

Association Between Gut and Nasal Microbiota and Allergic Rhinitis: A Systematic Review

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Abstract: Allergic rhinitis is a chronic non-infectious inflammation of the nasal mucosa mediated by specific IgE. Recently, the human microbiome has drawn broad interest as a potential new target for treating this condition. This paper succinctly summarizes the main findings of 17 eligible studies published by February 2024, involving 1044 allergic rhinitis patients and 954 healthy controls from 5 countries. These studies examine differences in the human microbiome across important mucosal interfaces, including the nasal and intestinal areas, between patients and controls. Overall, findings suggest variations in the gut microbiota between allergic rhinitis patients and healthy individuals, although the specific bacterial taxa that significantly changed were not always consistent across studies. Due to the limited scope of existing research and patient coverage, the relationship between the nasal microbiome and allergic rhinitis remains inconclusive. The article discusses the potential immune-regulating role of the gut microbiome in allergic rhinitis. Further well-designed clinical trials with large-scale recruitment of allergic rhinitis patients are encouraged.

Keywords: allergic rhinitis, microbiota dysbiosis, nasal microbiome, short-chain fatty acids, immunomodulation

Introduction

Allergic rhinitis (AR), a chronic and non-infectious IgE-mediated inflammation of the nasal mucosa, manifests through symptoms such as sneezing, congestion, pruritus, and rhinorrhea.^{1,2} The global incidence of AR has progressively escalated alongside industrialization and urban development. Afflicting 10–20% of the global population, AR has transcended into a pervasive health dilemma.³ Consequences of this condition are multifaceted, ranging from a decline in labor productivity to a deterioration in the quality of life for those affected. Notably, AR impairs sleep and cognitive functions, giving rise to increased levels of irritability and fatigue. It has been documented that AR is intricately linked with diminished academic and professional output, a concern that is accentuated during periods of high pollen exposure.¹ The socioeconomic burden of AR is substantial, engendering annual economic losses estimated between 30 to 50 billion euros within European Union nations alone, thereby emphasizing the significant impact of this condition on both individual well-being and economic stability.³

Tari Haahtela's biodiversity hypothesis posits that a rich human microbiota fosters an equilibrium in immunity, shielding individuals from allergies and other inflammatory conditions.⁴ In recent scientific discourse, researchers have identified a critical role for imbalances in microbiota populations across multiple key mucosal interfaces, such as the intestinal and nasal areas, in the onset and progression of allergic diseases. Such dysbiosis may detrimentally influence immune system functionality, precipitating conditions including asthma and allergic rhinitis.^{5–7} Alterations in the gut microbiota are closely intertwined with human physiological and pathological processes. The successful colonization and maintenance of a diverse gut microbiome serve as a formidable barrier against pathogenic bacterial invasion, curtailing nutritional competition between potentially harmful and commensal bacteria.⁸ Perturbations to the diversity or balance of gut microbiota can lead to gastrointestinal dysbiosis, precipitating alterations in microbial metabolism and immune responses, with consequential impacts on host health.⁹ Additionally, the gut microbiota is instrumental in stimulating the development of both innate and adaptive immunity through

its involvement in the metabolism of short-chain fatty acids (SCFAs), tryptophan (Trp), amino acids, vitamins, and bile acids, making it a potential target for modulating immune responses.^{10–12}

John Bienenstock's "common mucosal immune system" hypothesis envisages the mucosal immune apparatus scattered throughout the body as a comprehensive, interconnected network. Within this system, immune cells and structures across diverse mucosal tissues form a unified functional whole. This paradigm conceives the mucosal immune system as a cohesive "organ system" wherein internal immune cells facilitate effective communication and collaboration across various mucosal sites to collectively address external stimuli and uphold the host's immunological stability.^{13,14} Mucosal tissues, including those in the gastrointestinal, respiratory, and urogenital systems, are pivotal in the host's defense against the incursion of foreign pathogens. Despite the wealth of knowledge regarding these individual systems, a holistic appraisal of the mucosal immune system as a functional organ system is still markedly lacking.¹⁵ Addressing this issue, the current article consolidates recent literature on the variances in the human microbiome at several key mucosal interfaces, including the nasal and gut regions, between individuals with AR and controls, with the aim of enhancing insights into the systemic mucosal microbiota's association with AR.

Summary of Included Studies

Upon a systematic search of PubMed, Embase, CNKI, and Web of Science databases, this review includes 17 qualifying studies published as of February 2024 (Table 1). These studies were conducted in five nations, comprising 12 studies from China, two from the United States, and one each from Australia, Italy, and Japan. Sample sizes ranged from 6 to 572 across case and control cohorts. Within these reports, 8 studies focus on the gut microbiota, while 9 investigate the nasal microbiota.

The Gut Microbiome and AR

Gut Microbiota Presence Patterns in AR Patients

A total of eight studies involving 872 patients with AR focused on the gut microbiota (Table 1). Among the research on microbial diversity, six studies reported a marked dysbiosis and a significant reduction in microbial diversity in AR patients compared to healthy controls, with distinct abundance differences.

Research shows that the generation of allergic diseases such as AR has a close connection with the composition and its changes of intestinal microbial diversity.³³ More than one thousand diverse species inhabit the gastrointestinal tract,³⁴ and the quantity of bacterial cells is approximately ten times greater than that of eukaryotic cells within the human body.³⁵ The bacteria have evolved along with humans, and it transforms into a mutualistic relationship. Hence, the gut microbiota might be implicated in the progression of specific diseases, and the significance of the gut microbiota is worthy of investigation in the development of AR. Table 1 demonstrates the alterations of intestinal microbes in AR patients. Compared with healthy individuals, the intestinal microbial diversity of AR patients is decreased, the relative abundance of Firmicutes is significantly reduced, while the proportion of *Bacteroidetes* is increased. In particular, the colonization and alteration of intestinal microbes have been verified before any clinical manifestations occur in the early stages of life, indicating that the intestinal microbial dysbiosis is one of the causes of AR. Infants with less intestinal microbial diversity seem prone to developing AR. A clinical study of 411 children by Bisgaard et al showed that reduced gut microbiota diversity in infancy was associated with increased risk of school-age AR.³⁶ The research by Johansson et al shows that the colonization of early *Lactobacillus* (Firmicutes) seems to be associated with the reduction of the risk of allergic diseases at the age of 5.³⁷ It is reported that compared with Russia, the dust samples in Finnish families are found to have a more abundant content of *Oxalobacteraceae*, and therefore the incidence rate of atopic diseases in this region is 4 times lower than that in Russia.³⁸ Although these studies have not conducted intestinal microbial-related research on atopic disease patients in this region, they provide evidence for the potential connection between intestinal microbiota and the prevalence of atopic diseases.

Zhou et al observed dysbiosis in the gut microbiota of AR patients compared to healthy individuals, with decreased α and β diversity. The AR patients had a reduced abundance of Firmicute. At the genus level the abundance of *Blautia*, *Eubacterium*, *Romboutsia*, *Collinsella*, *Dorea*, *Subdoligranulum* and *Fusicatenibacter* was significantly lower in the AR group. Notably, fecal SCFAs levels were lower in AR patients, correlating with the presence of *Eubacterium hallii* and *Blautia*.¹⁶ Watts et al compared the gut microbiome of 57 AR patients with 23 healthy controls using 16S rRNA sequencing. The study showed a

Table 1 Changes in the gut and nasal microbiota of patients with allergic rhinitis

Author, year	Country	Organs	Number of patients (Male/Female)	Number of controls (Male/Female)	Age	BMI	Allergens	Microbiota associations
Zhou, 2021 ¹⁶	China	Gut	18 (6/12)	17 (7/8)	31.81±2.32	22.45±0.65	–	Compared to HCs, individuals with AR exhibit significant differences in gut microbiome composition, both in diversity and richness. At the phylum level, the abundance of Firmicutes is significantly lower in the AR group compared to HCs. Within the genus level, the AR group shows a notably reduced abundance of Blautia, Eubacterium_hallii_group, Romboutsia, Collinsella, Dorea, Subdoligranulum, and Fusicatenibacter when juxtaposed with HCs. Concentrations of SCFAs are significantly decreased in the AR group relative to HCs. Correlation analysis indicates a positive association between the Eubacterium_hallii_group and Blautia with the levels of short-chain fatty acids.
Watts, 2021 ¹⁷	Australia	Gut	57 (22/35)	23 (10/13)	38.34±12.54	25.47±4.28	Dust mite and plant pollen	In comparison to the HCs, the AR cohort demonstrated a significant reduction in species richness as determined by the Shannon index. A trend toward decreased counts in OTUs, as well as lowered inverse Simpson index and Chao 1 diversity indices, was also noted. The phylum Bacteroidetes was significantly more abundant in the AR group than in HCs. In contrast, the abundance of Firmicutes was notably lower in the AR group compared to CG. Increased abundance of the genus Parabacteroides was observed in the AR cohort relative to CG, alongside a decrease in the genera Oxalobacter and Clostridium.
Yamaguchi, 2022 ¹⁸	Japan	Gut	572	520	54.5±18.25	–	Inhaled allergens (JCP, HD, Grass-mix, and Weed-mix)	At the phylum level, among the age groups of 20–49 and those aged ≥50 years, the relative abundance of Bacteroidetes was lower, while that of Firmicutes was higher in the non-sensitized cohort compared to the sensitized group. At the order level, the proportion of Bacteroidetes in the non-sensitized group was significantly lower than that in the sensitized group across both age categories. Furthermore, the relative abundance of Clostridium within participants aged 20–49 and Lactobacillales in both age groups was often higher in the non-sensitized cohort. Multivariate analyses also revealed that within the timeframe of 20–49 years, the sensitization to any allergen was significantly higher in the Bacteroidetes compared to the non-sensitized group.

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Table I (Continued).

Author, year	Country	Organs	Number of patients (Male/Female)	Number of controls (Male/Female)	Age	BMI	Allergens	Microbiota associations
Liu, 2020 ¹⁹	China	Gut	93 (53/40)	72 (42/30)	27.02±17.47	–	–	Compared with HCs, patients with AR exhibited a significant reduction in gut microbiome α -diversity. Notable compositional differences in gut microbiota between the two study groups were observed. At the phylum level, the relative abundance of Bacteroidetes was higher in the AR group compared to HCs, whereas the relative abundance of Actinobacteria and Proteobacteria was lower. At the genus level, a significantly higher relative abundance of Shigella, Prevotella, and Parabacteroides was detected in the AR group compared to HCs. LefSe analysis identified Shigella, Ruminococcus, Parabacteroides, and Dialister as potential biomarkers for AR. Moreover, predicted metagenomic functional analysis revealed significant differences between the AR and HC groups in the metabolic pathways of pyruvate, porphyrin, chlorophyll, purine, and peptidoglycan biosynthesis.
Candela, 2012 ²⁰	Italy	Gut	19 (17 cases were AR)	12	–	–	Cow's milk, egg, soy bean, wheat, peanut, codfish, grass pollen, Dermatophagoides pteronyssinus Dermatophagoides farinae, and cat dander	In children with atopic conditions, a marked depletion was observed in the gut microbiota concerning members of the Clostridium cluster IV, Faecalibacterium prausnitzii, and Akkermansia muciniphila. Correspondingly, there was an increased relative abundance of the Enterobacteriaceae family.
Chiu, 2019 ²¹	China	Gut	28 (17/11)	26 (14/12)	5.76±0.86	–	D. pteronyssinus, D. farina, Egg white, Cow's milk	In children with allergic airway diseases, lower but not significantly different Chao1 and Shannon indices were observed. Early life fecal total IgE levels were closely associated with serum specific IgE to D. pteronyssinus and D. farinae, but not with food-specific IgE levels. In comparison to the healthy control group, there was a lower abundance of the genus Dorea, which was negatively correlated with total fecal IgE levels in children with rhinitis, while the abundance of the genus Clostridium was lower and positively correlated with fecal IgE levels in children with asthma.
Zhang, 2023 ²²	China	Gut	24	25	7.06±2.72	16.68±9.97	–	Children with AR exhibited a significant decrease in Shannon index and an increase in the Simpson index at both the family and genus levels. Regarding bacterial composition, at the phylum level, the abundance of Bacteroidetes in AR children was higher compared to HCs group and showed a significant positive correlation with Total Nasal Symptom Score. At the family level, the prevalence of Prevotellaceae and Enterobacteriaceae in children with AR was elevated relative to the HCs group, and was significantly positively correlated with TNSS, ESO, and total tIgE. At the genus level, a reduction in abundance of Agathobacter, Parasutterella, Roseburia, and Subdoligranulum was observed in the AR cohort compared to HCs, and these were significantly negatively correlated with TNSS, EOS, tIgE, Quality of Life, and fractional exhaled nitric oxide (FeNO). Children with AR from mainland China exhibited reduced microbial diversity and distinct microbial signatures when compared with HCs.

Zhu, 2020 ²³	China	Gut	33 (11/22)	31 (18/13)	31.92±9.53	21.86±2.87	–	The bacterial diversity in the AR group was significantly higher than in the non-AR group. Principal PCoA revealed a significant differentiation in microbial communities between the AR and non-AR groups, with greater intra-group variation observed in the non-AR group. Notable differences were seen in phylum-level groups such as Firmicutes, Fusobacteria, Actinobacteria, Cyanobacteria, and Chloroflexi, with the most distinctly varied genera including <i>Prevotella</i> , <i>Phascolarctobacterium</i> , <i>Roseburia</i> , <i>Megamonas</i> , <i>Alistipes</i> , <i>Lachnoclostridium</i> , and <i>Fusobacterium</i> . An increased network complexity was predominantly observed within the Firmicutes clades in the AR group. In the AR group, the average relative abundances of Bacteroidetes (49.27%) and Proteobacteria (3.61%) were lower compared to those of non-AR individuals. The non-AR group showed a reduced abundance of both Firmicutes and Fusobacteria but had a unique presence of the phylum Lentisphaerae.
Wu, 2019 ²⁴	China	Nasal	28 (14/14)	28 (14/14)	31.13±5.01	22.1±2.53	–	In the AR group, the relative abundances of the genus <i>Streptococcus</i> , <i>Staphylococcus aureus</i> , <i>Haemophilus</i> , <i>Clostridium</i> , <i>Sphingomonas</i> , and the phylum Proteobacteria were significantly higher than in the HCs. In contrast, the control group exhibited a significantly higher relative abundance of <i>Propionibacterium acnes</i> , Actinobacteria, <i>Propionibacterium</i> , <i>Veillonella</i> , <i>Bacillus</i> , and <i>Peptoniphilus</i> compared to the allergic rhinitis group.
Li, 2023 ²⁵	China	Nasal	40 (18/22)	20 (8/12)	24.60±2.48	–	–	No significant differences in microbial diversity were observed between the AR group and the HCs group. However, clear variations were evident at several taxonomic levels, with three phyla, five classes, and differences seen at the order, family, species, and genus levels. At the class level, the AR group exhibited higher proportions of Alphaproteobacteria (3%), Clostridia (17%), and Actinobacteria (21%) when compared to the healthy group, while percentages for Bacilli (22%) and members of the phylum Firmicutes (2%) were lower. Key taxa including Alphaproteobacteria, Moraxellaceae, <i>Acinetobacter</i> genus (P=0.006), Pseudomonadales, Burkholderiales, and <i>Johnsonella</i> could potentially serve as microbial markers for AR.
Hyun, 2018 ²⁶	USA	Nasal	20 (16/4)	12 (8/4)	31.38±3.96	–	Mast	Dysbiosis of the microbiota was significantly correlated with total IgE levels, indicative of a combined allergic response, but not with the incidence of disease, the number of sensitizing allergens, or the levels of specific IgE to house dust mite allergens. Compared to individuals with low total IgE levels (IgE low group), a reduced microbial biodiversity was observed in individuals with high serum total IgE levels (IgE high group), with a higher relative abundance of Firmicutes (<i>Staphylococcus aureus</i>) and a lower relative abundance of Actinobacteria (<i>Propionibacterium acnes</i>). Phylogenetic predictions of microbial functional potential based on 16S rRNA genes indicated an increase in signal transduction-related genes and a decrease in energy metabolism-related genes in the IgE high group, as demonstrated by the microbial signature of atopic and/or inflammatory diseases.

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Table I (Continued).

Author, year	Country	Organs	Number of patients (Male/Female)	Number of controls (Male/Female)	Age	BMI	Allergens	Microbiota associations
Wang, 2018 ²⁷	China	Nasal	15	15	–	–	–	At the OTU level, no statistically significant differences were observed between the two groups in terms of microbial richness indices, including the Ace and Chao1 indices, and evenness as measured by the Simpson's evenness index. PCoA revealed a significant difference in the nasal vestibule microbiota between the AR group and the HC group. At the phylum level, the AR group showed a decreased abundance of Actinobacteria and an increased abundance of Firmicutes, both of which were statistically significant. At the genus level, there were nine genera with statistically significant differences in abundance between the AR and HC groups. The genera <i>Bacillus</i> , <i>Peptoniphilus</i> , <i>Anaerococcus</i> , <i>Fusobacterium</i> , <i>Propionibacterium</i> , and <i>Dialister</i> saw a decrease in abundance, while the abundance of <i>Pseudomonas</i> , <i>Halomonas</i> , and <i>Micrococcus</i> increased, with the differences being statistically significant.
Zhang, 2023 ²⁸	China	Nasal	8	8	–	–	Dust mite	In the AR group, the species diversity indices, which include Chao1, Simpson, Shannon, Pielou's evenness, Observed species, and Faith's phylogenetic diversity, all displayed an upward trend, although the differences were not statistically significant. Some differences were observed in β -diversity between the two groups. At the class level, there was a significant decrease in the abundance of Bacilli and an increase in Clostridia in AR patients. At the genus level, <i>Propionibacterium</i> was found to have a higher abundance in the AR group and lower abundance in the CK group. Lower abundances of <i>Propionibacterium</i> , <i>Enhydrobacter</i> , <i>Lactobacillus</i> , <i>Staphylococcus</i> , <i>Propionicimonas</i> , <i>Paracoccus</i> , <i>Methylotenera</i> , <i>Candidatus_Microthrix</i> , <i>Nitrospira</i> , <i>Mycobacterium</i> , <i>Dok59</i> , <i>Hyphomicrobium</i> , and <i>Micrococcus</i> were observed in the AR group compared to the HC group. At the order level, the abundance of Clostridiales was reduced and that of Bacillales was increased in the AR group. At the family level, the abundance of Moraxellaceae decreased, while the abundances of Tissierellaceae and Brucellaceae increased in the AR group.
Choi, 2014 ²⁹	American	Nasal	19 (11/8)	20 (12/8)	26.49±4.05	–	Trees or grasses	During the allergy season, subjects with SAR exhibited a significantly higher variety of biota in the middle nasal meatus ($p < 0.036$) and an increase in bacterial diversity (Shannon index) as compared to non-allergic subjects. A significant positive correlation was observed between nasal passage bacterial diversity during the season and eosinophil counts in nasal lavage from SAR subjects. No significant changes were detected in the nasal vestibule ($p > 0.05$ for all comparisons).

Yuan, 2021 ³⁰	China	Nasal	28 (14/14)	15 (6/9)	38.06±3.73	23.02±0.67	–	–	We observed no significant difference in diversity between the disease group and the control group, yet there was a shift in microbial community structure. Compared to the HC group, the AR group demonstrated a significant increase in the abundance of one phylum (Actinobacteria) and seven genera (including Klebsiella, Prevotella, and Staphylococcus), while one genus (Pelomonas) showed a notable decrease in abundance.
Wang, 2016 ³¹	China	Nasal	8	7	29±6.75	–	–	–	Upon comparative analysis, it was found that the number of OTUs within the nasal microbiome of AR patients (3176±623.6) was higher than that of the normal population. Principal component analysis indicated that the greatest differences in the nasal cavities of AR patients and the normal population were found in the Actinomycetales, Lactobacillales, and Pseudomonadales orders. OTU analysis revealed that the quantities of Streptococcus mitis, Neisseria, and Halomonas in the nasal cavities of AR patients were significantly higher than in the normal population, with statistical significance. Conversely, the quantity of Bacillus within the nasal cavity of AR patients was significantly lower compared to the normal population and was statistically significant.
Miao, 2023 ³²	China	Nasal	55 (27/28)	105 (63/39)	32.22±10.22	–	–	–	The diversity of the microbiome in the AR group was significantly lower than in the HCs group (α -diversity, Shannon diversity index), and the composition of the microbiomes between the two groups was distinctly different (β -diversity, weighted UniFrac PCoA). We discovered that the most abundant OTUs in AR patients, constituting 12.69% of all OTUs in this group, was composed of a specific species, namely Streptococcus salivarius. The abundance of this OTU even surpassed the total of the principal Subdoligranulum OTUs, though they represent the entire genus. Compared to the HC group, this Streptococcus salivarius OTU was intensely and significantly increased in AR.

Abbreviations: AR, allergic rhinitis; SCFAs, short-chain fatty acids; HCs, healthy controls; OTU, operational taxonomic units; USA, United States of America; IgE, Immunoglobulin E; PCoA, Principal component analysis; SAR, seasonal allergic rhinitis; TNSS, Tinnitus Severity Score; ESO, eosinophil count; HD, house dust; JCP, Japanese cedar pollen.

significantly lower α -diversity in the AR group, based on Shannon index, OTU (operational taxonomic units counts), inverse Simpson index, and Chao1, compared to HCs. They found a greater presence of Bacteroidetes and a lower abundance of Firmicutes in AR patients. Moreover, an increased abundance of *Prevotella* and reduced levels of *Oscillospira* and *Fusobacterium* were noted in the AR cohort.¹⁷ In 2022, Yamaguchi assessed the gut microbiota diversity and composition in 1092 Japanese subjects, focusing on varying ages, allergen sensitivity, and symptom presence. They discovered significant disparities in gut microbiota between allergic and non-allergic individuals, with a marked reduction in α -diversity (including observed species, Chao1, and Shannon index) in allergen-sensitive subjects. However, no meaningful statistical difference was found between symptomatic and asymptomatic groups, suggesting that gut microbiota may not play a role in symptomatic allergic rhinitis episodes. At the phylum level, the allergen-sensitive subjects showed a higher relative abundance of Bacteroidetes and a lower abundance of Firmicutes. At the order level, the percentage of Bacteroidales was significantly higher in the sensitized group than in the unsensitized group in all cases, while the relative abundance of *Clostridiales* and *Lactobacillus* tended to be lower.¹⁸ Liu et al found significant differences in gut microbiota between 93 AR patients and 72 HCs, with the AR group displaying notably lower α -diversity (including Chao1 index, observed species index, Shannon index, and Simpson index). At the phylum level, Bacteroidetes were more abundant while Actinobacteria and Proteobacteria were less abundant in AR patients compared to HCs. At the genus level, the AR group showed significantly higher relative abundances of *Escherichia*, *Shigella*, *Prevotella*, and *Paraprevotella*.¹⁹ Candela et al included 19 atopic children (17 with AR) and 12 healthy controls aged 10–14, and discovered that the atopic children's gut microbiota were significantly depleted in species, such as those belonging to *Clostridium* cluster IV, *Faecalibacterium*, and *Akkermansia muciniphila*, while showing an increased relative abundance of *Enterobacteriaceae*. Unfortunately, the study did not investigate the diversity of gut microbiota between the two groups.²⁰ Chiu et al compared gut microbiota in 28 AR children with 26 HCs, observing lower, but not significantly different, Chao1 and Shannon indices in AR children, with similar microbial clustering to the HCs. The AR group also had notably less abundance of Firmicutes. Correlation analysis revealed that *Escherichia* positively correlated with house mite IgE, *Clostridium* with total fecal IgE, and a negative correlation between *Dorea* spp. and fecal IgE levels.²¹ Zhang et al conducted a study encompassing a cohort of 24 pediatric patients with AR and compared them to 25 HCs. The findings elucidate a reduction in microbial diversity among AR children in Mainland China when juxtaposed with the HCs group, highlighting distinct microbial signatures. Notably, a significant decrement in the Shannon diversity index and a concurrent marked escalation in the Simpson index were observed at both the phylum and genus taxonomic levels within the AR pediatric cohort.²²

Contrary to previous findings, Zhu et al's 2020 study on 33 AR patients revealed higher bacterial diversity in AR patients compared to HCs, potentially due to an expansion of Firmicutes. They observed a more complex network topology in AR patients' Firmicutes, suggesting a stubborn dominance in microbial crosstalk. The study noted a lower average relative abundance of Proteobacteria and higher Firmicutes and *Clostridiales* in AR patients, while the non-AR group possessed unique *Lentisphaerae* phyla.²³

Modulation of AR Immune Responses by Gut Microbiota and Their Metabolites

Regulation of AR Immune Responses by Gut Microbiota

Contemporary immunological frameworks suggest that AR is characterized by a predominant Th1/Th2 disequilibrium with a pronounced shift towards Th2 responsiveness.³⁹ Th1 cytokines are produced by interleukin 12 (IL-12) to stimulate initial T cell differentiation and reduce AR symptoms by producing anti-inflammatory factors such as interferon- γ (IFN- γ) and IL10 to suppress Th2 immune responses. Th2 cells are generated by IL-4 stimulated initial T cell differentiation and produce Th2-like cytokines such as IL-5 and IL-13, which act on inflammatory cells such as B lymphocytes, mast cells, eosinophils, and dendritic cells, thus causing a cascade response of inflammation.⁴⁰ At the same time, type 2 innate lymphocytes (ILC2) and dendritic cells (DC), generated under the stimulation of epithelial-derived cytokines such as IL25, IL33 and thymic stromal lymphopoeitin (TSLP), initiate the differentiation of native T cells into Th2 cells and coordinate the production of Th2 cytokines to assist in the generation of a series of inflammatory responses.⁴¹ Accumulating empirical data underscore the intestinal microbiota as a crucial regulator, intricately influencing the dynamic Th1/Th2 balance, thus impacting the immunological pathways implicated in AR.⁴² Chua et al found that infants with allergies had higher fecal *Lachnospiraceae* frequencies, linked to overgrowth of *R. gnavus*, compared to non-allergic infants. Further studies in sensitized mice revealed

that *R. gnavus* induces Th2 and dendritic cell expansion and eosinophilic infiltration in the colon by stimulating cytokine secretion (IL-25, IL-33, TSLP) from colonic epithelial cells. This infiltration could lead to systemic allergic inflammation via eosinophils mobilizing through blood and lymphatic routes.⁴³ Additionally, they observed that ovalbumin-sensitized mice orally administered with *R. gnavus* had increased levels of IL-25, IL-33, and TSLP in colonic tissue compared to controls, promoting enhanced Th2 differentiation and cytokine secretion. Mazmanian et al study demonstrates that in contrast to mice colonized with *Bacteroides fragilis*, germ-free mice exhibit a Th1/Th2 dysregulation with a propensity towards Th2 polarization. The underlying mechanism is hypothesized to be the ability of *Bacteroides fragilis* to modulate this dysregulation via polysaccharide A (PSA), thereby restoring immunological equilibrium.⁴⁴ The aforementioned research provides robust evidence supporting the role of intestinal bacteria in the immunological mechanisms of AR. These studies offer insight into the complex interactions between gut microbiota and host immunity, reaffirming the potential influence of microbial populations in the modulation of immune responses characteristic of AR.

In the immune response of AR, Toll-like receptors (TLRs) act as the initial element for recognizing and responding to pathogen-associated molecular patterns (PAMPs). TLRs are important pattern recognition receptors composed of cytoplasmic, transmembrane, and extracellular regions that induce the body's anti-microbial defense system and produce various inflammatory mediators and chemokines. There are 10 TLRs identified in the human body, TLR1 to TLR10, of which TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are distributed on the cell membrane⁴⁵ and can recognize PAMPs such as lipopolysaccharide, peptidoglycan, and yeast glycan, and when TLRs bind to these PAMPs, they initiate a signal transduction cascade to activate an innate immune response to eliminate pathogens that breach mucosal barrier.⁴⁶ Other TLRs, TLR3, TLR7, TLR8, and TLR9, detect nucleic acids intracellularly.⁴⁷ TLRs can regulate DCs, lymphocytes, mast cells and other cells closely related to AR, thus indirectly regulating the balance of the Th1/Th2 cytokine network, and playing an important role in the occurrence and development of AR.⁴⁸ He et al have demonstrated that TLRs in the gut microbiota can activate intestinal epithelial cells (IECs), thereby inducing the production of A Proliferation-Inducing Ligand (APRIL) and TSLP, which assist in the generation of Th2 cytokines and facilitate local inflammatory responses.⁴⁹ Sjögren et al demonstrated in a prospective study of 64 Swedish infants that the colonization intensity of *Bacteroides fragilis* in the first week and month after birth is negatively associated with TLR4 mRNA expression. It is speculated that *Bacteroides fragilis* may regulate the Th1/Th2 balance by suppressing the expression of TLR4, potentially inhibiting the incidence of AR.⁵⁰ The pediatric cohort study by Amenyogbe et al indicates a significant correlation between the response to TLR2 and the relative abundance of the *Bacteroides* and *Prevotella* genera in children from Canada and Ecuador. A higher abundance of *Prevotella* and a lower abundance of *Bacteroides* are associated with an increased cytokine response to TLR2.⁵¹ The capsular PSA of the gut commensal *Bacteroides fragilis* has been proven to be a typical immunomodulatory molecule in the gut, capable of limiting pathological inflammation in the intestinal and distal tissues.⁵²⁻⁵⁴ PSA requires both innate and adaptive immune responses to exert a protective influence, according to Dasgupta et al. They revealed that plasmacytoid dendritic cells (PDCs) exposed to PSA do not produce pro-inflammatory cytokines because PSA preferentially binds to TLR2 on PDCs, which prompts the secretion of the anti-inflammatory cytokine IL10 by regulatory T cells (Treg).⁵⁵

Recent scholarly research suggests that an imbalance between T helper cell 17 (Th17) and Treg is closely associated with the pathogenesis of AR.⁵⁶ Treg and Th17 cells are both derived from CD4+ T cells and are mediated by a common signaling pathway by transforming growth factor- β (TGF- β). In vitro and in vivo studies have shown that TGF- β promotes the development of Th17 and Treg cells by inducing the expression of retinoic acid receptor-related orphan receptor γ (ROR γ t) and Forkhead box protein P3 (Foxp3), respectively.⁵⁷ Th17 and Treg cells maintain a dynamic balance, producing an immune response of appropriate intensity and contributing to the maintenance of a stable immune state in vivo. When CD4+ T cells differentiate towards pro-inflammatory Th17, the body then develops a series of inflammatory manifestations. Studies have shown that Th17 activates Th2 cells, resulting in increased serum IgE specificity and aggregation of eosinophils and neutrophils in the nasal mucosa.^{58,59} At the same time, Th17 secretes pro-inflammatory factors such as IL-17A, IL-17F, IL-6 and tumor necrosis factor (TNF)- α , which cause a specific inflammatory response in the nasal cavity. Among them, IL-17 is the most important pro-inflammatory factor. Clinical studies have shown that serum levels of Th17, IL-17, and TGF- β are elevated in AR patients compared to controls, and that IL-17 correlates with the degree of clinical symptoms inflammation.⁶⁰ In addition et al found that knockdown of IL-17A in mice significantly reduced allergic symptoms.⁶¹ Treg cells are a small but critical subpopulation of CD4+ T with a

role in maintaining immune homeostasis. Treg cells, a small but critical subpopulation of CD4+T, develop from TGF- β -induced Foxp3 and play a role in maintaining immune homeostasis in AR. Treg cells are a small but critical subpopulation of CD4+ T that play a role in maintaining immune homeostasis in AR. TGF- β promotes Treg cell development by inducing Foxp3 expression, and under Treg-induced conditions, cells fail to differentiate into Th17 cells, which eventually develop into Foxp3+ Treg cells.⁶² Nguyen et al found that alpha-lipoic acid (LA) significantly alleviated nasal symptoms such as rubbing and sneezing in AR mice through upregulation of the Treg cytokine IL-10 and the transcription factor Foxp3.⁵⁶ Jiao et al showed that Notch2 suppresses the development of allergic rhinitis by promoting Foxp3 expression and Treg cell differentiation.⁶³ The intestinal microbiome and its metabolic byproducts are increasingly recognized as critical players in the regulation of the Th17/Treg balance. Atarashi et al demonstrated that regulatory Treg are most abundant in the colonic mucosa of mice, with clusters IV and XIVa of the genus *Clostridium* enhancing the accumulation of Treg cells.⁶⁴ Additionally, they found that the colonization of spore-forming Clostridia in the mouse colon creates a rich TGF- β milieu, influencing the immune status both within the gut and systemically through an increase in Foxp3+ Treg numbers.⁶⁵ Dasgupta et al discovered that PSA, as a typical immunomodulatory molecule from the gut symbiont *Bacteroides fragilis*, can induce regulatory T cells to secrete the anti-inflammatory cytokine IL10, thereby limiting pathological inflammation in the intestine and distal organs.⁶⁶ (Figure 1)

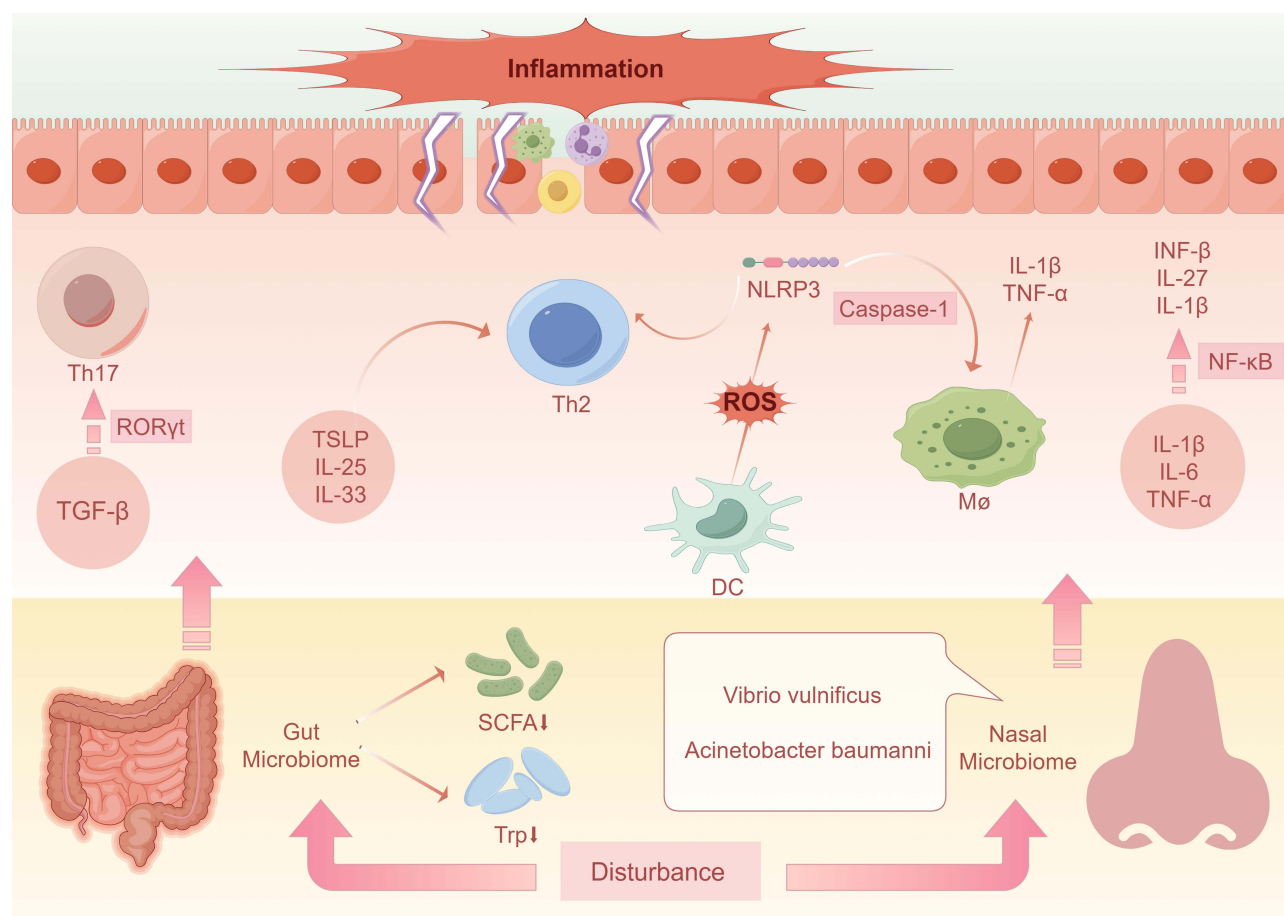


Figure 1 Impact of gut and nasal microbial dysbiosis on AR. Disturbance of the gut microbiota and a decrease in intestinal metabolites (eg. short-chain fatty acids and tryptophan,) induces the production of TSLP, IL-25, and IL-33, which contributes to Th2 cytokine production and promotes localized inflammatory responses. It also creates an environment rich in transforming growth factor- β , which promotes cellular differentiation toward pro-inflammatory Th17 by increasing the amount of ROR γ -t. *Vibrio* traumaticus in the nasal cavity induces cytokines such as IL-1 β , IL-6, and TNF- α , participates in NF- κ B signaling, and elicits allergic reactions by releasing IFN- β , IL-27, and IL-1 β . *A. baumannii* activates the Nod-like receptor NLRP3 via caspase-1, which promotes the release of IL-1 β and TNF- α from macrophages, thereby triggering AR. In addition, *A. baumannii* induces the production of reactive oxygen species from dendritic cells, which activates NLRP3 and promotes the differentiation of cells towards pro-inflammatory Th2, triggering the immune response typical of AR.

Abbreviations: Th17, T helper cell 17; TGF- β , transforming growth factor β ; TSLP, transforming growth factor β ; IL, Interleukin; Th2, T helper cell 2; DC, Dendritic cells; ROS, reactive oxygen species; m ϕ , Macrophages; IFN- β , Interferon- β ; TNF- α , Tumor necrosis factor- α . By Figdraw.

Regulation of Immune Responses in Allergic Rhinitis by Metabolic Products of Gut Microbiota

The gut microbial community is a complex micro-ecosystem, its biodiversity supported by a spectrum of distinct microbial species.⁶⁶ The dynamic equilibrium of this community is vital for the homeostasis of the host's immune system.^{67,68} In the interaction between the host and gut microbiota, SCFAs as key metabolic by-products of microbial communities, play a significant role.^{69–72} SCFAs are metabolic products generated by gut microbiota via the fermentation of indigestible dietary fibers, primarily including acetate, propionate, and butyrate. Recent studies indicate that SCFAs have important roles in modulating immune responses and exerting anti-inflammatory effects, particularly in the onset and development of allergic diseases.^{73,74} Studies have identified SCFAs as key metabolites facilitating the differentiation of naïve T lymphocytes into Treg cells in the intestinal tract. Interaction with initial T cells by butyrates and propionates enhances the acetylation of the Foxp3 transcription factor promoter, which is essential for Treg differentiation.⁷⁵ Remarkably, Rooks et al have demonstrated that a high-fiber diet or supplementation with SCFAs not only mitigates colonic inflammation but also suppresses allergic airway disease by augmenting the suppressive activity of Foxp3+ Treg cells.⁷⁶ Consequently, by modulating the gut microbiome and its metabolic byproducts, we can effectively influence the host's immune response, providing new avenues for the treatment of allergic diseases.

Roduit's research has revealed that infants with reduced levels of SCFAs are more prone to develop allergic conditions. The study shows that in toddlers, those with higher butyrate levels tend to have significantly lower rates of food allergies and allergic rhinitis. In addition, oral administration of SCFAs in mice significantly mitigated symptoms of allergic airway inflammation.⁷⁷ Cheng et al have corroborated this conclusion, delineating an association between lower levels of gut short-chain fatty acids in early life and an elevated susceptibility to atopic outcomes in childhood.⁵⁸ Moreover, Chen et al developed an AR mouse model with dysbiosis of the gut microbiome induced by vancomycin and ovalbumin (OVA) sensitization.⁷⁸ They discovered that such dysbiosis could increase the susceptibility and clinical severity of allergic airway diseases by reducing the bacteria that produce SCFAs and the levels of SCFAs themselves. The supplementation of SCFA-producing bacteria or SCFAs was found to alleviate allergic airway diseases.^{79–81} Synthesizing current research findings, it becomes apparent that an imbalance in the gut microbiome and reduced SCFAs levels are key drivers in the progression of allergic airway inflammatory diseases. Strategic enhancement of SCFA-producing microbes or direct supplementation of SCFAs may offer a novel interventional route for the prevention and treatment of such conditions. This approach has the potential to modulate the host's immune response and alleviate inflammation, carving out new therapeutic directions for the clinical management of allergic airway diseases.

Another key product in microbial metabolic processes, Trp, has been demonstrated to safeguard the intestinal barrier's integrity and ensure the stability of immune cells through the activation of the aryl hydrocarbon receptor (AhR).^{82,83} Consequently, they are recognized as vital active biomarkers.⁸⁴ Tryptophan, as an important intestinal metabolic product, undergoes metabolism through three distinct routes under homeostatic conditions: Firstly, the Kynurenine Pathway (KP), which is facilitated by the action of the enzyme indoleamine 2,3-dioxygenase 1 (IDO1); secondly, the production of 5-Hydroxytryptamine within enterochromaffin cells, a process catalyzed by Tryptophan hydroxylase 1 (Tph1); and thirdly, the direct conversion of tryptophan into indole, its derivatives, and tryptamine by intestinal microbiota using the enzyme tryptophanase, leading to the synthesis of a diverse array of metabolites such as Indole-3-acetic acid (IAA), Indole-3-acetaldehyde (IAAld), Indole-3-aldehyde (IAld), Indolepyruvic acid (IPA), and Indoleacetaldehyde (IA).⁸⁵ Studies have shown that tryptophan metabolites have a major impact on the immune system, especially at the mucosal barrier. Their ability to reduce the viability of T cell responses and stimulate the production of Treg is critical for immune regulation.^{86,87} Reduced levels of these potentially anti-inflammatory tryptophan metabolites may bias the immune system toward a Th2-dominant response, which may increase susceptibility to Th2-mediated diseases such as allergic rhinitis.

Research indicates that Kyn is capable of elevating the expression levels of the Foxp3 transcription factor, which plays a crucial role in enhancing the differentiation of Treg cells. Simultaneously, it inhibits the proliferation of Th17 type cells.^{88–91} Hossain et al demonstrated that in the absence of IDO, mice respond to viral infections with pronounced Th17 and Th1-type airway inflammation. This pathological state is marked by intense neutrophil infiltration, increased levels of IL-17 and IFN- γ , and significant airway hyperresponsiveness.⁹² Within the murine model of asthma, stimulation of TLR-9 via bacterial DNA sequences has been shown to trigger the upregulation of IDO and the aromatic receptor,⁹³

leading to a reduction in inflammatory airway hyperresponsiveness. Based on the findings presented by Kepert, the pre-administration of D-tryptophan prior to the experimental induction of asthma in murine models resulted in an augmented presence of regulatory T cells in the pulmonary system, a diminished Th2 type immune reaction, and a notable amelioration in both allergic airway inflammation and hyperresponsiveness.⁹⁴ A different metabolite of tryptophan, 3-Hydroxy-Anthranilic acid (3-HAA), has been identified to specifically inhibit the phosphorylation of 3-phosphoinositide-dependent protein kinase 1 (PDK1), thereby obstructing the activation of NF- κ B induced by T cell antigen receptors. This action results in the impairment and apoptosis of activated Th2 cells within the organism, effectively mitigating experimental asthma prompted by Th2 immune reactions in murine models.⁹⁵ Consequently, despite the precise function of tryptophan metabolism in the etiology of atopic disorders including asthma and allergic rhinitis remaining somewhat elusive, the significance of tryptophan metabolism and its intermediary metabolites as critical regulators of immune responses is undeniable.⁹⁶

The Nasal Microbiome and AR

Patterns of Nasal Microbiota in Patients with AR

Nine studies examining the nasal microbiome of 447AR patients (Table 1) yielded divergent conclusions. Most studies observed no significant change or difference in microbial diversity between AR patients and healthy controls. However, two studies reported a greater species diversity in the AR group compared to controls, while another study indicated a notably lower microbial diversity in AR patients. All nine studies found significant variances in microbial abundance between the AR group and healthy controls.

Wu et al incorporated 28 Chinese AR patients and 28 HCs in their study and found no statistically significant differences in the alpha diversity indices (including Ace, Chao1, Shannon, Simpson, and Coverage) of nasal microbiota between the two groups. In the allergic rhinitis cohort, the relative abundance of *Streptococcus*, *Staphylococcus aureus*, *Haemophilus*, *Clostridium*, *Veillonella*, and *Proteobacteria* was significantly higher compared to controls, while the relative abundance of *Propionibacterium acnes*, *Actinobacteria*, *Propionibacterium*, *Corynebacterium*, *Rodentibacter*, and *Propionibacterium* was notably lower. Furthermore, Pearson correlation analysis demonstrated a significant positive correlation between *Proteobacteria* and IgE levels, and a significant negative correlation between *Propionibacterium acnes* and IgE levels, confirming a certain relationship between nasal microbiota and IgE in AR patients.²⁴ In a comparative study by Li et al, involving nasal microbiome markers and metabolites of 40 individuals with AR and 20 HCs, no discernible differences were found in the alpha and beta diversities of nasal microbes. At a higher taxonomic level, the AR group had elevated levels of *Alphaproteobacteria*, *Clostridia*, and *Actinobacteria*, while *Bacilli* and *Firmicutes* were reduced compared to the healthy subjects.²⁵ Hyun and their team investigated the relationship between mucosal microbiota and AR, the number of sensitizing allergens, and specific and total IgE levels by comparing AR subjects with healthy controls. Participants, 42 in total, were categorized into three groups: non-sensitized, mono-sensitized to a single allergen, and polysensitized to multiple allergens, with no observed differences in microbial diversity or community composition among the groups. Further analyzing nasal microbiota in relation to serum IgE sensitization, they divided subjects into high AR-specific/total serum IgE, low AR-specific/total serum IgE, and non-AR/low total IgE levels. They reported lower microbial biodiversity and higher relative abundance of *Firmicutes* (notably *Staphylococcus aureus*) and lower *Actinobacteria* (specifically *Propionibacterium acnes*) in individuals with high total IgE compared to those with low IgE levels.²⁶ In a study conducted by Wang et al, a comparative analysis of the microbiota of the nasal vestibule between AR patients and HC was performed. A total of 30 subjects were included, with 15 in each group, AR and HC. Through PCA, the research identified significant differences in the structure of the microbial communities between the two groups. However, when examining the OTUs, no statistically significant differences were observed in the richness (such as the Ace index and Chao1 index) and evenness (such as the Simpsons even index) of the microbial communities between the two groups. Further analysis revealed that at the phylum level, there was a significant reduction in the relative abundance of *Actinobacteria* in the AR group, while there was a significant increase in the relative abundance of *Fusobacteria*, with these differences being statistically significant. At the genus level, nine genera were identified to have significant differences in abundance between the AR and HC groups. Specifically, the abundance of *Corynebacterium*, *Peptoniphilus*, *Anaerococcus*, *Finegoldia*, *Propionibacterium*, and *Brachybacterium* was reduced in the

AR group compared to the HC group. Conversely, the abundance of *Shewanella*, *Halomonas*, and *Paracoccus* was increased in the AR group, and these differences were also statistically significant.²⁷ In a small-scale study by Zhang et al, even though an uptrend in species diversity indices was noted among six AR patients, these changes were not statistically significant when compared to six HCs. Notably, there was a significant decrease in *Bacillales* and an increase in *Clostridiales* within the AR group. At the genus level, *Propionibacterium* was more abundant in AR patients, whereas various other genera, including *Lactobacillus* and *Staphylococcus*, were less prevalent. At higher taxonomic hierarchies, a shift toward lower *Clostridiales* and higher *Bacillales* was observed, with altered abundances in certain families, signifying variable microbiota profiles between AR sufferers and healthy individuals.²⁸ Choi et al have observed a significant proliferation of microbial species within the middle meatus of the nasal cavity among subjects with Seasonal Allergic Rhinitis (SAR) during the allergic season, as opposed to non-allergic subjects. This observation was accompanied by an increase in bacterial diversity, quantified by the Shannon diversity index. Furthermore, a significant positive correlation was detected between the bacterial diversity within the middle meatus during the allergic season and the eosinophil count in nasal lavage fluid from SAR subjects.²⁹ Yuan et al found no difference in the alpha diversity (Chao1 and Simpson indices) of nasal microbiota between 28 AR patients and HCs. Nevertheless, notable shifts in microbial composition were observed, the AR group showed a significant increase in *Actinobacteria*, and genera such as *Klebsiella*, *Prevotella*, and *Staphylococcus*, with a marked decrease in the abundance of *Pelomonas*.³⁰ Wang et al analyzed the nasal microbiota of 8 AR patients and 7 HCs in China, finding a statistically significant increase in species diversity (including Chao1, ACE, Shannon, npShannon, and Simpson indices) in the AR group. The study also highlighted a significant rise in the relative abundance of *Proteobacteria* and a decrease in *Actinobacteria* and *Firmicutes* among AR patients compared to healthy controls. At the genus level, a noteworthy deficit in *Bacillus* was detected in the AR patients' nasal microenvironment, indicating clear microbial distinctions between the two groups.³¹ Miao and co-researchers, contrasting the nasal microbiota of 55 AR patients with 105 HCs, reached a divergent conclusion, noting a significant discrepancy in microbial composition, with reduced diversity in AR individuals. At the phylum level, an enhanced presence of *Firmicutes* was recorded. Moreover, they identified the most prevalent OTU in AR patients as a specific strain of *Streptococcus salivarius*. Compared to HCs, this particular OTU displayed a marked and significant increase in AR patients, suggesting a unique and strong association with AR within the nasal microbiome.³²

The Impact of Microbial Dysbiosis on AR

The nasal microbiota serves as a microbial shield against external irritants and an immune regulatory interface, predominantly nested in the mucus layer atop epithelial cells. Encompassing a diverse array of microorganisms—bacteria, fungi, viruses, protozoa, and archaea—this ecosystem is both populous and compositionally varied.⁹⁷ In the context of AR, individuals exhibit distinct patterns of nasal microbiome diversity and abundance compared to healthy individuals. Dysbiosis may prompt the proliferation of specific pathogens, leading to nasal mucosal inflammation. For instance, *Pseudomonas* possesses the capacity to survive and replicate within phagocytes, triggering the activation of immunocompetent cells in hypersensitivity reactions, particularly in immunocompromised hosts.⁹⁸ *Burkholderia cepacia* complex, a conditionally pathogenic organism, colonizes the nasal cavity and compromises the integrity of the nasal epithelial cells, precipitating a cascade of inflammatory responses.⁹⁹ In a study by Che et al, an investigation into the nasal microbiome characteristics of patients with AR versus Non-Allergic Rhinitis (NAR) revealed a significantly higher mean relative abundance of *Vibrio vulnificus* and *Acinetobacter baumannii* in the AR group.⁹⁷ *Vibrio vulnificus*, commonly known as marine vibrio, is a Gram-negative bacterium capable of inducing cytokine production, namely IL-1 β , IL-6, and TNF- α .¹⁰⁰ These cytokines instigate inflammation by recruiting and activating immune cells such as neutrophils, monocytes, and macrophages. They activate the mTOR pathway, engage NF- κ B signaling via TLRs or NLRs, and incite allergic responses through the release of GM-CSF, IFN- β , IL-27, and IL-1 β . Moreover, *Vibrio vulnificus* has been shown to prompt proliferation and inflammatory reactions in Kupffer cells, aligning with the pathogenic mechanisms of AR.^{101–103} *Acinetobacter baumannii*, on the other hand, activates the Nod-like receptor NLRP3 via caspase-1, promoting the release of IL-1 β and TNF α from macrophages, hence triggering asthma.¹⁰⁴ Furthermore, *Acinetobacter* comes equipped with various virulence factors, including pore-forming toxins, and its outer membrane protein A induces reactive oxygen species (ROS) production in dendritic cells, activating NLRP3 and fostering immune reactions typical of asthma and AR.¹⁰⁵ (Figure 1)

Discussion

In the current academic landscape, the correlation between the diversity of the human microbiota at essential mucosal interfaces, such as the nasal and gastrointestinal tracts, and the development of allergic rhinitis has captivated increasing interest. The homeostasis of the microbiota is a cornerstone of human well-being, with imbalances potentially triggering disease onset. Contemporary studies suggest that the gastrointestinal tract's resistance to extrinsic disturbances may positively correlate with the diversity and equilibrium of its resident microbial populations.¹⁰⁶ Furthermore, metrics of microbial richness could serve as pivotal indicators in evaluating the stability or "adaptive capacity" of the gut microbiome.¹⁰⁶ Current research consistently supports the observation that significant differences exist between the gut microbiota of patients with AR and those of healthy cohorts. A majority of these studies document a trend towards diminished diversity and dysbiosis within the gut microbiome of individuals suffering from AR when compared to healthy counterparts. Notably, numerous investigations have highlighted an increased abundance of the phyla *Bacteroidetes* and *Proteobacteria*, and a conspicuously reduced presence of *Firmicutes* in the AR population. Within the realms of gastrointestinal microbiology, the phyla *Bacteroidetes* and *Firmicutes* are heralded as the most abundant bacterial taxonomies populating the gut environment. Their roles are quintessential in gastrointestinal integrity and immunomodulation.¹⁰⁷ *Bacteroidetes* are particularly associated with the production of SCFAs such as acetate and propionate, while *Firmicutes* are more intimately linked with butyrate generation.¹⁰⁸ Integrity disruption in the intestinal barrier can precipitate an increased permeability to pro-inflammatory molecules and antigens, thereby facilitating their translocation into the submucosal layers and systemic circulation, provoking both localized and systemic inflammatory responses. In certain scenarios, a relative preponderance of *Bacteroidetes* over *Firmicutes* may result in a reduced synthesis of butyrate, subsequently impacting the fortitude of the intestinal barrier. It is noteworthy that clinical and experimental investigations have unearthed heightened gut permeability in individuals with allergic diseases as compared to their healthy counterparts.^{109–113}

Nine distinct studies have elicited variations in the observed changes to the nasal microbiota of AR patients, rendering a consensus elusive and posing a conundrum. The studies in question exhibit substantial variability in sample sizes, with the smallest incorporating only 15 participants and the largest encompassing 160, which could contribute to the disparate outcomes. It is also worth noting the methodological heterogeneity in specimen types collected, encompassing nasal secretions, inferior turbinate mucosa, and aseptic swabs of both the vestibules and the lower nasal passages, potentially influencing the results. Despite these variations in methodology, sample size, and source of specimen, a consistent finding across all nine studies emerges: AR patients exhibit a significantly different microbial abundance compared to the healthy control group. Concomitantly, it has been observed that 3 studies denote a correlation between changes in microbial abundance (within both the gut and the nasal cavity) in patients with AR and levels of IgE. Specifically, the Actinobacteria phylum has been reported in three separate studies as being inversely related to IgE concentrations.^{17,78,80} Further investigations have illuminated that *Propionibacterium acnes*, predominant in the bacterial community of the inferior turbinate in healthy individuals,⁸ can potentially ameliorate atopic symptoms by inducing Th1 and Treg responses,¹¹⁴ suggesting that a diminished abundance of *P. acnes* may be implicated in exacerbating AR. Building upon these research findings, it may be postulated that as constituents of the nasal microbiota, members of the Actinobacteria phylum could play a pivotal role in safeguarding the host against allergic incursions by participating in the maintenance of microbial equilibrium. Future studies are expected to shed light on the direct or indirect involvement of Actinobacteria in the pathogenesis of Allergic Rhinitis and determine their viability as potential therapeutic targets. In summary, the Actinobacterial members of the human microbiota might exert an influence on the pathophysiology of Allergic Rhinitis to a certain degree, necessitating further research to elucidate their specific mechanisms and clinical relevance.

Mucosal tissues, encompassing the gastrointestinal, respiratory, constitute the host's primary line of defense against external pathogens. While substantial knowledge has been gleaned from studying these components in isolation, a comprehensive examination of the mucosal immune system as an interconnected systemic organ remains to be conducted. The common mucosal immune system hypothesis posits that immunological activities within the respiratory tract may be interconnected with immunoregulatory functions occurring in the gastrointestinal milieu.¹¹⁵ This hypothesis suggests that antigens within the gastrointestinal system provoke the local lymphocytes, which, once activated, may migrate to other submucosal regions of the upper and lower respiratory tracts.¹¹⁵ During this immunological cascade,

antigens are captured by Peyer's patches and transported to antigen-presenting cells.¹¹⁶ Naive T cells and B cells demonstrate heightened sensitivity to antigens situated within Peyer's patches and possess the capability to enter the bloodstream, consequently exerting their functions across various mucosal tissues such as those found in the intestines and respiratory system.¹¹⁶ Emerging evidence indicates that the gut microbiota can modulate the immune status of the nasal mucosa via the production of metabolic byproducts, such as SCFAs. Butyrate, in particular, has been shown to regulate the function of immune cells, including dendritic cells and T cells, thereby modulating inflammatory responses and immunological reactions. Furthermore, the metabolic byproducts of the gut microbiota can disseminate to the nasal cavity through the bloodstream, influencing the immunological barrier function of the nasal mucosa, and could potentially affect the incidence and progression of allergic diseases, such as AR. Additionally, dysbiosis of the gut microbiota may lead to systemic inflammation, which can impact distant organs, including the nasal passages, via the circulatory system, thereby affecting the immune status and barrier function of the nasal mucosa.¹¹⁷

Although current research has yet to confirm a direct correlation between gut and nasal microbiota, it is hypothesized that these two microbiomes, as significant components of the human microbiome, play a critical role in maintaining host health, and there is likely an interconnected relationship between them. Current evidence, albeit limited due to study heterogeneity and variable outcome measures, suggests that oral administration of probiotics may confer benefits in alleviating symptoms and enhancing the quality of life for patients with Allergic Rhinitis.^{118–123} Research posits that the gut microbiota can influence systemic immune responses through the generation of metabolic byproducts, such as SCFAs, which can be disseminated to distal organs, including the nasal cavity, via the bloodstream.¹²⁴ The metabolites produced by the gut microbiota may exert an effect on the immune status of the nasal mucosa, thereby influencing the composition and function of the nasal microbiome.¹²⁴ Future research should delve into the mechanisms through which the gut microbiota impacts the nasal microbiota, including interactions via the immune system, metabolites, or the nervous system. Investigations into the direct and indirect pathways between the gut and the respiratory tract are pertinent, which might encompass exploring how the gut microbiota asserts influence on nasal health through the gut-brain axis or the gut-lung axis.

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Disclosure

The authors report no conflicts of interest in this work.

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