate the potential use of MR in this area.

2 | THE PATHOPHYSIOLOGY OF AID

AID occur when the immune system mistakenly attacks the body's own tissues, leading to tissue damage and systemic disturbances.[10] AID include a range of diseases, from rheumatoid arthritis (RA) to systemic lupus erythematosus (SLE).[11,12] Distinctly marked by the immune

system's heightened reactivity to self-antigens, AID often result in inflammation and damage in various tissues.[13] The exact etiology behind these diseases is multifactorial, often rooted in a combination of genetic susceptibilities, environmental triggers, and at times, hormonal influences.[14–16] Of note is the prevalence of AID, which stands at approximately 4.5%, with a marked gender disparity: females exhibit a 6.4% prevalence rate compared to 2.7% in males, underlining potential gender-based disparities in the immune response.[17]

2.1 | Immune cells

The pathogenesis of AID may be intricately linked with immunocyte dysfunction.[18] Within the T-cell subgroups, regulatory T-cells (Tregs) play an indispensable role in maintaining immune tolerance.[19] Compromised function of Tregs may pave the way for effector T-cells to target self-tissues.[20] In addition, T-helper 17 (Th17) cells primarily work in autoimmune pathologies via interleukin-17 (IL-17) secretion, which leads to recruitment of neutrophils, activation of innate immune cells, enhancement of B-cell functionality, and the induction of pro-inflammatory cytokines.[18] Th1 cells are typical cellular actors in cell-mediated inflammation and delayed-type hypersensitivity reactions. They are deemed pivotal in immunity against intracellular pathogens. Moreover, interferon-γ (IFN-γ), a signature cytokine of Th1 subset, has been historically related to the pathophysiology of several AID, including type 1 diabetes (T1D), multiple sclerosis (MS), and RA.[18] Th2 cells were initially characterized as anti-inflammatory, based on their capacity to counteract cell-mediated or Th1 disease models. Genain's group reported that in marmosets with experiment allergic encephalomyelitis, cytokine production was shifted from a Th1 to Th2 pattern, and titers of autoantibodies to myelin oligodendrocyte glycoprotein were increased. They hypothesized that Th2 response might exacerbate autoimmunity by amplifying the production of pathogenic autoantibodies.[21]

Additionally, while B-cells are the primary source of antibodies, anomalies in certain subgroups may related to AID pathogenesis.[22] Excessive immune responses can lead to an overabundance of self-antibodies, ultimately resulting in autoimmune disorders. For example, neutrophils may pose an exaggerated response against self-tissues particularly in conditions like SLE.[23] Neutrophil extracellular traps can expose self-antigens, activating T-cells, B-cells, and macrophages. This instigates autoimmune reactions and results in tissue or organ damage.[24,25] Overactive macrophages may stimulate protease secretion, leading to a significant rise in soluble CD163 levels in peripheral blood, ultimately causing tissue damage and accelerating disease progression.[26–28]

2.2 | Gut microbiota

The gut microbiota, consisting of diverse microbes, holds a critical position in human health. They not only facilitate nutrient absorption and metabolism but also greatly influence our immune functions. Human gut microbiota enriched of an estimated 1000 unique species with gradient concentrations vary from a mere 10^{2-3} bacteria per gram in the stomach to 10^{11-12} bacteria per gram in the large intestine.[29]

Changes in the composition and metabolic functions of the gut microbiota are correlated with numerous pathological conditions. Dysbiosis, or the imbalance in the gut microbial ecosystem, can trigger inflammatory responses and is suspected to promote autoimmune conditions like RA and inflammatory bowel disease.[30] In addition, the metabolic byproducts of these gut microbiota can regulate the function and proliferation of immune cells. For example, short-chain fatty acids can promote the proliferation of Tregs.[31] Meanwhile, beneficial microbes, primarily *Bifidobacterium* and *Lactobacillus*, also play crucial roles in promoting Tregs and maintaining immunological tolerance.[32,33] Furthermore, these beneficial microbes bolster the integrity of intestinal mucosal barrier, protecting bloodstream from harmful agents, and pathogens infiltration.[34,35] The dynamic relationship between the gut microbiota and the human immune system is fundamental for maintaining immunologic balance and preventing AID.

Recent studies have shed light on the relationship between gut microbiota and AID.[36] Dysbiosis has been consistently linked to conditions such as RA and SLE.[30,37] In particular, individuals with AID have demonstrated a marked reduction in the abundance of beneficial bacteria and an increase in certain microbial species.[38] Furthermore, therapeutic strategies like fecal microbiota transplantation have shown promise in improving dysbiosis and AID-associated symptoms.[39] Nevertheless, comprehensive and multifaceted studies are still required to understand the complex interactions between the gut microbiota and AID.

3 | MR ANALYSIS

3.1 | Basic concepts and methodological features

MR is a genetic-based instrumental analytical tool for evaluating causal relationships in epidemiological studies. This statistical method uses genetic variants, primarily single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to discern the causal effect of exposures on outcomes.[40]

3.1.1 | Basic concepts

Genetic IVs: IVs refer to genetic variants that are associated with the exposures but not with confounders.[41]

Assumptions: MR analysis has three core assumptions. (1) The genetic variant should be robustly associated with the exposure. (2) The variant should affect the outcome only through exposure. (3) The variant should be independent of any confounder of the exposure-outcome relationship.[42]

3.1.2 | Methodological characteristics

Thanks to the random assortment of alleles during gamete formation and the Mendelian law of segregation, individuals inherit genetic variants independent of confounding factors. This genetic lottery offers a sort of "natural experiment", allowing MR to sidestep many biases observed in traditional observational studies.[43] Subsequently, reverse causation is a main challenge in epidemiology research. By deploying genetic variants fixed at conception, MR can effectively avoid this issue, since these variants precede the onset of disease or outcome.[44] Moreover, although MR may be biased to pleiotropy, advanced MR techniques, such as MR-Egger regression and weighted median methods, have been developed to address pleiotropic effects and provide more valid causal estimates.[45] While MR provides a powerful platform for causal inference, it's not without limitations. For instance, the method depends on the availability of robust genetic instruments, and the results can be skewed if the aforementioned assumptions are violated. Furthermore, MR conclusions are population-specific, owing to genetic differences across populations.[46] In conclusion, MR offers a unique window into causal relationship investigation, drawing strength from the principles of genetics. As with all statistical methods, while it has several advantages, it also demands a judicious understanding of its assumptions and potential pitfalls.

4 | RESEARCH PROGRESS ON GUT MICROBIOTA AND SLE

The term "lupus" was created by physicians in the 19th century to describe cutaneous manifestations, and it took nearly a century to realize that the disease is systemic and caused by abnormal autoimmune reactions.[47] Currently, lupus or SLE is defined as a medical condition where the immune system mistakenly attacks and damages normal cells and tissues across the entire body.[48] It primarily impacts females in their reproductive years and manifests in multiple organs, encompassing the skin, joints, and kidneys.[49]

Globally, the estimated adult SLE prevalence ranges from 30 to 150 per 100,000 people, with annual incidence rates between 2.2% and 23.1% per 100,000 people.[50] SLE is characterized by abnormal immune system activation, resulting in exaggerated response of B and T cells and the loss of immune tolerance to self-antigens. SLE clinical symptoms include mild fatigue and articular pain, as well as severe life-threatening organ injury.[48]

Possible etiologies of SLE involve genetic, environmental, hormonal, and immunological factors.[47] Genome-wide association studies (GWAS) have identified over 60 SLE susceptibility risk loci.[51] Various environmental factors, including ultraviolet exposure, silica exposure, smoking, as well as viral and bacterial infections, all contribute to the development of SLE.[52–56] The treatment options currently available for SLE consist of glucocorticoids, immunosuppressive drugs, and antimalarial medications; however, their application is restricted due to the occurrence of severe adverse effects.[48,57] Recently, increased research has revealed that the gut microbiota, as an environmental factor, plays a role in the advance of SLE,[58] and adjusting the gut microbiota seems like an available therapeutic approach.[59]

4.1 | Gut microbiota changes and SLE

The gut microbiota is significantly dysregulated in subjects with SLE. In 2014, Hevia et al. first reported the limited gut microbiota diversity in lupus patients compared to healthy individuals.[60] Similarly, Azzouz et al. also found that disease activity in lupus was negatively correlated with gut microbiota biodiversity. Moreover, in SLE patients with higher disease activity, the abundance of the anaerobic genus *Ruminococcus gnavus* was five times higher than normal levels on average.[37] Additionally, a previous research indicated the changed composition of the gut microbiota in SLE patients, and seven enriched microbes experienced reduction after treatment.[58]

The *Bacteroidetes* and *Firmicutes* are the dominant bacteria groups in human body.[61] In SLE patients, however, there is an increase in *Bacteroidetes* and a decrease in *Firmicutes*, leading to a significant decline in the *Firmicutes*/*Bacteroidetes* (F/B) ratio.[62] Widhani et al. also reported that the F/B ratio was lower in lupus subjects with moderate or high disease activity compared to those with mild disease activity.[63] Moreover, studies have demonstrated a negative correlation between *Firmicutes* and the SLE disease activity index,[64] suggesting that *Firmicutes* may delay lupus progression. Therefore, a decreased F/B

ratio is an important indicator of gut microbiota in SLE patients.

Furthermore, research indicated that certain bacterial genera were enriched in SLE patients, such as *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Actinomyces*, and *Flavonifractor*, while *Dialister* and *Pseudobutyrivibrio* were significantly reduced.[60,62] In a systematic review including SLE patients, there was an abundance decline of *Ruminococcaceae*, a rise in *Enterobacteriaceae* and *Enterococcaceae*, and no significant changes in *Spirochaetaceae* and *Bacteroidaceae*.[65]

In summary, SLE patients exhibit significant changes in gut microbiota, including microbial diversity, abundance of specific microbes, and F/B ratio. These changes may be related to the development of SLE.

4.2 | The role of gut microbiota in SLE

Although observational correlation between the gut microbiota and SLE has been extensively studied, whether a causal relationship exists remains unclear.

An MR study selected SNPs related to the human gut microbiota from GWAS involving 18,473 individuals and 122,110 variant loci.[66] A total of 25 population-based cohorts from various countries participated in this extensive multi-ethnic GWAS. The primary objective was to investigate the relationship between ordinary genetic variations on autosomes and the gut microbiota. To extract the effect estimates of relevant SNPs, data from a substantial SLE GWAS comprising 7219 cases and 15,991 controls of European ancestry were utilized.[67] This study indicated negative correlations between *Bacteroides*, *Faecalibacterium*, *Ruminococcus*, and *Actinobacteria* and the risk of SLE. *Bacilli*, *Lactobacillus*, and *Eggerthella* were identified as potential risk factors for SLE, supporting a potentially beneficial or detrimental cause and effect from the gut microbiota components to SLE risk.[9]

In addition, Xu et al. carried out another study to verify the relationship between the gut microbiota and AID.[8] Data for gut microbiota were derived from GWAS meta-analysis with 340,240 individuals from 18 cohorts.[66] Exploration of microbial composition was conducted using three distinct variable regions within the 16S rRNA gene. To account for variations in sequencing depth, all datasets were standardized to include 10,000 reads per sample. A comprehensive set of 211 taxa were incorporated. Summary statistics pertaining to SLE were derived from publicly accessible GWAS that encompassed 7219 cases and 15,991 controls.[67] The results indicated that higher genetic predicted *Bifidobacterium* were related to a lower risk of SLE, while higher levels of *Ruminococcus* were positively correlated with SLE risk.[8]

In conclusion, MR analyses support a potential causality between components of the gut microbiota and SLE risk.

5 | RESEARCH PROGRESS ON THE GUT MICROBIOTA AND MS

MS is a progressive neuro-inflammatory and neurodegenerative disease, which typically begins in early adulthood.[68] It has a female tendency, with an estimated prevalence of 450.1 per 100,000 for women and 159.7 for men.[69] Immune activation plays a key role in MS pathological mechanism, involving T cells, B cells, and microglia. T cell subsets like $CD8^+$ T cells, $CD4^+$ Th1 cells, and Th17 cells are linked to MS.[70] Autoreactive T cells also produce cytokines contributing to MS, including interferon-gamma, IL-17, and granulocyte-macrophage colony-stimulating factor.[71] Besides, B-cell depletion in MS can attenuate the pro-inflammatory activity of $CD4^+$ and $CD8^+$ T cells.[72,73] Moreover, in early active MS lesions, approximately 40% of phagocytic cells are pro-inflammatory microglia, and their activation can result in axonal injury, demyelination, and blood–brain barrier disruption, among others.[74]

The etiology of MS remains unclear, with potential risk factors including genetics,[75] low vitamin D levels,[76] Epstein–Barr virus exposure,[77] smoking,[78] and the gut microbiota.[79] Several studies have linked low vitamin D levels with an increased risk of MS.[80,81] Across numerous meta-analyses, Epstein–Barr virus antibody seropositivity and infectious mononucleosis have consistently been associated with an increased risk of MS.[82] Of note, the gut microbiota is essential for the onset and maturation of the immune system.[83] It connects the immune system to certain environmental factors and helps it tolerate harmless external and self-antigens.[84]

5.1 | Gut microbiota changes and MS

Previous studies have reported changes in the gut microbiota composition of MS patients. Galluzzo et al. found that MS patients had a lower abundance of *Firmicutes* and a higher abundance of *Bacteroidetes*.[85] In MS-discordant monozygotic twins, the untreated MS twin had a higher level of *Akkermansia* than the healthy twin.[86] MS patients also had lower levels of *Prevotella*, *Faecalibacterium prausnitzii*, and *Bacteroides*, and higher levels of *Akkermansia muciniphila*.[87,88] Moreover, Cantarel et al. found less *Faecalibacterium* in fecal samples from seven MS patients compared with eight healthy controls in the USA.[89] Chen et al. reported increased *Blautia*, *Mycoplasma*, and *Dorea*, along with decreased *Prevotella* and *Adlercreutzia* in

relapsing–remitting MS patients.[90] Furthermore, a case–control study found that patients with MS had higher levels of *Methanobrevibacter* and *Akkermansia*, while *Butyricimonas* was less abundant.[87]

5.2 | Relationship between gut microbiota and MS by MR

The association between the gut microbiota and MS has been widely researched, but a causal link is still uncertain.

We have searched one MR study of gut microbiota and MS. Xu et al. used a two-sample MR to reveal a causality between the gut microbiota and AID including MS.[8] They used summary statistics of gut microbiota from a GWAS meta-analysis, including 340,240 individuals from 18 cohorts.[66] Meanwhile, summary-level data for MS were downloaded from the most recent GWAS meta-analysis by the International MS Genetics Consortium, which included 14,802 MS cases and 26,703 controls of European ancestry.[91] SNPs associated with gut bacterial taxa with $p < 5.0 \times 10^{-8}$ were selected as potential IVs. Finally, the analysis results indicated a causal association between the *Bifidobacterium* and MS, with higher *Bifidobacterium* abundance being associated with a higher MS risk.[8]

6 | RESEARCH PROGRESS ON GUT MICROBIOTA AND RA

RA is a chronic systemic AID primarily affecting the joints, with symmetric peripheral joint inflammation (such as wrist and metacarpophalangeal joints) as its main characteristic. The affected joint structures undergo progressive damage and are often accompanied by systemic symptoms.[92,93] RA affects 0.5% to 1% of the global population, with a female incidence rate 2–3 times higher than that of males.[93] In China, the prevalence is estimated to be 0.42%, with a total affected population of approximately 5 million, and a male-to-female ratio of about 1:4.[94] RA not only impairs the physical function, social participation of patients and quality of life but also imposes a significant economic burden on families and society.[95,96] The pathogenesis of RA is still unclear. Current research suggests that its development involves a complex interaction between genetic, environmental, and immune factors.[97] Genetic factors determine 60% to 70% of the risk of RA, and those with a family history of RA have a 3- to 9-fold increased risk of developing the disease.[98,99] Environmental factors like smoking, silica exposure, and infections are also involved in the development of RA by disrupting immune tolerance to post-translationally modified proteins.[100,101] Dendritic cells (DCs) subsequently present these proteins to T-cells, which then activate B-cells to undergo plasma cell differentiation and thus secrete autoantibodies.[102,103] These autoantibodies form immune complexes to activate immune cells, which further attract other inflammatory cells into the joints, resulting in local damage. Additionally, DCs promote the differentiation of Th17 cells and inhibit the differentiation of Treg cells, shifting the balance of T cells toward inflammation. Subsequently, activated T cells stimulate effector cells and their effector molecules, including macrophages, fibroblasts, osteoclasts, and chondrocytes, leading to cartilage and bone destruction.[92] Furthermore, the connection between dietary risk factors and the pathogenesis of RA is still being explored. Increasing evidence suggests that a healthy diet can prevent the development of RA.[104] Research indicates that the influence of dietary factors may be mediated by the gut microbiota, intestinal permeability, or local immune system.[105] Recent epidemiological studies also suggest a link between gastrointestinal and urinary tract infections and a reduced risk of RA, indicating that disruption of gut microbiota may play a role in this disease.[106] Unfavorable alterations in the composition of the gut microbiota also referred to as dysbiosis, can impact the autoimmune response and disease outcomes in RA.[107–109] For instance, these alterations can promote the growth of potential pathogenic microorganisms and a reduction in the beneficial bacteria.[110,111]

6.1 | Gut microbiota changes and RA

Data from some arthritis animal models suggest gut microbiota plays a critical role in the development of the disease.[112] In a preclinical model in RA mice, a significant enrichment of *Prevotellaceae*, *Lachnospiraceae*, *Ruminococcaceae*, and *Bacteroidaceae*, particularly *Prevotella copri*, has been observed.[38,113–115] In RA rat models, an increase in *Prevotella* abundance and a decrease in the relative abundance of *Lactobacillus hominis*, *Lactobacillus reuteri*, and *Lactobacillus vaginalis* have been found.[116,117]

Most bacteria in the human gut belong to the *Firmicutes* and *Bacteroidetes* phylum. *Bacteroides* and *Prevotella* genera, as dominant members of *Bacteroidetes*, play a pivotal role in maintaining the balance of the gut microbiota. *Prevotellaceae* is a major bacterial family linked to dysbiosis. The abundance of *Prevotella* is consistently increased in RA patients, both before and after clinical diagnosis.[113,118,119] It has been found that in new-onset untreated RA patients, the increase in *Prevotella* abundance is associated with a decrease in *Bacteroides* and the loss of beneficial microorganisms.[30] Apart from *Prevotella*, preliminary evidence suggests that dysbiosis

of other microorganisms is also linked to the onset of RA. Chen et al. confirmed that RA patients had a higher abundance of *Collinsella* and *Eggerthella* compared to first-degree relatives of patients with RA and healthy controls, accompanied by an overall decrease in gut diversity.[120] Muñiz Pedrogo et al. found there was an increase in the numbers of *Clostridiaceae* and *Epsilonproteobacteria* in RA patients.[121] Furthermore, Zhang et al. observed an increase in *Lactobacillus salivarius* and a decrease in *Haemophilus* species in the gut of Chinese patients with RA[108]. Meanwhile, a reduced abundance of *Faecalibacterium prausnitzii* has been demonstrated to help maintain gut barrier function, modulate the Th17/Treg balance, and exhibit significant anti-inflammatory effects.[122] In addition, other studies have shown increased abundance of *Klebsiella*, *Enterococcaceae*, *Escherichia-shigella*, *Comamonadaceae*, *Moraxellaceae*, *Akkermansia*, *Eisenbergiella*, *Streptococcus*, *Lactobacillus*, and *Flavobacterium* in RA patients, while the abundance of genera *Bacteroides fragilis*, *Fusicatenibacter*, *Megamon*, *Bifidobacterium*, *Clostridium*, *Sarcina*, and *Enterococcus* was reduced.[123–129]

Besides, an elevated abundance of *Ascomycota* and a reduced abundance of *Basidiomycota* have been observed in synovial fluid samples from RA patients at the phylum level.[130] The fecal samples from Chinese RA patients demonstrated an increased abundance of *Wallemia* and *Candida* species and a decreased abundance of *Scedosporium*, *Pholiota*, and *Trichosporon*.[131]

6.2 | Relationship between gut microbiota and RA by MR

Studies have indicated that changes in gut microbiota are associated with RA.[118,132] However, due to potential confounding factors and other limitations, it remains difficult to assess a causal association between the two through case–control studies. Therefore, the existence of a causal relationship between them remains uncertain.

Xu et al. extracted summary GWAS data for RA, including 14,361 European ancestry RA cases and 43,923 controls from 18 studies, and identified 17 independent SNPs linked to 12 genera of RA[8]. These MR studies revealed no causal relationship between these gut microbiota taxa and RA. Similarly, an MR study by Inamo included a total of 19,234 RA cases and 61,565 controls from both Asian and European populations. This study obtained 26 SNPs associated with reduced bacterial taxa from gut microbiota GWAS. The results showed that association p values from three methods, inverse variance weighting (IVW), weighted median (WM), and MR-Egger were all non-significant (all $p > 0.05$), with no evidence of heterogeneity (heterogeneity $p > 0.166$), suggesting null causal relationship between gut microbiota and RA risk.[133]

However, Lee conducted two-sample MR analyses using the same data as Inamo's MR analysis and demonstrated a significant correlation between gut microbiota and the risk of RA. A total of 32 SNPs were selected. The results showed that the MR estimates determined by IVW and MR-Egger regression analyses supported a causal relationship between the gut microbiota and RA (IVW: $\beta = -0.024$, $p = 0.0006$; MR-Egger: $\beta = -0.027$, $p = 0.005$), while the WM approach yielded no evidence of a causal relationship ($\beta = -0.005$, $p = 0.144$).[134] Of note, Inamo only extracted SNPs related to reduced bacterial taxa in the gut microbiota as IVs, which accounts for the different SNPs set in their studies. On the other hand, although Lee found a significant association through IVW and MR-Egger analyses, the β coefficient was negative. If dysbiosis had a causal effect on the occurrence of RA, the β coefficient might be expected to be positive.[135]

Overall, the results of MR analyses may support a relationship between gut microbiota and RA, but further research is needed to investigate the extent to which gut microbiota influences the development of RA. In addition, longitudinal studies are needed to demonstrate that specific microbial dysbiosis occurs prior to the development of RA, and relevant in vivo studies and microbiome-centered intervention trials are needed to further validate this view.[135,136]

7 | CONCLUSION

We have reviewed the possible involvement of gut microbiota in causing AID. The composition of gut microbiota is altered in patients with AID, which suggests it could be used as a biomarker for diagnosis, prevention, and treatment of these diseases.

MR analysis results suggest that gut microbiota, specifically microbes such as *Bifidobacterium*, *Faecalibacterium*, and *Ruminococcus*, may have a causal relationship with AID. Of note, the feasibility of MR studies depends on the availability of robust genetic variations in the diseases. We thus need more suitable GWAS datasets that reflect a relevant measure of dysbiosis in AID. By conducting more relevant MR studies, we can improve our understanding of the role of gut microbiota in AID and provide better guidance to patients. Besides, we should not be limited to changes in individual bacteria but the bacterial networks based on functionality, metabolites, and how these networks affect the diseases.

In summary, we have gained a clearer understanding of the relationship between gut microbiota and AID.

Future research can use diverse population samples, advanced molecular biology techniques, and animal models to explore gut microbiota-related interventions and therapeutics for AID.

AUTHOR CONTRIBUTIONS

Fangxiang Mu conceived and designed the research, and wrote the original draft; Gusbakti Rusip and Florenly reviewed and edited the draft. All authors were involved in drafting and revising the manuscript.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Gusbakti Rusip https://orcid.org/0000-0002-9094-7155

REFERENCES

1. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486:207-214.
2. Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. The application of ecological theory toward an understanding of the human microbiome. *Science*. 2012;336:1255-1262.
3. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505:559-563.
4. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157:121-141.
5. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19:55-71.
6. Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. *Gastroenterol Clin N Am*. 2017;46:77-89.
7. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol*. 2019;195:74-85.
8. Xu Q, Ni JJ, Han BX, et al. Causal relationship between gut microbiota and autoimmune diseases: a two-sample Mendelian randomization study. *Front Immunol*. 2021;12:746998.
9. Xiang K, Wang P, Xu Z, et al. Causal effects of gut microbiome on systemic lupus erythematosus: a two-sample Mendelian randomization study. *Front Immunol*. 2021;12:667097.
10. Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med*. 2001;345:340-350.
11. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature*. 2003;423:356-361.
12. Mu Q, Zhang H, Luo XM. SLE: another autoimmune disorder influenced by microbes and diet? *Front Immunol*. 2015;6:608.
13. Shlomchik MJ. Activating systemic autoimmunity: B's, T's, and tolls. *Curr Opin Immunol*. 2009;21:626-633.
14. Wu H, Chang C, Lu Q. The epigenetics of lupus erythematosus. *Adv Exp Med Biol*. 2020;1253:185-207.
15. Liu JL, Woo JMP, Parks CG, Costenbader KH, Jacobsen S, Bernatsky S. Systemic lupus erythematosus risk: the role of environmental factors. *Rheum Dis Clin N Am*. 2022;48:827-843.
16. Ysrraelit MC, Correale J. Impact of sex hormones on immune function and multiple sclerosis development. *Immunology*. 2019;156:9-22.
17. Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmun Rev*. 2012;11:754-765.
18. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine*. 2015;74:5-17.
19. Chou WC, Guo Z, Guo H, et al. AIM2 in regulatory T cells restrains autoimmune diseases. *Nature*. 2021;591:300-305.
20. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3$^+$ regulatory T cells in the human immune system. *Nat Rev Immunol*. 2010;10:490-500.
21. Genain CP, Abel K, Belmar N, et al. Late complications of immune deviation therapy in a nonhuman primate. *Science*. 1996;274:2054-2057.
22. Mauri C, Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol*. 2012;30:221-241.
23. Denny MF, Yalavarthi S, Zhao W, et al. A distinct subset of proinflammatory neutrophils isolated from patients with systemic lupus erythematosus induces vascular damage and synthesizes type I IFNs. *J Immunol*. 2010;184:3284-3297.
24. Lood C, Blanco LP, Purmalek MM, et al. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat Med*. 2016;22:146-153.
25. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, et al. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. *Sci Transl Med*. 2013;5:178ra140.
26. Fabriek BO, Møller HJ, Vloet RP, et al. Proteolytic shedding of the macrophage scavenger receptor CD163 in multiple sclerosis. *J Neuroimmunol*. 2007;187:179-186.
27. Matsushita N, Kashiwagi M, Wait R, et al. Elevated levels of soluble CD163 in sera and fluids from rheumatoid arthritis patients and inhibition of the shedding of CD163 by TIMP-3. *Clin Exp Immunol*. 2002;130:156-161.
28. Daly A, Walsh C, Feighery C, O'Shea U, Jackson J, Whelan A. Serum levels of soluble CD163 correlate with the inflammatory process in coeliac disease. *Aliment Pharmacol Ther*. 2006;24:553-559.
29. Fava F, Rizzetto L, Tuohy KM. Gut microbiota and health: connecting actors across the metabolic system. *Proc Nutr Soc*. 2019;78:177-188.
30. Scher JU, Sczesnak A, Longman RS, et al. Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *elife*. 2013;2:e01202.

31. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*. 2013;341:569-573.
32. Round JL, Mazmanian SK. Inducible Foxp3^{+} regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci USA*. 2010;107:12204-12209.
33. Kwon HK, Kim GC, Kim Y, et al. Amelioration of experimental autoimmune encephalomyelitis by probiotic mixture is mediated by a shift in T helper cell immune response. *Clin Immunol*. 2013;146:217-227.
34. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nat Rev Immunol*. 2014;14:141-153.
35. Bron PA, Kleerebezem M, Brummer RJ, et al. Can probiotics modulate human disease by impacting intestinal barrier function? *Br J Nutr*. 2017;117:93-107.
36. Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes*. 2012;3:4-14.
37. Azzouz D, Omarbekova A, Heguy A, et al. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. *Ann Rheum Dis*. 2019;78:947-956.
38. Liu X, Zeng B, Zhang J, et al. Role of the gut microbiome in modulating arthritis progression in mice. *Sci Rep*. 2016;6:30594.
39. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet*. 2017;389:1218-1228.
40. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol*. 2004;33:30-42.
41. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27:1133-1163.
42. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
43. Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. *eLife*. 2018;7:e34408.
44. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. *Am J Epidemiol*. 2013;178:1177-1184.
45. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Eepidemiol*. 2015;44:512-525.
46. Palmer TM, Sterne JA, Harbord RM, et al. Instrumental variable estimation of causal risk ratios and causal odds ratios in Mendelian randomization analyses. *Am J Epidemiol*. 2011;173:1392-1403.
47. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011;365:2110-2121.
48. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med*. 2020;172:ITC81-ITC96.
49. Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. *Ann Rheum Dis*. 2023;82:351-356.
50. Durcan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet*. 2019;393:2332-2343.
51. Teruel M, Alarcón-Riquelme ME. The genetic basis of systemic lupus erythematosus: what are the risk factors and what have we learned. *J Autoimmun*. 2016;74:161-175.
52. Wolf SJ, Estadt SN, Gudjonsson JE, Kahlenberg JM. Human and murine evidence for mechanisms driving autoimmune photosensitivity. *Front Immunol*. 2018;9:2430.
53. Gonzalez-Quintial R, Mayeux JM, Kono DH, Theofilopoulos AN, Pollard KM, Baccala R. Silica exposure and chronic virus infection synergistically promote lupus-like systemic autoimmunity in mice with low genetic predisposition. *Clin Immunol*. 2019;205:75-82.
54. Speyer CB, Costenbader KH. Cigarette smoking and the pathogenesis of systemic lupus erythematosus. *Expert Rev Clin Immunol*. 2018;14:481-487.
55. Kim JW, Kim HA, Suh CH, Jung JY. Sex hormones affect the pathogenesis and clinical characteristics of systemic lupus erythematosus. *Front Med*. 2022;9:906475.
56. Illescas-Montes R, Corona-Castro CC, Melguizo-Rodríguez L, Ruiz C, Costela-Ruiz VJ. Infectious processes and systemic lupus erythematosus. *Immunology*. 2019;158:153-160.
57. Fava A, Petri M. Systemic lupus erythematosus: diagnosis and clinical management. *J Autoimmun*. 2019;96:1-13.
58. Chen BD, Jia XM, Xu JY, et al. An autoimmunogenic and proinflammatory profile defined by the gut microbiota of patients with untreated systemic lupus erythematosus. *Arthritis Rheumatol*. 2021;73:232-243.
59. Deng Y, Wang L, Huang J, Ding H, Wong MCS. Associations between potential causal factors and colorectal cancer risk: a systematic review and meta-analysis of Mendelian randomization studies. *J Dig Dis*. 2022;23:435-445.
60. Hevia A, Milani C, López P, et al. Intestinal dysbiosis associated with systemic lupus erythematosus. *MBio*. 2014;5:e01548-14.
61. Qin J, Li R, Raes J, Arumugam M, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464:59-65.
62. He Z, Shao T, Li H, Xie Z, Wen C. Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus. *Gut Pathog*. 2016;8:64.
63. Widhani A, Djauzi S, Suyatna FD, Dewi BE. Changes in gut microbiota and systemic inflammation after synbiotic supplementation in patients with systemic lupus erythematosus: a randomized, double-blind, placebo-controlled trial. *Cells*. 2022;11:3419.
64. He J, Chan T, Hong X, et al. Microbiome and metabolome analyses reveal the disruption of lipid metabolism in systemic lupus erythematosus. *Front Immunol*. 2020;11:1703.
65. Xiang S, Qu Y, Qian S, et al. Association between systemic lupus erythematosus and disruption of gut microbiota: a meta-analysis. *Lupus Sci Med*. 2022;9:e000599.
66. Kurilshikov A, Medina-Gomez C, Bacigalupe R, et al. Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nat Genet*. 2021;53:156-165.
67. Bentham J, Morris DL, Graham DSC, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet*. 2015;47:1457-1464.
68. Ward M, Goldman MD. Epidemiology and pathophysiology of multiple sclerosis. *Continuum*. 2022;28:988-1005.
69. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: a population-based estimate using health claims data. *Neurology*. 2019;92:e1029-e1040.

70. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015;15:545-558.
71. Wagner CA, Roqué PJ, Goverman JM. Pathogenic T cell cytokines in multiple sclerosis. *J Exp Med*. 2020;217:e20190460.
72. Comi G, Bar-Or A, Lassmann H, et al. Role of B cells in multiple sclerosis and related disorders. *Ann Neurol*. 2021;89:13-23.
73. Bar-Or A, Fawaz L, Fan B, et al. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Ann Neurol*. 2010;67:452-461.
74. Zrzavy T, Hametner S, Wimmer I, Butovsky O, Weiner HL, Lassmann H. Loss of 'homeostatic' microglia and patterns of their activation in active multiple sclerosis. *Brain*. 2017;140:1900-1913.
75. Goris A, Vandebergh M, McCauley JL, Saarela J, Cotsapas C. Genetics of multiple sclerosis: lessons from polygenicity. *Lancet Neurol*. 2022;21:830-842.
76. Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: an update. *Mult Scler Relat Disord*. 2017;14:35-45.
77. Jakimovski D, Weinstock-Guttman B, Ramanathan M, Dwyer MG, Zivadinov R. Infections, vaccines and autoimmunity: a multiple sclerosis perspective. *Vaccine*. 2020;8:50.
78. Arneth B. Multiple sclerosis and smoking. *Am J Med*. 2020;133:783-788.
79. Tremlett H, Waubant E. Gut microbiome and pediatric multiple sclerosis. *Mult Scler*. 2018;24:64-68.
80. Yeh WZ, Gresle M, Jokubaitis V, Stankovich J, van der Walt A, Butzkueven H. Immunoregulatory effects and therapeutic potential of vitamin D in multiple sclerosis. *Br J Pharmacol*. 2020;177:4113.
81. Miclea A, Bagnoud M, Chan A, Hoepner R. A brief review of the effects of vitamin D on multiple sclerosis. *Front Immunol*. 2020;11:781.
82. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol*. 2015;14:263-273.
83. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe*. 2015;17:852.
84. Shaheen WA, Quraishi MN, Iqbal TH. Gut microbiome and autoimmune disorders. *Clin Exp Immunol*. 2022;209:161-174.
85. Galluzzo P, Capri FC, Vecchioni L, et al. Comparison of the intestinal microbiome of Italian patients with multiple sclerosis and their household relatives. *Life*. 2021;11:620.
86. Berer K, Gerdes LA, Cekanaviciute E, et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. *Proc Natl Acad Sci USA*. 2017;114:10719-10724.
87. Jangi S, Gandhi R, Cox LM, et al. Alterations of the human gut microbiome in multiple sclerosis. *Nat Commun*. 2016;7:12015.
88. Mirza A, Forbes JD, Zhu F, et al. The multiple sclerosis gut microbiota: a systematic review. *Mult Scler Relat Disord*. 2020;37:101427.
89. Cantarel BL, Waubant E, Chehoud C, et al. Gut microbiota in multiple sclerosis: possible influence of immunomodulators. *J Investig Med*. 2015;63:729-734.
90. Chen J, Chia N, Kalari KR, et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. *Sci Rep*. 2016;6:28484.
91. International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. 2019;365:eaav7188.
92. Dagar S, Singh J, Saini A, et al. Gut bacteriome, mycobiome and virome alterations in rheumatoid arthritis. *Front Endocrinol*. 2022;13:1044673.
93. van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2018;32:174-187.
94. Chinese Rheumatology Association. 2018 Chinese guideline for the diagnosis and treatment of rheumatoid arthritis [in Chinese]. *Chin J Intern Med*. 2018;57:242-251.
95. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023-2038.
96. Sokka T, Kautiainen H, Pincus T, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Res Ther*. 2010;12:R42.
97. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. *J Autoimmun*. 2020;110:102400.
98. Rodríguez-Elías AK, Maldonado-Murillo K, López-Mendoza LF, Ramírez-Bello J. Genetics and genomics in rheumatoid arthritis (RA): an update. *Gac Med Mex*. 2016;152:218-227.
99. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. *Arthritis Rheum*. 2009;60:661-668.
100. Chang K, Yang SM, Kim SH, Han KH, Park SJ, Shin JI. Smoking and rheumatoid arthritis. *Int J Mol Sci*. 2014;15:22279-22295.
101. Mehri F, Jenabi E, Bashirian S, Shahna FG, Khazaei S. The association between occupational exposure to silica and risk of developing rheumatoid arthritis: a meta-analysis. *Saf Health Work*. 2020;11:136-142.
102. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365:2205-2219.
103. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014;506:376-381.
104. Hu Y, Sparks JA, Malspeis S, et al. Long-term dietary quality and risk of developing rheumatoid arthritis in women. *Ann Rheum Dis*. 2017;76:1357-1364.
105. Finckh A, Gilbert B, Hodkinson B, et al. Global epidemiology of rheumatoid arthritis. *Nat Rev Rheumatol*. 2022;18:591-602.
106. Sandberg ME, Bengtsson C, Klareskog L, Alfredsson L, Saevarsdottir S. Recent infections are associated with decreased risk of rheumatoid arthritis: a population-based case-control study. *Ann Rheum Dis*. 2015;74:904-907.
107. Horta-Baas G, Romero-Figueroa MDS, Montiel-Jarquín AJ, Pizano-Zárate ML, García-Mena J, Ramírez-Durán N. Intestinal dysbiosis and rheumatoid arthritis: a link between gut microbiota and the pathogenesis of rheumatoid arthritis. *J Immunol Res*. 2017;2017:4835189.
108. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med*. 2015;21:895-905.
109. Kang Y, Cai Y, Zhang X, Kong X, Su J. Altered gut microbiota in RA: implications for treatment. *Z Rheumatol*. 2017;76:451-457.
110. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*. 2009;9:313-323.

111. Hill DA, Artis D. Intestinal bacteria and the regulation of immune cell homeostasis. *Annu Rev Immunol*. 2010;28:623-667.
112. Honda K, Littman DR. The microbiome in infectious disease and inflammation. *Annu Rev Immunol*. 2012;30:759-795.
113. Maeda Y, Kurakawa T, Umemoto E, et al. Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine. *Arthritis Rheumatol*. 2016;68:2646-2661.
114. Rogier R, Evans-Marin H, Manasson J, et al. Alteration of the intestinal microbiome characterizes preclinical inflammatory arthritis in mice and its modulation attenuates established arthritis. *Sci Rep*. 2017;7:15613.
115. Nii T, Maeda Y, Motooka D, et al. Genomic repertoires linked with pathogenic potency of arthritogenic *Prevotella copri* isolated from the gut of patients with rheumatoid arthritis. *Ann Rheum Dis*. 2023;82:621-629.
116. Zhang Y, Liu Y, Peng F, et al. Cedrol from ginger alleviates rheumatoid arthritis through dynamic regulation of intestinal microenvironment. *Food Funct*. 2022;13:11825-11839.
117. Pan H, Guo R, Ju Y, et al. A single bacterium restores the microbiome dysbiosis to protect bones from destruction in a rat model of rheumatoid arthritis. *Microbiome*. 2019;7:107.
118. Alpizar-Rodriguez D, Lesker TR, Gronow A, et al. Prevotella copri in individuals at risk for rheumatoid arthritis. *Ann Rheum Dis*. 2019;78:590-593.
119. Kishikawa T, Maeda Y, Nii T, et al. Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population. *Ann Rheum Dis*. 2020;79:103-111.
120. Chen J, Wright K, Davis JM, et al. An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. *Genome Med*. 2016;8:43.
121. Muñiz Pedrogo DA, Chen J, Hillmann B, et al. An increased abundance of Clostridiaceae characterizes arthritis in inflammatory bowel disease and rheumatoid arthritis: a cross-sectional study. *Inflamm Bowel Dis*. 2019;25:902-913.
122. Zhou L, Zhang M, Wang Y, et al. Faecalibacterium prausnitzii produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. *Inflamm Bowel Dis*. 2018;24:1926-1940.
123. Vaahtovuo J, Munukka E, Korkeamäki M, Luukkainen R, Toivanen P. Fecal microbiota in early rheumatoid arthritis. *J Rheumatol*. 2008;35:1500-1505.
124. Lee JY, Mannaa M, Kim Y, Kim J, Kim GT, Seo YS. Comparative analysis of fecal microbiota composition between rheumatoid arthritis and osteoarthritis patients. *Genes*. 2019;10:748.
125. Sun Y, Chen Q, Lin P, et al. Characteristics of gut microbiota in patients with rheumatoid arthritis in Shanghai, China. *Front Cell Infect Microbiol*. 2019;9:369.
126. Rodrigues GSP, Cayres LCF, Gonçalves FP, et al. Detection of increased relative expression units of *Bacteroides* and *Prevotella*, and decreased *Clostridium leptum* in stool samples from Brazilian rheumatoid arthritis patients: a pilot study. *Microorganisms*. 2019;7:413.
127. Chen Y, Ma C, Liu L, et al. Analysis of gut microbiota and metabolites in patients with rheumatoid arthritis and identification of potential biomarkers. *Aging*. 2021;13:23689-23701.
128. Yu D, Du J, Pu X, et al. The gut microbiome and metabolites are altered and interrelated in patients with rheumatoid arthritis. *Front Cell Infect Microbiol*. 2021;11:763507.
129. Mena-Vázquez N, Ruiz-Limón P, Moreno-Indias I, Manrique-Arija S, Tinahones FJ, Fernández-Nebro A. Expansion of rare and harmful lineages is associated with established rheumatoid arthritis. *J Clin Med*. 2020;9:1044.
130. Hammad DBM, Liyanapathirana V, Tonge DP. Molecular characterisation of the synovial fluid microbiome in rheumatoid arthritis patients and healthy control subjects. *PLoS One*. 2019;14:e0225110.
131. Sun X, Wang Y, Li X, et al. Alterations of gut fungal microbiota in patients with rheumatoid arthritis. *PeerJ*. 2022;10:e13037.
132. Malmström V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. *Nat Rev Immunol*. 2017;17:60-75.
133. Inamo J. Non-causal association of gut microbiome on the risk of rheumatoid arthritis: a Mendelian randomisation study. *Ann Rheum Dis*. 2021;80:e103.
134. Lee YH. Causal association of gut microbiome on the risk of rheumatoid arthritis: a Mendelian randomisation study. *Ann Rheum Dis*. 2022;81:e3.
135. Inamo J. Response to: 'Causal association of gut microbiome on the risk of rheumatoid arthritis: a Mendelian randomisation study' by Lee. *Ann Rheum Dis*. 2022;81:e4.
136. Alpizar Rodriguez D, Lesker TR, Gilbert B, Strowig T, Finckh A. Response to: 'Non-causal association of gut microbiome on the risk of rheumatoid arthritis: a Mendelian randomisation study' by Inamo. *Ann Rheum Dis*. 2021;80:e104.

How to cite this article: Mu F, Rusip G, Florenly F. Gut microbiota and autoimmune diseases: Insights from Mendelian randomization. *FASEB BioAdvances*. 2024;6:467-476. doi:10.1096/fba.2024-00037