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Nasal-gut microbiome axis in health and disease

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ABSTRACT

The nasal and gut microbiomes are recognised as key regulators of mucosal and systemic immunity. While each has been studied extensively in isolation, evidence suggests they are connected through a bidirectional network of immune signalling, microbial metabolites, and barrier integrity, forming what may be termed "the nasal–gut microbiome axis". This review synthesises current knowledge on the composition and function of these microbiomes, highlighting shared features, environmental influences, and patterns of dysbiosis observed in conditions such as asthma, allergic rhinitis, and chronic rhinosinusitis. We examine potential mechanisms of cross-talk, including cytokine and chemokine exchange, short-chain fatty acid mediated epigenetic regulation, and dendritic cell–driven immune priming across mucosal sites. Clinical implications are explored, with particular attention to dual-site microbiome modulation strategies, concurrent nasal–gut microbial profiling for diagnostics, and microbiome-informed precision therapies. Despite promising early evidence, knowledge gaps persist, particularly the scarcity of longitudinal, multi-omic studies and mechanistic human data. Framing the nasal and gut microbiomes as components of an integrated mucosal network, this review aims to advance understanding of their connection, and encourage research that could transform prevention and treatment strategies for immune-mediated respiratory disease.

1. Introduction

The human microbiome, a complex and dynamic ecosystem of microorganisms residing in and on our body, plays a pivotal role in maintaining health and contributing to disease. Comprising bacteria, viruses, fungi, and archaea, the microbiome influences a wide range of physiological processes, including immune function, metabolic regulation, and even neural activity [1]. Studies in microbiome research have revealed the significant impact of microbial communities on both local and systemic health [2–5], highlighting their essential role in disease prevention and progression.

Among the many interactions that the microbiome facilitates, the concept of microbial axes has emerged as a compelling area of investigation. These axes represent the bidirectional communication between microbiomes located in different regions of the body. Notable examples include the gut-brain axis, which links gut microbiota to neurological function and behaviour [6], and the gut-lung axis, which emphasizes how gut microbes influence lung immunity and disease [7]. These discoveries have opened new avenues for understanding how the microbiota can affect diverse body systems and have spurred interest in uncovering other potential microbiome axes.

A relatively nascent but promising concept is the nasal-gut microbiome axis, which posits that interactions between the nasal and gut microbiota may jointly influence host immunity and disease [8,9]. While the gut and nasal microbiomes have been studied separately, evidence suggests that dysbiosis (an imbalance in microbial communities) in one could have profound implications for the other. This cross-talk may be particularly relevant in diseases that involve immune dysregulation, such as asthma, chronic rhinosinusitis (CRS), and allergies, where both the gut and nasal microbiota may contribute to pathogenesis [10,11].

The rationale for examining this nasal-gut microbiome cross-talk lies in the potential to uncover shared mechanisms by which these microbiomes influence mucosal immunity and systemic inflammation. Exploring interactions between the nasal and gut microbiota, this review proposes a new framework that could reshape our understanding of immune system regulation. This concept is not only novel but also vital for advancing microbiome-based therapeutic approaches, such as dual-site microbiome modulation, which may offer new strategies for managing conditions like asthma, allergic rhinitis (AR), and other immune-

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mediated diseases.

Understanding the nasal-gut microbiome axis could provide a more integrated view of host-microbe interactions, highlighting the interconnectedness of different microbial ecosystems and their collective influence on health. This review seeks to explore this emerging field, providing a foundation for future research that may unlock novel diagnostic and therapeutic pathways for microbiome-related diseases.

2. Shared features of nasal and gut microbiomes

2.1. Microbial diversity

Although the nasal cavity and the gastrointestinal tract represent distinct anatomical and physiological environments, they form interconnected ecosystems through the nasal-gut axis, which operates independently from the well-characterized gut-lung interactions. While the gut-lung axis primarily involves systemic dissemination of microbial metabolites and immune cells, the nasal-gut axis features bidirectional communication through both direct microbial translocation and neural pathways, with unique nasal-specific taxa playing specialized roles in systemic immunity. Both microbiomes contribute to mucosal immunity and systemic homeostasis, and their disruption has been implicated in a range of inflammatory and infectious diseases (Fig. 1, Table 1).

The gut microbiome, residing in a nutrient-rich, anaerobic environment, is dominated by obligate anaerobes from the phyla *Firmicutes* and *Bacteroidetes*, including genera such as *Bacteroides, Faecalibacterium,* and *Clostridium*, which are crucial for short-chain fatty acid (SCFA) production and immune modulation [12,13]. In contrast, the nasal microbiome features a distinct community of aerotolerant and facultative genera including *Staphylococcus, Corynebacterium, Moraxella*, and *Streptococcus* that have evolved specialized adaptations to the nasal environment's exposure to ambient oxygen and environmental particulates [14].

Notably, certain nasal residents play unique systemic roles beyond airway protection. *Corynebacterium* species, for instance, can restrict *Staphylococcus aureus* colonization by producing antimicrobial metabolites and interfering with virulence signalling pathways [15], thereby shaping not only local microbial ecology but also systemic immune tone through reduced pathogen burden and altered host–microbe interactions. Similarly, *Dolosigranulum pigrum*, a nasal commensal, can enhance antiviral immunity in the respiratory tract by stimulating epithelial interferon responses: in human epithelial (Calu-3) cells, pre-treatment with *D. pigrum* 040417 significantly increases IFN-β and interleukin-6 (IL-6) production, decreases inflammatory chemokines (CXCL8, CCL5, CXCL10), and reduces SARS-CoV-2 replication and epithelial damage [16].

Table 1
Comparative Features of Nasal vs. Gut Microbiomes.

Feature	Gut Microbiome	Nasal Microbiome	Shared Influences
Dominant Taxa	*Bacteroides*, *Faecalibacterium*	*Staphylococcus*, *Corynebacterium*	Proteobacteria (increase in inflammation)
Diversity (Healthy)	High ($H' = 4.2 \pm 0.5$)	Low ($H' = 2.1 \pm 0.7$)	Reduced in urban environments
Key Disruptors	Antibiotics, low-fibre diet	Air pollution, smoking	Stress, systemic inflammation

The nasal-gut axis demonstrates distinctive characteristics compared to gut-lung interactions. While both axes involve microbial metabolite signalling, the nasal-gut connection features more rapid communication through the trigeminal and olfactory nerves [17,18], allowing nasal microbial compounds to directly influence central nervous system function and gut motility. Additionally, commensal bacteria in the nasal cavity can produce antimicrobial compounds, such as peptides from *Staphylococcus lugdunensis,* that influence local colonization resistance and epithelial immunity [19], suggesting that nasal microbiota can shape systemic or distal immune responses in ways that differ from the well-described gut–lung interactions.

Alpha diversity also differs between the two sites (Table 1). The gut consistently exhibits higher microbial richness and evenness, with a typical Shannon diversity index ranging from 3.5 to 5.0, compared to 1.5 to 3.0 in the nasal cavity [20,21]. This disparity is largely attributed to

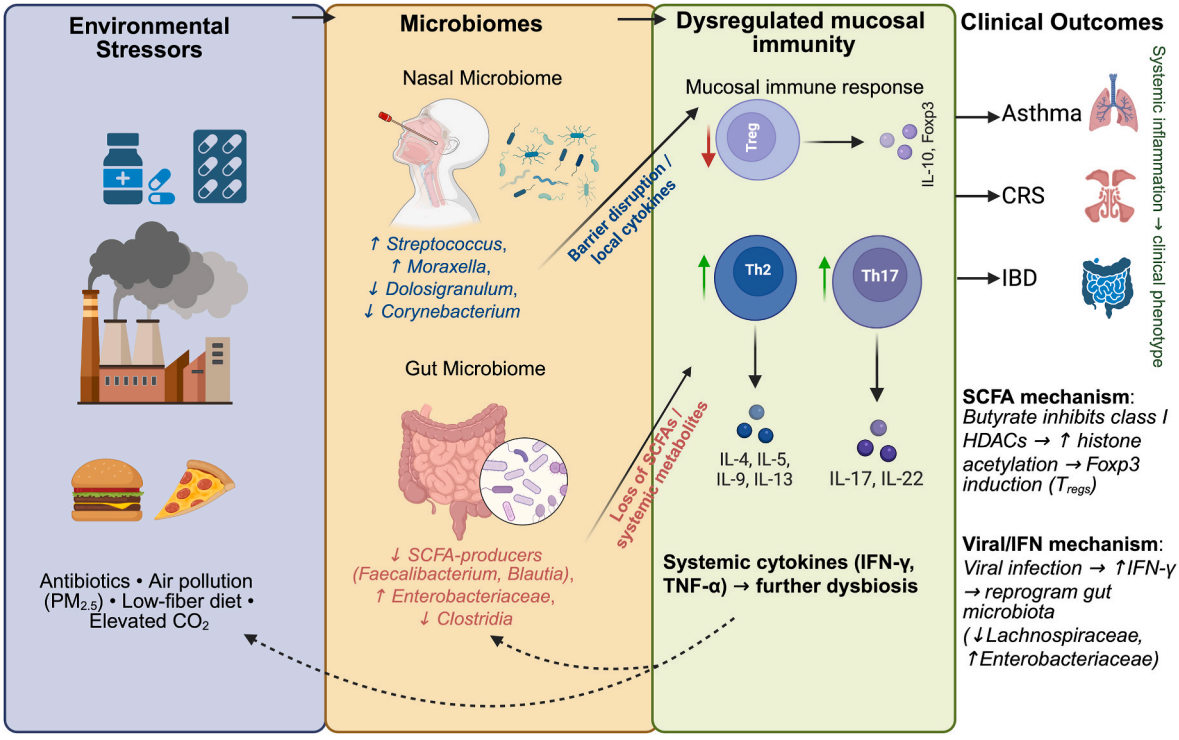

Fig. 1. Environmental–Microbiome–Immune Axis Model.

the gut's relatively stable internal environment and abundant substrate availability. Nonetheless, both microbiomes experience diversity loss in disease states. For example, reduced gut diversity has been linked to inflammatory bowel disease (IBD) [22], while diminished nasal microbial diversity is associated with CRS and AR [23].

Environmental factors play a crucial role in shaping microbial communities at both sites. Antibiotic exposure is a well-documented disruptor, with broad-spectrum agents such as amoxicillin reducing the abundance of beneficial *Bifidobacterium* in the gut and *Lactobacillus* in the nasal passages [24,25]. This disruption often permits opportunistic pathogens like *Clostridioides difficile* and *S. aureus* to flourish. Dietary composition further influences microbial ecology. A low-fibre, high-fat diet leads to a reduction in SCFA-producing *Clostridiales* in the gut [26], impairing epithelial integrity and immune regulation. Concurrently, excessive sugar intake has been associated with an increased abundance of *Staphylococcus* in the nasal microbiome [27], a shift that may exacerbate upper respiratory tract inflammation and sinusitis. Environmental pollution, particularly exposure to fine particulate matter ($PM_{2.5}$), exerts systemic effects on both microbiomes. Studies have shown that $PM_{2.5}$ exposure leads to a depletion of *Akkermansia* in the gut [28] and *Corynebacterium* in the nasal cavity [29], both of which are associated with mucosal barrier maintenance. This microbial depletion contributes to increased epithelial permeability, heightened inflammation, and greater susceptibility to allergic sensitization and infection.

2.2. Immune interactions

The nasal and gut microbiomes play important roles in shaping both local and systemic immune responses, and evidence suggests that they operate not as isolated systems, but as interconnected immunological hubs. At each site, the resident microbiota influences host immunity through antigen presentation, modulation of inflammatory signalling, and maintenance of epithelial barrier integrity (Fig. 1).

In the gut, commensal bacteria such as *Bacteroides fragilis* have been shown to induce colonic regulatory T cells (T_{regs}) through the expression of polysaccharide A (PSA), thereby suppressing pro-inflammatory T_h17 responses and promoting immune tolerance [30]. In the nasal cavity, the commensal bacterium *Corynebacterium accolens* does not directly induce TLR-2-dependent IL-10 secretion or anti-inflammatory macrophage polarization. Instead, it contributes to mucosal homeostasis via a 'gatekeeper' mechanism: it hydrolyzes host triacylglycerols into free fatty acids (e.g. oleic acid) [31], which inhibit common respiratory pathogens such as *Streptococcus pneumoniae*. Additionally, *C. accolens* has been shown to preserve epithelial barrier integrity and suppress epithelial IL-6 and IL-8 release in response to *S. aureus* supernatants [31], effects not mediated by IL-10 or TLR-2. These local immune interactions are essential for preventing chronic inflammatory conditions such as IBD and CRS, respectively.

Beyond their local effects, the nasal and gut microbiota also engage in systemic immune cross-talk. Gut-derived metabolites, including SCFAs like butyrate (an anti-inflammatory metabolite that exerts systemic effects), can enter the circulation and enhance antiviral responses in distal mucosal tissues. For instance, butyrate has been shown in a murine model to potentiate $CD8^+$ T-cell responses in the nasal mucosa during influenza infection, improving pathogen clearance [32]. Conversely, respiratory viral infections that trigger nasal production of interferon gamma (IFN-γ) have been observed to decrease the abundance of *Lactobacillus* species in the gut [33], illustrating a feedback loop often referred to as the gut–lung axis.

Dysbiosis at either site can amplify systemic inflammation. Elevated nasal levels of *Moraxella* have been associated with increased serum immunoglobulin E (IgE) [34], a marker of allergic sensitization, while gut overgrowth of Enterobacteriaceae is linked to heightened IL-6 production and worsened asthma severity [35,36]. These findings suggest that disruptions in microbial communities, whether in the upper airway or gastrointestinal tract, may exacerbate immune dysregulation across the mucosal network.

2.3. Environmental influences

As discussed in the microbial diversity section, environmental disruptors such as antibiotics, low-fibre diets, and fine particulate matter profoundly affect both gut and nasal ecosystems, not only altering taxonomic composition but also weakening mucosal barrier integrity and immune regulation (Fig. 1). Dietary exposures not only shape the microbial diversity of each site but also mediate inter-site interactions through metabolite signalling. For example, butyrate produced by gut commensals like *Roseburia* has been implicated in modulating nasal microbial ecology, suppressing potential pathobionts such as *Staphylococcus* via systemic epigenetic mechanisms, including histone deacetylase (HDAC) inhibition [37–40]. Similarly, food allergens such as peanuts have been shown to influence gut microbial composition, particularly reducing protective *Clostridia* species, which impairs the development of T_{regs} (e.g., $ROR\gamma t^+$), weakens intestinal barrier function, and promotes systemic T_h2-skewed immunity [41–43]. These changes contribute not only to food allergy but may also facilitate allergic airway inflammation through nasal–lung immune crosstalk.

Early-life microbial exposure is another crucial determinant. Children raised in farm environments tend to have increased exposure to diverse environmental microbes, which is associated with greater gut microbial diversity, particularly enrichment of *Clostridiaceae, Akkermansia*, and *Blautia* and a lower risk of allergic disease [44]. While exposure to farm dust may deliver beneficial nasal microbes like *Lactococcus* or *Acinetobacter* via inhalation [45], consistent evidence of their colonization in the nasal cavity or gut of farm-raised children remains limited. This early-life microbial exposure promotes immune tolerance by driving regulatory T cell differentiation through transforming growth factor-beta (TGF-β)–mediated mechanisms. Elevated SCFA production (e.g. butyrate, propionate) and exposure to environmental microbes induce T_{reg} expansion and IL-10 secretion, which collectively suppress T_h2-type allergic inflammation and are associated with substantially lower asthma risk in children [46–48].

However, it is important to note that most of these findings come from Western populations. Studies in non-Western contexts reveal both parallels and important distinctions. In Central Asia, rural Kazakh populations exhibit elevated *Ligilactobacillus* and *Sutterella* alongside higher microbial diversity, contrasting with urban microbiomes dominated by *Coprococcus* and *Parasutterella* [49]. Similarly, a study in Malaysia demonstrated that ethnicity significantly influences gut microbiome composition, explaining variation even after controlling for diet and environment [50]. Indian gut microbiomes show characteristically high abundances of *Prevotella copri* and enriched carbohydrate-active enzymes for digesting plant-based polysaccharides, reflecting traditional high-fibre diets [51,52]. These geographical and ethnic variations underscore that while the protective effects of microbial diversity may be universal, the specific taxonomic signatures associated with health can vary significantly across populations.

The process of urbanization appears to drive convergent microbial changes across geographical contexts, though with region-specific patterns. Urban residents in Kazakhstan show $\leq$5 % *Prevotella* abundance compared to ~25 % in rural counterparts [49], paralleling Western observations but with distinct taxonomic differences. These microbial shifts associated with urbanization demonstrate similar functional consequences across populations, as seen in studies of Indian immigrants to Canada who showed transition toward Westernized microbiomes (reduced *Prevotella*, increased *Bacteroides*) associated with dietary acculturation and increased inflammatory disease risk [51].

The stability and resilience of these microbial communities are also modulated by external pressures. Prolonged antibiotic use, particularly beyond five days, has been shown to cause lasting depletion of beneficial taxa such as *Faecalibacterium* in the gut and *Corynebacterium* in the nasal

cavity, leading to dysbiosis and increased susceptibility to conditions like CRS [53–55]. These shifts create ecological niches that can be exploited by opportunistic pathogens. Furthermore, climate change introduces additional complexity. For instance, elevated atmospheric carbon dioxide (CO_2) levels have been shown to increase pollen production and allergenicity in plants such as ragweed [56]. This heightened allergen exposure exacerbates mucosal inflammation, which in turn can disrupt both nasal and gut microbial communities, potentially favouring pro-inflammatory taxa and weakening colonization resistance. These climate-related effects may have particularly pronounced impacts in developing regions experiencing rapid environmental change alongside urbanization and dietary transitions.

3. Evidence of cross-talk and shared dysbiosis

Literature suggests that microbial imbalance at one mucosal site, whether the gut or nasal cavity, may ripple across and influence systemic immune regulation at the distant site. This framework offers information into why conditions such as asthma, AR, and CRS frequently coincide with gastrointestinal disorders.

3.1. Dysbiosis

Dysbiosis arises when a balanced microbial ecosystem becomes destabilised, marked by a decline in beneficial taxa, reduced taxa diversity, and the expansion of potentially inflammatory bacteria. In the gut, this commonly involves a loss of SCFA-producing genera such as *Faecalibacterium* and *Roseburia*, accompanied by an overgrowth of *Bacteroides* or *Enterobacteriaceae* (linked to Crohn's disease, ulcerative colitis, asthma, and metabolic dysfunction) (Table 2). In the nasal cavity, a parallel loss of protective taxa like *Corynebacterium* or *Dolosigranulum* and enrichment of *S. aureus*, *Streptococcus*, or *Moraxella* is commonly observed in CRS, AR, and uncontrolled asthma (Table 2).

A more evident pattern is beginning to emerge beneath these site-specific dysbiosis: immune and metabolic alterations that originate in one niche frequently correspond to compensatory or consequential changes in the other (Fig. 2A). Gut dysbiosis that impairs SCFA availability is associated with a skewing toward T_h2 immunity, which increases airway hyperresponsiveness [57] (Fig. 2B). In contrast, nasal dysbiosis that disrupts barrier integrity and increases local inflammation can potentiate systemic cytokine release and exacerbate intestinal inflammation through the gut–lung axis [58,59] (Fig. 2C).

3.2. Nasal-gut microbiome interaction

Beyond these correlative associations, evidence suggests active signalling between the sites. Circulating SCFAs produced in the gut modulate gene expression epigenetically, primarily by inhibiting class I HDACs, thereby enhancing histone acetylation and bolstering regulatory T-cell differentiation [60]. This barrier-stabilising and anti-inflammatory effect can reach the mucosal immune environments of the nasal cavity, even in the absence of direct microbial contact [40]. Conversely, nasal dysbiosis and inflammation, such as that induced by viral infection or microbial imbalance, can lead to local cytokine release (e.g., IFN-γ, IL-1β). These cytokines enter systemic circulation and drive alterations in gut microbial communities, depleting beneficial taxa like *Lachnospiraceae* and promoting expansion of pathobionts [33], thereby inducing intestinal barrier dysfunction and mucosal inflammation through established gut–lung immune pathways [61].

SCFAs and other microbial metabolites produced in the gut engage host receptors, including FFAR2 (GPR43), FFAR3 (GPR41), GPR109A, and the aryl hydrocarbon receptor (AhR), to modulate epithelial barrier integrity, immune cell differentiation, and cytokine production [11]. These metabolite-receptor interactions not only shape gut immunity but can also influence distal mucosal sites, including the nasal mucosa, by enhancing regulatory T-cell responses, suppressing T_h2/T_h17 skewing, and supporting mucosal tolerance, thereby providing a mechanistic link for gut–nasal immune cross-talk [62]. These receptor-mediated pathways converge on canonical intracellular hubs: SCFA-driven histone deacetylase inhibition and AhR activation modulate gene expression, while bile-acid signalling and nutrient cues regulate mTOR activity [63–66]. Downstream, mTOR and NF-κB integrate metabolic and pathogen-sensing inputs to control cytokine production, cell survival, and barrier function. These pathways are pivotal in mucosal immunity, with gut-derived metabolites influencing both intestinal and nasal immune responses through shared signalling mechanisms [9]. Autophagy is another central node: microbial ligands and metabolites can either stimulate or suppress autophagic flux in epithelial and immune cells, thereby affecting antigen processing, intracellular pathogen handling and secretion of antimicrobial peptides [67].

Some studies underscore a shift from viewing mucosal diseases as site-specific conditions to understanding them as outcomes of interconnected microbial–immune ecosystems involving parallel shifts in microbial metabolism and immunity across anatomically distinct mucosal surfaces. For example, bronchiectasis involves coordinated gut–lung microbial network dysbiosis linked to disease severity; gut dysbiosis in PAH is associated with parallel pulmonary pathology; and microbial metabolites like SCFAs exhibit immune-modulatory effects that span beyond the gut [68,69] (Fig. 2D). Also, asthma is marked not only by gut microbial depletion of SCFA–producing taxa but also by an upper airway microbiome enriched in *Proteobacteria*, most notably *Moraxella*, that may perpetuate T_h2-driven inflammation and increase exacerbation risk [70–72]. While most data come from cross-sectional cohorts or pre-clinical models, they support this wider conceptual framework. Ongoing longitudinal profiling, multi-omic network analysis, and interventional trials that address multiple mucosal sites may soon enable a paradigm shift toward treating mucosal disorders through ecosystem-wide strategies rather than organ-specific approaches.

3.3. Immune cell networks orchestrating Nasal–Gut crosstalk

Literature reveals that the mucosal immune system functions as an integrated network rather than isolated epithelial compartments. Key among the mediators of this cross-compartmental communication are dendritic cells (DCs), which not only sample antigens locally but also imprint tissue-specific homing cues on naïve T cells, enabling coordinated immune responses across distant mucosal sites such as the gut and nasal cavity.

In the gut-associated lymphoid tissue (GALT), $CD103^+$ DCs, particularly those located in the small intestine and mesenteric lymph nodes produce retinoic acid (from vitamin A metabolism), which imprints gut-homing markers such as CCR9 and α4β7 integrin on naïve T cells [80,

Table 2
Dysbiosis signatures in key diseases.

Disease	Gut Dysbiosis Features	Nasal Dysbiosis Features	Reference
AR	↓ *Faecalibacterium*, ↑ *Bacteroidetes*	↑ *Streptococcus*, ↓ *Corynebacterium*	[9,73]
Asthma	↓ SCFA producers, ↑ *Enterobacteriaceae*	↑ *Moraxella*, ↓ *Dolosigranulum*	[74,75]
CRS (eCRSwNP)	↓ *Faecalibacterium*, ↓ *Akkermansia*	↑ *S. aureus*, ↓ *Lactobacillus*	[76,77]
IBD	↑ *Proteobacteria*, ↓ *Clostridium* IV cluster	Not applicable	[78,79]

* eCRSwNP: eosinophilic chronic rhinosinusitis with nasal polyps.

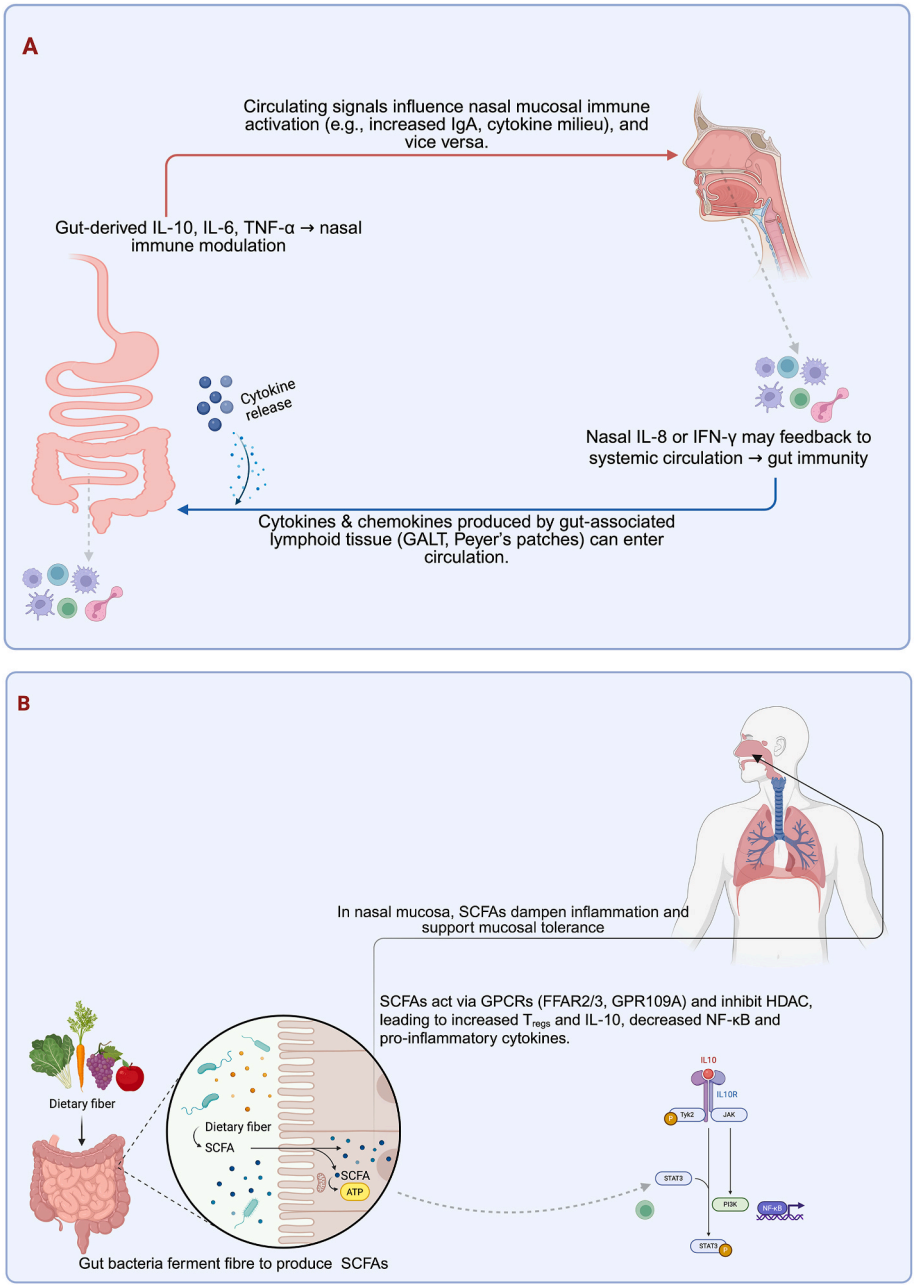

Fig. 2. Mechanisms of Immune and Microbial Cross-Talk Between Gut and Nasal Compartments. A: Immune Signalling (Gut ↔ Nasal). B: Microbial Metabolites (SCFAs). C: Epithelial Barrier Integrity. D: Gut Derived Immune Priming.

81]. These cells can then migrate to the intestinal lamina propria, where they contribute to immune surveillance and tolerance. $CD103^{+}CD11b^{+}$ DCs further modulate T cell differentiation, promoting T_h17 responses in the presence of microbial signals like segmented filamentous bacteria, via secretion of IL-6 and IL-23 [82]. In parallel, CX_3CR1^{+} phagocytes extend dendritic processes into the gut lumen to sample antigens and relay them to $CD103^{+}$ DCs through gap junctions, supporting antigen presentation and T_{reg} induction [82]. These coordinated activities illustrate how gut DCs both control local tolerance and prime lymphocytes that can recirculate to other mucosal tissues.

Similarly, in nasal-associated lymphoid tissue (NALT), DCs capture inhaled antigens and migrate to regional lymph nodes, such as cervical nodes where they initiate adaptive immune responses. Nasal delivery of antigen with specific adjuvants can expand $CD8^{+}$ DC populations in NALT, leading to robust antigen-specific responses, including IL-4–mediated T_h2 skewing [83,84]. These mechanisms parallel those seen in Peyer's patches and highlight conserved immune programming across mucosal sites [81].

DCs serve not only as local antigen-presenting cells but also as vehicles for mucosal immune integration. In Peyer's patches, DCs access luminal antigens either directly through M cells or by sampling IgA–antigen complexes [85,86]. A similar process is observed in NALT, where DCs intercept inhaled particles for presentation to T and B cells [87]. Both GALT and NALT are part of the broader mucosa-associated lymphoid tissue (MALT) system, structurally resembling lymph nodes, containing high endothelial venules (HEVs) and a rich milieu of immune cells that coordinate antigen processing and lymphocyte activation [88, 89]. In a well-characterized mouse model, respiratory (lung) dendritic cells were shown to induce expression of gut-homing integrin α4β7 and CCR9 on $CD4^{+}$ T cells following intranasal immunization, thus

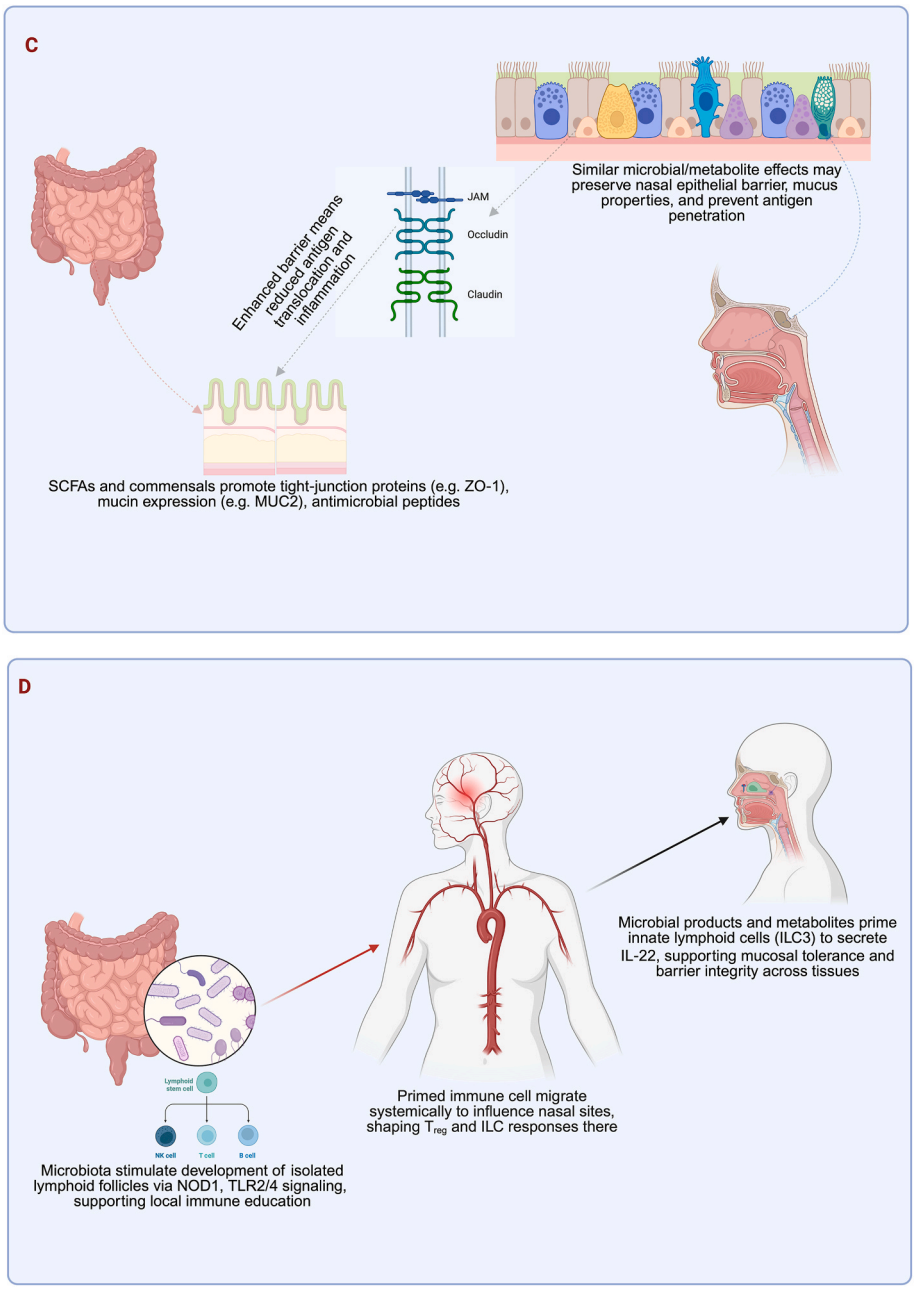

Fig. 2. (*continued*).

showcasing functional bidirectional mucosal cross-talk. These gut-imprinted T cells migrated to the intestinal mucosa and provided protective immunity against oral *Salmonella*, demonstrating functional mucosal cross-talk across disparate immunological compartments [90].

While DCs are pivotal, a wider cellular network orchestrates nasal–gut immune crosstalk. T_{reg} cells induced by DCs in one compartment can home to another mucosal site and impose tolerance there, whereas effector T cell subsets such as T_h2 and T_h17 populations contribute to site-specific inflammation that may have systemic repercussions. Innate lymphoid cells, particularly type 3 innate lymphoid cells (ILC3s) and type 2 innate lymphoid cells (ILC2s), respond rapidly to microbial or cytokine signals (e.g., IL-33, IL-25, IL-1β, IL-23), playing crucial roles in epithelial barrier maintenance, epithelial repair, and mucosal homeostasis via production of cytokines like IL-13 and IL-22. While predominantly tissue-resident, ILC2s have the capacity to migrate under inflammatory conditions, and importantly, ILC-derived soluble mediators (such as IL-22) can exert immunomodulatory effects at distal sites, illustrating an extensive scope of mucosal cross-talk. Macrophages and monocyte-derived cells in both gut and nasal tissues participate in antigen clearance, cytokine production and regulation of local homeostasis; shifts in their activation state can therefore propagate inflammatory or tolerogenic signals across compartments [91,92]. Plasmacytoid dendritic cells (pDCs) are essential mediators of antiviral defence, rapidly producing IFN-I that shape adaptive immune responses (e.g., T, B, NK cells) in response to viral activation of TLR7/TLR9. Moreover, pDC trafficking and functionality are influenced by microbiota-dependent chemokine cues (e.g., CCL2/CCR2), and pDCs integrate microbial signals, such as the previously mentioned *B. fragilis* PSA to promote regulatory T-cell mediated immunoregulation via IL-10 induction [93,94]. B-cell responses and mucosal IgA production, shaped by DC–T cell interactions provide another mechanism by which nasal mucosal immunity can influence microbial ecology and immune protection at distant sites. In NALT, antigen exposure elicits germinal-centre formation and IgA^+ B-cell expansion via DC–T-cell help [95]. Mucosal IgA,

traditionally known for its homeostatic role in the gut, coats commensal microbes to maintain microbial diversity and immune tolerance [96]. Furthermore, secreted nasal IgA localizes to the nasal turbinate and glandular acini following NALT activation [97], illustrating functional distribution of protective IgA responses.

Multiple trafficking pathways and soluble carriers enable DCs and other immune cells to mediate inter-site communication. Migratory DCs and lymphocytes traverse between tissues and lymph nodes via lymphatic drainage, high endothelial venules (HEVs), and sphingosine-1-phosphate (S1P)-dependent egress, whereas extracellular vesicles and soluble cytokines allow for systemic immune modulation without requiring physical cell migration [98–100]. These cellular and molecular routes create a flexible network capable of both local defence and coordinated multi-site responses to microbial and environmental perturbations.

4. Clinical relevance: microbiome-based therapeutic innovations

4.1. Microbiome-based therapies

The crosstalk between the nasal and gut microbiomes suggests that co-targeting both sites may yield new treatments for respiratory and allergic diseases. For example, oral probiotics (such as *Lactobacillus* and *Bifidobacterium* strains or synbiotic combinations) or synbiotics can restore gut microbial balance and expand T_{regs} and SCFAs that suppress T_h2 inflammation in the lungs [101,102]. Likewise, tailored nasal microbiome therapies can directly neutralize pathogens: *Corynebacterium pseudodiphtheriticum*, a commensal nasal bacterium, produces factors that selectively kill *S. aureus* (including Methicillin-resistant *S. aureus*) in the sinuses, thereby helping to dismantle chronic biofilms [103]. Clinical studies already hint at dual-site synergy. For instance, oral synbiotic supplementation (e.g., *Lactobacillus/Bifidobacterium* plus inulin or fructo-oligosaccharide) has been shown in randomized controlled trials to reduce clinical symptoms and IgE levels in AR, outperforming either component alone [104–106]. Similarly, oral probiotics (such as *L. paracasei* and *L. fermentum*) may reduce asthma exacerbations and improve lung function [107,108]. While combined oral and nasal microbiome interventions have not yet been directly tested, emerging data point to their potential for synergistic benefits. Even faecal microbiota transplantation (FMT) is being explored: preliminary data from animal asthma models demonstrate that FMT from healthy donors can replenish gut microbiota (including SCFA-producing taxa like *Prevotella*), thereby boosting SCFA levels that modulate immune responses systemically, supporting lung immunity and attenuating airway inflammation via the gut–lung axis (e.g. enhanced T_{reg} numbers, reduced T_h2/T_h17 skewing) [109,110].

4.2. Dual-site microbiome monitoring

Concurrently monitoring both nasal and gut microbiomes holds promise for precision diagnostics and therapy. In a recent paediatric study, full-length 16S rRNA sequencing of stool and nasal swabs from children with combined AR, eczema, and food allergy revealed distinct multi-site microbial signatures: genera such as *Peptoniphilus*, *Prevotella* and *Anaerococcus* were enriched in the gut, whereas taxa like *Pseudomonas* were overrepresented in nasal/skin samples of affected children [111]. This illustrates how integrated nasal–gut profiling can uncover disease-associated taxa that single-site surveys miss. However, most studies to date derive from Western populations, raising concerns about their global applicability. For instance, research on paediatric Crohn's disease in Saudi Arabia revealed gut microbial alterations, such as depletion of *Roseburia*, *Clostridium*, and *Lactobacillus*, and enrichment of *Fusobacterium* and *Peptostreptococcus*, similar yet distinct from Western profiles [112]. Studies of healthy nasal and gut microbiota across geographic, ethnic, and lifestyle contexts have also shown substantial divergence; hunter-gatherer and rural populations, for example, harbour dominant *Prevotella* and *Spirochaetes*, whereas Westernized communities are enriched in *Bacteroides* and *Firmicutes* [113–115]. Moreover, a large cohort study in Amsterdam demonstrated that immigration and generational shifts reshape gut microbiome clusters, with *Prevotella* declining and *Bacteroides/Blautia/Bifidobacterium* increasing in second-generation groups [116].

Metabolomic profiling has been successfully applied to link gut-derived SCFAs and other microbial metabolites to patient phenotypes (e.g., asthma, food allergy) [117], while nasal lipidomics can reveal inflammatory signatures (e.g., arachidonic acid) and mitochondrial dysfunction in sinus disease [118,119]. Meanwhile, metatranscriptomics enables identification of active microbial pathways in each niche, beyond static taxonomic analysis by capturing transcriptionally expressed genes even in seemingly similar communities [120]. Advanced computational approaches are being developed to interpret such datasets. For instance, metabolomic profiling across multiple biofluids has revealed that gut-derived SCFAs such as butyric and acetic acid correlate with allergic indicators like mite-specific IgE in children with asthma, indicating that SCFA signatures can reflect and potentially predict disease phenotypes across compartments [121]. Similarly, integrative lipidomic–immune profiling in CRS has revealed that altered fatty acid metabolism, particularly involving arachidonic acid-derived lipids, is associated with distinct immune endotypes. For example, metabolomic signatures of enhanced unsaturated fatty acid oxidation correlate with eosinophilic inflammation and IL-5 expression, while increased uric acid aligns with neutrophilic cytokines like IFN-γ and IL-8 [122]. Lipidomic analysis further highlights enrichment of arachidonate-containing cholesteryl esters in nasal polyp tissue, reinforcing the link between lipid metabolism and immune activation in CRS [123]. Even consumer-focused firms have begun offering AI-enhanced microbiome analysis. Some integrate saliva, stool, and blood data for personalized dietary and supplement guidance via metatranscriptomic profiling, while others employ large language models to interpret gut microbiome data for tailored recommendations. Though integrated nasal–gut kits are not yet documented, these platforms reflect a movement toward microbiome-informed precision health. Implementing such strategies faces real challenges, especially standardizing nasal sampling (e.g., swab versus lavage, brushes) and accounting for spatial heterogeneity within the sinuses, but the potential for richer, dual-site biomarkers is clear.

4.3. Microbial modulation in respiratory health

Studies are illuminating why dual modulation works. Gut-derived SCFAs (especially butyrate and propionate) are known to signal through receptors like GPR43 on lung immune cells, reducing pro-inflammatory cytokines (e.g. IL-6, IL-8) and enhancing pathogen clearance. In fact, experiments in high-fibre diet models show that elevated SCFAs reduce neutrophil-driven airway inflammation while improving viral and bacterial lung immunity [32]. Similarly, certain airway commensals "train" local defences: airway *Prevotella* species activate TLR2-dependent pathways and induce neutrophil TNFα responses, accelerating clearance of *S. pneumoniae* in infection models [109]. These bench-side insights are now inspiring new treatments. For example, phage therapy has re-emerged for CRS: intranasal sprays of bacteriophage cocktails targeting *S. aureus* (such as AB-SA01) have been shown to safely reduce sinus pathogen burden, acting only on the pathogen while sparing beneficial flora [124]. Beyond increasing SCFA producers like *Bacteroides*, recent studies highlight how dietary fibres can selectively modulate the functional capacity of the microbiome, reshaping microbial metabolic pathways related to mucosal immunity. For instance, fibre-driven microbiota shifts promote production of secondary metabolites such as indole derivatives and phenolic acids, which have been shown to enhance epithelial barrier integrity in both the gut and upper airway mucosa via activation of the AhR [125–127]. This receptor

signalling pathway fine-tunes local immune tolerance by upregulating IL-22, which activates epithelial STAT3 to enhance antimicrobial peptide and mucin expression, and by directly regulating Muc2 production in epithelial cells, thereby strengthening barrier defences against pathogens such as *Moraxella* [128,129].

As earlier stated, a high-fibre diet increases circulating levels of SCFAs and protects against allergic airway inflammation by altering bone marrow haematopoiesis, producing lung dendritic cells with reduced T_h2-promoting ability and enhanced phagocytic function [130]. Similarly, fibre-derived SCFAs, such as propionate, alter innate immune responses and ameliorate allergic airway diseases [130]. Feeding patterns themselves can modulate host–microbe interactions: time-restricted feeding restores diurnal oscillations in gut microbial composition and function, aligning microbial activity with host circadian rhythms [131]. Such alignment has been shown to improve immune regulation and metabolic homeostasis [132], providing a plausible pathway through which dietary timing could influence airway inflammatory diseases.

Looking ahead, next-generation microbiome-based therapies are on the horizon. The previously mentioned *C. pseudodiphtheriticum* has been shown to exploit virulence pathways of *S. aureus* in a contact-independent antimicrobial strategy, suggesting new avenues for live probiotic interventions [103]. Meanwhile, recombinant endolysin engineering, including formulation with nanoparticle or delivery systems is advancing rapidly as a promising method to target resistant pathogens [133]. While commercial platforms profiling the combined nasal and gut microbiome at birth are not yet documented, studies have shown that neonatal gut microbiome signatures alone can predict later allergic outcomes. For example, one-month-old infants with specific microbial patterns were three times more likely to develop asthma or allergic reactions, and *Bifidobacterium*-dominant enterotypes, associated with higher propionate, were linked to lower food sensitization risk [134,135].

5. Research gaps and future directions

5.1. Current knowledge limitations

Despite evidence supporting nasal–gut microbiome interactions, several knowledge gaps persist. Direct mechanistic evidence of bidirectional communication remains limited, with most human studies relying on correlational data rather than causal demonstrations. Concurrent sampling of both microbiomes is rare, as only a minute percentage of published microbiome studies in asthma or CRS analyse nasal and gut communities simultaneously. Furthermore, existing research disproportionately focuses on disease states, creating a deficit in understanding baseline microbiome dynamics in healthy individuals across the lifespan.

5.2. Priority research areas

Large-scale birth cohorts tracking nasal and gut microbiomes from infancy are essential. Longitudinal research from the COPSAC cohort has shown that infants with low gut *Bifidobacterium* and overall immature microbial composition at 1 year of age are at a significantly increased risk of developing asthma by age 5, particularly among children of asthmatic mothers [136–138], but equivalent nasal–gut temporal data are lacking. Future studies could incorporate standardized sampling protocols, such as matched nasal swabs and stool collections, alongside environmental exposure tracking that records diet, antibiotic use, and pollution levels. These studies could also include multi-timepoint immune profiling, for example, measuring cytokines and SCFAs. Such designs could identify essential developmental windows during which microbiome interventions might prevent progression along the allergic march.

Beyond 16S rRNA sequencing, integrated metagenomic, metabolomic, and transcriptomic approaches are needed to resolve functional interactions. Metatranscriptomics could reveal how gut-derived metabolites, such as butyrate, regulate gene expression in nasal epithelial cells. Similarly, metabolomic profiling of paired serum and nasal lavage samples may identify systemic mediators that link gut dysbiosis to upper airway inflammation. Applying machine learning pipelines to these multidimensional datasets could uncover predictive biomarkers for diseases such as eosinophilic chronic rhinosinusitis (eCRS).

Based on literature, it is plausible to hypothesize that combined oral administration of *Lactobacillus rhamnosus* GG with nasal probiotic application (e.g., *Lactococcus lactis* W136 or other anti-inflammatory commensals) might provide superior outcomes in CRS compared to targeting either site alone. While not yet tested, this rationale is supported by single-site evidence showing symmetric benefits and tolerability [139,140]. Well-designed clinical trials must therefore evaluate dual-microbiome modulation strategies. Although specific studies have not yet tested whether high-fibre diets augment the efficacy of nasal probiotics, current evidence supports key foundational mechanisms. High-fibre intake increases systemic SCFA levels that enhance lung immune regulation and suppress type 2 inflammation. This provides a strong rationale for future trials examining whether dietary fibre can synergize with nasal probiotic interventions.

Phage therapy holds promise for treating recalcitrant *S. aureus* sinus disease. In early human trials, intranasal administration of the AB-SA01 phage cocktail was safe and well-tolerated, with preliminary signs of efficacy in CRS [124]. Ex vivo studies further demonstrate that phage cocktails can effectively disrupt *S. aureus* biofilms from CRS patients and reduce the risk of resistance development [141]. Importantly, case reports show clinical benefit in MRSA-associated CRS when phages are used systemically and intranasally [142]. Also, phage therapy appears to preserve gut microbiome stability, offering an advantage over conventional antibiotic treatments [143]. Advancing this field requires collapsing rigid academic divisions. ENT specialists and gastroenterologists could co-develop registries with matched nasal and gut samples from patients with comorbid conditions such as asthma and IBD. Microbiologists and immunologists must work together to establish consensus on sampling protocols, such as nasal swab versus lavage, and on standardised metadata reporting. Partnerships with industry could accelerate translational solutions, including inhaled postbiotic nanoparticles or microbiome-based diagnostic panels.

5.3. Key challenges

Several substantive barriers remain. Spatial heterogeneity is a major issue, as sinus sub-niches such as the middle meatus and sphenoethmoidal recess harbour distinct microbial communities [144], complicating nasal sampling. Ethnic and racial variability also affects microbiome composition, yet studies disproportionately involve Western populations, limiting generalisability [145]. Finally, socioeconomic barriers could exacerbate health inequities if microbiome-based therapies remain costly and inaccessible.

6. Conclusion

The evidence reviewed supports the view that the nasal–gut microbiome axis is an integral component of mucosal immunity and systemic health. The studies discussed highlight that the nasal and gut microbiota are not isolated entities but parts of a connected microbial–immune network, capable of influencing each other through immune signalling, microbial metabolites, and barrier integrity. These interactions have clear clinical relevance, shaping susceptibility to conditions such as asthma, chronic rhinosinusitis, and allergic disease.

While the concept is compelling, many of the mechanisms remain only partially understood. Advancing this field will require coordinated efforts to collect concurrent nasal and gut data, apply multi-omic

approaches, and design intervention trials that address both sites simultaneously. Such work has the potential to uncover key developmental windows for prevention, refine diagnostic tools, and guide targeted therapies that restore balance across the mucosal network.

There is now an opportunity for the microbiome research community to embrace this integrated perspective and explore the nasal–gut axis with the same depth given to the gut–brain or gut–lung axes. Doing so could open the way for innovative microbiome-based therapies, whether through diet, probiotics, postbiotics, or phage therapy that work across compartments to improve health outcomes. Analysing microbial communities within the nasal cavity alongside immune markers enables researchers to detect shifts that correlate with respiratory infections, antimicrobial resistance, environmental exposures, and zoonotic spillovers.

CRediT authorship contribution statement

Jude Oluwapelumi Alao: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Conceptualization. **Favour Oluwadara Bamigboye:** Visualization.

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