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The influence of the microbiome on the development and course of bronchial asthma – a comprehensive review

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Abstract

Background

Asthma is a chronic airway disease increasingly linked to alterations in the human microbiome. Early-life disruptions in gut, airway, and skin microbiota are associated with impaired immune maturation and higher susceptibility to asthma and allergies.

Aim

The aim of this study is to review current knowledge on how the human microbiome influences the development, course, and severity of bronchial asthma, including its role in immune regulation, asthma phenotypes, the gut-lung axis, and potential microbiome-based therapies.

Materials and Methods

This review integrates current evidence using literature from PubMed, Google Scholar, and academic texts with keywords related to the microbiome, gut–lung axis, asthma, dysbiosis, and microbiome-targeted interventions. Experimental, cohort, and clinical studies were analysed.

Results

The microbiome plays a crucial role in asthma development, especially early in life. Microbial composition is shaped by delivery mode, breastfeeding, antibiotic exposure, and environmental diversity. Cesarean delivery and persistent dysbiosis increase asthma risk, while breastfeeding promotes protective profiles. Early gut dysbiosis - such as reduced SCFA-producing bacteria - affects immune maturation and contributes to distinct asthma phenotypes. Airway colonization by Proteobacteria (e.g., *Haemophilus, Moraxella*) is associated with severe disease, steroid resistance, and frequent exacerbations. Microbiome-targeted strategies, including probiotics, postbiotics, and fecal microbiota transplantation, show therapeutic potential.

Conclusions

The microbiome is a key regulator of immune development and a major contributor to asthma risk. Microbiome-based interventions are promising but require further well-designed clinical research.

Keywords: microbiome, gut microbiota, gut-lung axis, bronchial asthma, dysbiosis, probiotics, prebiotics

1. Introduction

Asthma remains one of the most prevalent chronic respiratory diseases worldwide, affecting more than 300 million people [1] and contributing substantially to global morbidity and healthcare costs. It is defined as a heterogeneous airway disease characterized by chronic inflammation and variable bronchial remodeling, leading to time-varying respiratory symptoms, airflow limitation and bronchial hyperresponsiveness, with a variable course and response to treatment [2]. The pathophysiology of bronchial asthma is complex and multifactorial, encompassing genetic susceptibility, environmental influences (such as allergens, air pollutants, respiratory infections), and immune dysregulation characterized by T helper 2 (Th2)-dominant inflammation, IgE production, and eosinophilic airway infiltration [3]. Despite significant advances in understanding its immunopathogenesis, the variability in clinical phenotypes, disease progression, and treatment response indicates that other modulatory factors may be involved.

In recent years, increasing attention has been directed toward the human microbiome, an integral yet often overlooked component influencing host health. The microbiome refers to the community of microorganisms that coexist within a specific environment, together with their genetic material, metabolites, and surrounding conditions that shape their interactions [4]. These microbial communities play essential roles in digestion, metabolism, immune maturation, contributing to the maintenance of host homeostasis [5].

Scientific evidence indicates that the composition of the gut microbiota can influence respiratory health through immunological and metabolic interactions, commonly referred to as the gut-lung axis. Early microbial colonization has been shown to affect immune system development, promoting tolerance to environmental antigens and reducing the risk of allergic sensitization [6]. Conversely, disturbances in microbial balance - known as dysbiosis - have been implicated in allergic and inflammatory diseases, including asthma. Both the intestinal and airway microbiota are now recognized as potential modulators of disease onset and severity [1].

Against this background, the present narrative review aims to summarize and critically evaluate current evidence on the influence of the microbiome - particularly intestinal and respiratory - on the development, clinical course and treatment response of bronchial asthma. We highlight findings from experimental, epidemiological, and clinical studies and discuss potential implications for microbiome-targeted preventive and therapeutic interventions.

Aim

The aim of this study is to review current knowledge on the influence of the human microbiome on the development and course of bronchial asthma. The paper will discuss the characteristics of the gut and respiratory microbiome, their role in immune regulation, and their relationship with asthma phenotypes and severity. It will also outline key immunological mechanisms within the gut-lung axis and highlight potential therapeutic approaches, including probiotics, prebiotics, and microbiome-based interventions.

The collected data were carefully analyzed to identify consistent findings, methodological limitations and emerging research trends.

2. Research materials and methods

2.1 Data collection and analysis

A comprehensive literature review was conducted using the PubMed and Google Scholar databases. The search included keywords such as microbiome, gut microbiota, gut-lung axis, bronchial asthma, dysbiosis, probiotics, and prebiotics.

The analysis focused on studies exploring the relationship between the microbiome and the development and course of bronchial asthma, including its immunological mechanisms and potential therapeutic implications.

3. Research results

3.1 The human microbiome and its importance for the immune system

3.1.1 Characterization of the gut and respiratory microbiome

In healthy individuals, the gut and respiratory microbiomes exhibit high diversity and stability, which are essential for maintaining immune balance and defending against pathogenic microbes.

Gut Microbiome

The human gut microbiome comprises trillions of microorganisms, along with their genes and metabolic products, forming a complex ecosystem that establishes itself from birth. Microbial density and composition vary along the gastrointestinal tract: the small intestine contains relatively low numbers of microbes - up to several hundred million per gram - including oxygen-tolerant Firmicutes and Proteobacteria. In contrast, the colon hosts dense, largely anaerobic populations (up to 10^{11} cells per gram), predominantly Firmicutes

(Ruminococcaceae, Lachnospiraceae), Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia such as *Akkermansia* [7].

Environmental gradients, including pH, oxygen levels, redox potential, mucus, bile, and immune factors, along with physical features such as gut architecture and transit time, strongly influence microbial distribution. In the small intestine, microbial communities in the duodenum and jejunum participate in nutrient processing, bile acid metabolism, and modulation of local immune responses. In the colon, specialized bacteria degrade mucus and ferment dietary fibers to produce short-chain fatty acids (SCFA) like acetate, propionate and butyrate, which help regulate immune function and maintain metabolic balance. The gut microbiome is highly individualized, dynamic, and responsive to diet, lifestyle, and pharmacological interventions, making it a crucial determinant of health and a target for therapies such as fecal microbiota transplantation [7].

Respiratory Microbiome

The upper respiratory tract of healthy individuals - encompassing the nasopharynx and oropharynx - is dominated by bacterial phyla such as Firmicutes, Actinobacteria, and Bacteroidetes, with key genera including *Streptococcus*, *Corynebacterium*, *Dolosigranulum*, and *Veillonella*. The lower airways, once believed to be sterile, contain a low-density but metabolically active microbial community, largely seeded from microaspiration and dispersal from the upper airway. A balanced respiratory microbiome contributes to mucosal immune tolerance, helps prevent the overgrowth of pathogens, and supports effective antiviral and antibacterial defenses [1].

3.1.2 The gut-lung axis and communication between the microbiota and the immune system

The gut-lung axis refers to the bidirectional relationship between the gut and lung microbiota and the immune system, forming an interconnected network that influences immune function and susceptibility to respiratory diseases [8,9]. The gut microbiota affects pulmonary immunity through its metabolites, such as SCFA, as well as bacterial structural components like lipopolysaccharide (LPS), which activate various immune signaling pathways [10]. Signals originating in the gut can stimulate $CD8^+$ T cells, Th17 cells and influence the production of cytokines including IL-25, IL-13 and PGE2, thereby modulating immune responses within the lungs [8]. The gut-lung axis also involves processes such as the migration of immune cells and the circulation of microbiota-derived metabolites throughout the body [11].

The microbiota plays a key role in shaping immune development - especially early in

life, and disturbances in its composition may predispose individuals to allergic and inflammatory respiratory conditions [12], a topic that will be discussed further in the following sections of our article.

Disruptions of the gut-lung axis are associated with an increased risk of asthma, respiratory infections and chronic obstructive pulmonary disease [11].

3.1.3 The influence of the microbiome on the regulation of the immune response

The gut microbiota plays a crucial role in the development and function of the enteric nervous system (ENS). Bacterial metabolites, including tryptophan derivatives, activate the aryl hydrocarbon receptor (AHR) in enteric neurons, regulating their maturation, excitability, and intestinal motility. Microbial signals also engage toll-like receptors (TLR2 and TLR4), promoting neuronal survival and the generation of new enteric neurons. Additionally, the microbiota stimulates enterochromaffin cells to release serotonin, which activates ENS neurons, initiates motor reflexes, and integrates gut signals with the nervous system. Indirectly, the microbiota modulates gut immune responses, with cytokines such as IL-33 influencing neuronal activity and intestinal homeostasis. Overall, the microbiota shapes ENS development, excitability, and function, integrating neural, immune, and metabolic signals to maintain proper motility and gut homeostasis [13,14].

The gastrointestinal tract hosts approximately 70-80% of the body's immune cells, and through continuous interactions with the intestinal epithelium, the gut microbiota generates immune signals essential for maintaining epithelial integrity and mucosal homeostasis, with studies in germ-free and gnotobiotic mice demonstrating that commensal microbes shape the development and function of both innate and adaptive immunity, while disturbances in microbiota composition can disrupt this balance and lead to excessive inflammation [15]. Innate immune recognition begins with intestinal epithelial cells, which detect microbial molecules through pattern-recognition receptors (PRRs). Activation of these receptors induces protective cytokine and chemokine responses, while excessive activation can lead to inflammatory or autoimmune disorders. Epithelial cells also produce antimicrobial peptides, the expression of which is strongly influenced by the microbial composition [15].

Microbiota-derived metabolites, including SCFA, tryptophan metabolites, and bile acid derivatives, modulate immune responses by promoting epithelial repair, regulating T and B cell differentiation, controlling inflammation, and influencing systemic immunity through circulating microbial products [15].

The gut microbiome has a particularly profound impact on T-cell differentiation,

including the balance between Th1, Th2, Th17, and regulatory T-cells. Through these mechanisms, commensal microbes support appropriate immune activation, enhance pathogen clearance, and prevent excessive inflammation. Dysbiosis, therefore, compromises both local and systemic immune responses [16,17].

Another study showed that children with a high cesarean section-associated microbial score at 1 year of age exhibit a weaker immune response in the airways during acute infections compared to those with a low microbial score. This diminished response involves multiple key immune mediators, including IL-12p70, TNF-α, IL-4, IL-13, IL-1β, and chemokines such as CCL4, CCL11, CCL13, and CXCL8 [18].

3.1.4 The impact of the microbiome on allergic responses

Some epidemiological studies supported the "hygiene hypothesis": children raised on farms [19] or attending day nursery early [20] showed a lower incidence of allergic diseases, indicating that early-life exposure to diverse microorganisms during critical periods of gut microbiota development may reduce future allergy risk [21].

According to Shohei Akagawa and Kazunari Kaneko, despite numerous studies on dysbiosis in children with allergic diseases, no consistent patterns or clear mechanistic links between dysbiosis and allergic conditions have been established [21].

Several studies have investigated differences in the gut microbiota between healthy children and those with allergic diseases, including food allergy (FA), atopic dermatitis (AD), asthma, and food sensitization (FS). Across multiple cohorts, common patterns of microbial alterations have emerged, although some inconsistencies remain.

In children with FA or AD, several studies reported decreased levels of *Bacteroides, Lactobacillus, Akkermansia, Bifidobacterium, and Faecalibacterium,* alongside increased levels of *Gemella*, *Rhodotorula,* and various families such as Lachnospiraceae, Leuconostocaceae, and Streptococcaceae [22,23,24,25]. These findings suggest that reduced abundance of beneficial bacteria, including butyric acid-producing bacteria (BAPB), may be linked to allergic disease development in early life.

In children with asthma or wheezing, studies reported decreased levels of *Alistipes, Bacteroides, Bifidobacterium, Collinsella, Dialister, Dorea, Faecalibacterium, Flavonifractor, Roseburia*, and *Ruminococcus* and increased levels of *Escherichia, Gemmiger, Streptococcus*, and *Veillonella* [26,27,28]. These alterations were observed both in early infancy and in later childhood, suggesting that early-life dysbiosis may influence immune development and respiratory outcomes.

In studies focusing on food sensitization or egg allergy, there were reports of decreased genera such as *Citrobacter*, *Clostridium*, *Dialister*, *Dorea*, *Haemophilus*, *Lactococcus*, and *Oscillospira*, and increased levels of families Lachnospiraceae, Leuconostocaceae, and Streptococcaceae [22,23].

Notably, the abundance of BAPB at the genus level was lower in children with allergic diseases in four out of six studies, highlighting a potential role of SCFA-producing bacteria in allergy prevention.

Overall, these studies indicate that children with allergic diseases exhibit reduced diversity of beneficial gut microbes and increased abundance of potentially pro-inflammatory taxa, particularly during early life when the gut microbiota undergoes critical development. While exact patterns vary between studies, the consistent observation is that dysbiosis in early life may contribute to the onset of allergic diseases.

Recent studies have highlighted the role of the nasopharyngeal microbiome in shaping inflammatory and allergic responses in early childhood. In a cohort of 244 infants followed through their first 5 years of life, the dominant bacterial genera during the first two years included *Moraxella*, *Streptococcus*, *Corynebacterium*, *Alloiococcus*, *Haemophilus*, and *Staphylococcus*, belonging to the phyla Firmicutes, Proteobacteria, or Actinobacteria. Lower respiratory illnesses in this period were positively associated with *Moraxella*, *Streptococcus*, and *Haemophilus*, whereas *Corynebacterium*, *Alloiococcus*, and *Staphylococcus* were negatively correlated. Notably, *Moraxella* associated with respiratory illness may disrupt microbial balance by forming biofilms that support co-survival of pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [1,29]. Importantly, early colonization of the upper airways with *Moraxella*, *Streptococcus*, and *Haemophilus* in children with early allergic sensitization was linked to an increased risk of chronic wheezing at 5 years of age. Elevated allergen-specific IgE levels were detectable as early as 6 months, suggesting that perturbations in the nasopharyngeal microbiome can prime the immune system toward heightened inflammatory and allergic responses later in childhood [1,29].

Studies of 56 tree species showed that phyllosphere communities are dominated by a few bacterial phyla - Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria - the same phyla prevalent in the healthy human lung. Pollen grains also harbor bacteria, including single cells, clusters, or biofilm-like structures, with Proteobacteria and Actinobacteria more abundant than Firmicutes and Bacteroidetes. Airborne pollen from wind-pollinated plants can thus transport these bacteria to the human respiratory tract. Pollen allergenicity may be influenced not only by allergenic proteins but also by bacterial components such as endotoxins and pollen-

associated lipid mediators, which can modulate immune responses. Therefore, pollen carries its own microbiome that can impact allergic sensitization, lung inflammation, and potentially promote asthma development [1,30].

Adaptive immunity declines with age. Adults aged 86-94 show reduced B-cell diversity, largely due to a loss of memory B cells, which may impair immune responses to the microbiota [31]. Age-related loss of $CD28^+$ T cells further weakens antigen-driven T-cell activation and survival, increasing susceptibility to infections. Microbial diversity also decreases after age 70, and elderly individuals with asthma display a distinct airway microbiome, including reduced *Moraxella* compared with non-asthmatics [14,32,33].

Specific bacterial patterns correlate with disease severity. Nasal microbiota can predict nasal polyp recurrence better than clinical data alone. In asthma, early-life presence of *Corynebacterium* and *Dolosigranulum* lowers disease risk [34]. Delivery mode and breastfeeding strongly shape these early microbial communities, while antibiotics and corticosteroids can disrupt them [35]. Helminth exposure may increase diversity and offer protection [36]. Aging further alters the gut-lung microbiome link and contributes to immune dysfunction [37]. The first months of life are the key period for shaping a protective airway microbiome. Reduced microbial diversity is consistently associated with respiratory allergic diseases, highlighting the future importance of microbiome-based interventions [38].

3.2 The relationship between the microbiome and bronchial asthma

The study from 2023 included 1,949 infants, of whom 667 (34.2%) were exclusively breastfed, 353 (18.1%) received mixed feeding, and 929 (47.7%) were exclusively formula-fed. In the exclusively breastfed group, 76.9% were non-Hispanic White, whereas this proportion was lower among formula-fed infants (59.7%), who also had more than twice the proportion of non-Hispanic Black infants (22.4% vs. 9.8%). Findings from the study conducted by Christian Rosas-Salazar et al. demonstrated that exclusive breastfeeding reduced the risk of lower respiratory tract infections in infancy and asthma at age 4, an effect mediated in part by its influence on the gut microbiome ($p = 0.03$). [39].

Another study proved that breastfeeding has been demonstrated to enhance lung development and respiratory function and is associated with a lower likelihood of asthma [40].

Gut microbial changes following cesarean section are most pronounced during the first month and increase asthma risk only if the microbiota at one year still reflects a cesarean-associated composition. Additionally, heritable vaginal bacteria and microbial functional genes may influence immune tolerance and associate with allergy markers in infancy. During the first

year of life, gut microbiota composition differed by delivery mode, with cesarean-delivered infants showing lower Bacteroidetes and Actinobacteria and higher Firmicutes and Proteobacteria at 1 week and 1 month, though these differences disappeared by 1 year. At the genus level, 16 genera differed at 1 week, 12 at 1 month, and only 3 at 1 year, with cesarean delivery consistently associated with higher Enterobacteriaceae and *Escherichia*/*Shigella* by 1 year. Vaginal delivery with intrapartum antibiotics generally produced intermediate microbial profiles. Overall, cesarean delivery–associated microbial patterns were stable across time, as reflected by highly correlated cesarean microbial scores ($p < 0.001$). In a cohort of 653 children with complete follow-up, 7% (n = 48) had asthma at age 6 years, while 15% (n = 98) had previously diagnosed asthma but were in remission. Among 684 children with blood samples, 12% (n = 84) showed allergic sensitization (specific antibodies IgE > 0.35 kU/L) by 18 months. Of the 644 children with data on both outcomes, 6.5% had asthma only, 10.3% had allergic sensitization only, 1.7% had both, and 82.3% had neither, with asthma and allergic sensitization significantly associated (OR 2.39, 95% CI 1.16-4.91, p = 0.018). Cesarean section delivery was associated with an increased risk of asthma at age 6 (OR 2.45, 95% CI 1.32-4.55, p = 0.004), corresponding to a prevalence of 13% versus 6% in vaginally delivered children. Cesarean delivery also significantly increased the risk of allergic sensitization (17% vs. 11%; OR 1.68, 95% CI 1.01-2.79, p = 0.046) and of having both asthma and allergic sensitization (OR 5.16, 95% CI 1.54-17.25, p = 0.008), although this involved a small number of children (n = 11). No association was observed for children who outgrew asthma before age 6. Asthma risk did not differ between elective and emergency cesarean sections (p = 0.57). In vaginally delivered children, intrapartum antibiotic exposure showed a nonsignificant trend toward higher asthma risk (OR 1.76, 95% CI 0.69-4.49, p = 0.24) but was not associated with allergic sensitization (p = 0.95) [18]. To conclude the cesarean section-associated gut microbiota score at 1 year was significantly linked to asthma risk at age 6 (p = 0.022). Cesarean delivery increased the number of asthma-like episodes in the second and third years of life, and children with a high cesarean-associated microbial score at 1 year had a 20% risk of asthma at age 6, compared to 7% in children with a low score. These findings suggest that both delivery mode and retention of a cesarean-associated gut microbiota contribute to childhood asthma risk.

Even the skin microbiota can influence asthma prevalence in the population. Commensal coagulase-negative *Staphylococcus* species (e.g., *S. epidermidis, S. hominis*) produce antimicrobial compounds that limit colonization by pathogenic bacteria such as *S. aureus*. Additionally, *S. epidermidis*, the dominant bacterial inhabitant of healthy skin, promotes the induction of IL-17A$^+$ CD8$^+$ T cells, thereby augmenting innate barrier immunity

[41,42].

It is worth mentioning that atopic individuals show reduced environmental biodiversity around their homes and lower overall skin diversity of Gammaproteobacteria [43]. In contrast, healthy individuals with higher skin abundance of *Acinetobacter* exhibit increased IL-10 expression in peripheral blood mononuclear cells, highlighting a link between environmental biodiversity and the skin microbiota in allergy [43]. Similarly, greater exposure to green environments (forests and farmland) around the home has been associated with reduced atopic sensitization in children over 6 years of age and with alterations in skin microbiota composition [44]. Another study showed that higher levels of *Acinetobacter* on the skin and in the nose correlate with lower prevalence of asthma and allergy [14,44].

Higher abundance of Proteobacteria in asthmatics has been linked to poorer asthma control and exacerbations, accompanied by induction of Th17-related genes [45]. In particular, increased levels of *Haemophilus* and *Moraxella* (Gammaproteobacteria) correlate with severe airway obstruction and neutrophilic inflammation [46,47]. Most mechanistic studies on airway microbiota and asthma have been conducted in mouse models, but one human study showed that *Haemophilus parainfluenzae* can activate Toll-like receptor 4 (TLR4), inducing pro-inflammatory factors like IL-8 while inhibiting corticosteroid-related pathways, potentially contributing to steroid resistance [48]. In another study authors compared airway microbiota in mild atopic asthma, atopic non-asthmatic, and healthy non-atopic individuals, finding that high Th2-associated inflammation corresponded with lower bacterial diversity. Asthmatics were enriched in Proteobacteria (*Haemophilus*, *Neisseria*) as well as *Fusobacterium* and *Porphyromonas*, while Lactobacillaceae, important for regulatory T cell development, were reduced [49]. In contrast, bacterial dysbiosis linked to atopy (but not asthma) included Pasteurellaceae (*Aggregatibacter*), *Prevotella*, and *Corynebacterium*. These findings suggest that allergen-sensitized individuals harbor distinct airway microbial communities compared to non-sensitized subjects [1].

Parallel to airway findings, early-life gut microbiome disturbances have been strongly associated with later asthma development. Colonization by *Clostridium difficile* at one month of age predicts wheeze and asthma at six years [50]. Infants at high risk for asthma display significantly reduced relative abundance of several beneficial genera-including *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*-within the first 100 days of life. It is worth mentioning that children with the asthma-wheeze phenotype were 21.5 times more likely to be diagnosed with asthma by the age of three. [51]. Subsequent studies have shown that decreased *Lachnospira* alongside increased *Clostridium neonatale* in early infancy correlates with asthma

diagnosis at preschool age [52]. In children already diagnosed with asthma, gut dysbiosis includes lower levels of *Faecalibacterium* and *Roseburia* and higher levels of *Clostridium.* The reduced abundance of the butyrate-producing genera *Faecalibacterium* and *Roseburia*, together with the increased abundance of *Clostridium* spp., in children with asthma ($p < 0.01$) is associated with lower fecal butyrate levels, which has been linked to an increased risk of asthma development in early childhood. [53]. High-risk infants, who are predisposed to asthma, showed delayed gut microbiota diversification, a pattern previously linked to increased risk of atopy and recurrent wheeze. *Lactobacillus rhamnosus GG (LGG)* supplementation partially corrected this dysbiosis by increasing *Lactobacillus* abundance ($p < 0.0001$) and normalizing the rate of microbial diversification ($p = 0.63$). Because LGG-derived metabolites can induce T-regulatory cell expansion and IL-10 production ex vivo, these findings suggest a mechanistic link whereby early-life microbiota modulation may reduce immune dysregulation associated with the development of asthma. However, persistent deficits in microbial richness at 12 months ($p = 0.02$) indicate that dysbiosis may continue to contribute to asthma risk despite partial improvement [54].

Collectively, these findings underscore a consistent pattern: microbial dysbiosis in both the airways and gut-especially early in life-modulates immune pathways that shape asthma susceptibility, phenotype, and severity.

3.3 The microbiome, phenotypes, and disease severity

Asthma is a heterogeneous disease encompassing various clinical and inflammatory phenotypes, and a growing body of evidence indicates that the microbiome plays a central role in shaping these differences as well as the overall severity of the disease. Variations in microbial composition in the gut, airways, and upper respiratory tract are increasingly recognized as important determinants of immune system maturation, airway inflammation, and responsiveness to environmental exposures [55,56].

3.3.1 Microbiome-driven differentiation of asthma phenotypes

Studies have shown that distinct microbial profiles are associated with classical asthma endotypes, particularly Th2-high and Th2-low inflammation [57].

Th2-high asthma is frequently linked to early-life gut dysbiosis, characterized by reduced abundance of *Bifidobacterium*, *Lactobacillus*, and SCFA-producing bacteria. This dysbiosis impairs regulatory T-cell (Treg) development and promotes exaggerated IgE responses [58,59]. In the airways, overrepresentation of *Moraxella*, *Haemophilus*, or *Streptococcus* is often

associated with eosinophilic inflammation and increased susceptibility to viral-induced exacerbations [60].

Th2-low asthma, typically neutrophilic or paucigranulocytic, has been linked to airway colonization by Proteobacteria, including *Haemophilus influenzae* and *Pseudomonas spp.* These microbes drive IL-17 - mediated pathways and contribute to steroid resistance, leading to more severe disease and difficult-to-control symptoms [61].

Thus, microbial dysbiosis not only correlates with asthma phenotypes but also appears to mechanistically support the development of distinct inflammatory trajectories.

3.3.2 Microbiome and disease severity

Differences in microbiome composition are closely associated with asthma severity, frequency of exacerbations, and treatment responsiveness.

Severe asthma is often characterized by reduced microbial diversity in both the gut and airway microbiota. Low diversity is linked to impaired epithelial barrier function, exaggerated innate immune activation, and increased production of pro-inflammatory cytokines [58].

Airway colonization by *Moraxella*, *Haemophilus*, and *Neisseria* has been repeatedly associated with more frequent exacerbations, decreased lung function, and poor response to inhaled corticosteroids [62].

Conversely, the presence of SCFA-producing gut bacteria supports anti-inflammatory immune pathways and correlates with milder disease and improved treatment outcomes [63].

3.3.3 Early-life microbiome as a determinant of later severity

Longitudinal cohort studies indicate that early-life disruptions of the microbiome - caused by cesarean section, antibiotic exposure, formula feeding, or low environmental microbial diversity - predispose individuals to more severe asthma later in life. Critical “windows of susceptibility” during the first 100 days appear to determine long-term immune programming, highlighting both predictive markers of risk and potential microbiome-based intervention points [51].

3.4 Therapeutic possibilities

Probiotic bacteria primarily belong to lactic acid–producing taxa, including *Lactobacillus, Streptococcus,* and *Enterococcus* (phylum Firmicutes, order Lactobacillales), as well as *Bifidobacterium* species (phylum Actinobacteria, order Bifidobacteriales) and certain non-pathogenic strains of *Escherichia coli*. These microorganisms exert several beneficial

effects, such as promoting the maturation and functional integrity of the intestinal barrier and supporting the development of tolerogenic dendritic cells. In turn, these cells shape both local gut immunity and systemic immune responses. Therefore, targeting microbiome dysbiosis in allergy and asthma through probiotic supplementation appears to be a promising therapeutic strategy [1,64,65].

The study enrolled 184 infants randomized to probiotic (LGG) or control. Baseline characteristics were similar between groups. Cumulative incidence at 5 years was 17.4% in the control group vs 9.7% in the LGG group. The difference was not statistically significant (HR = 0.88; 95% CI 0.41-1.87; p = 0.25). Children with prior eczema had a higher asthma risk (HR = 3.64; 95% CI 1.66-7.96). Numbers of infants born by cesarean section or exclusively formula-fed were too small for subgroup conclusions. To conclude, LGG supplementation did not significantly reduce eczema or asthma incidence in this cohort [66].

In a trial of children aged 4-10 years with atopic asthma, 12-week treatment with probiotic containing *L. acidophilus, B. bifidum, L. delbrueckii* led to better lung function, fewer exacerbations, and reduced bronchodilator use compared with placebo. Immunologically, children receiving probiotics showed significantly higher HLA-DR expression on monocytes and lower $CD8^{+}CD45RA^{+}$ T-cell levels [67]. However, a limitation of the study is the small group size, with only 17 children receiving the probiotic and 13 receiving placebo.

In another study 147 children with asthma were randomized into four groups: *Lactobacillus paracasei* (LP, n = 38), *Lactobacillus fermentum* (LF, n = 38), a combination of both probiotics (LP+LF, n = 36), and placebo (n = 35). Baseline demographic characteristics, asthma severity, IgE levels, allergic sensitization, and lung function were comparable across all groups (all $p > 0.05$). Probiotic supplementation significantly improved asthma control as measured by Childhood Asthma Control Test scores in all treatment groups compared with placebo (LP: $p = 0.005$; LF: $p < 0.001$; LP+LF: $p < 0.001$). Asthma severity was also reduced in all probiotic groups (LP: $p = 0.024$; LF: $p = 0.038$; LP+LF: $p = 0.007$). Peak expiratory flow rate (PEFR) improved significantly only in the LP+LF group (33.81 L/min, $p = 0.009$). No significant changes were observed in quality-of-life scores (PAQLQ) or Pediatric Asthma Severity Scores (PASS). Regarding immune biomarkers, total serum IgE decreased significantly only in the LP+LF group (from 748.22 to 377.29 kU/L, $p < 0.05$). No significant changes were observed in cytokine levels (IFN-γ, IL-4, TNF-α, all $p > 0.3$) or in skin prick test reactivity to allergens. In summary, supplementation with LP and LF probiotics improved asthma control and reduced severity in children, with the combination LP+LF showing additional benefits in lung function and IgE reduction. Other parameters, including quality-of-

life measures, cytokine levels, and allergen sensitization, remained largely unchanged [68].

In study including mice, probiotics and prebiotics reduce airway hyperresponsiveness, eosinophil infiltration in perivascular tissue and bronchoalveolar lavage fluid (BALF), mucus secretion, and goblet cell hyperplasia. They also decrease levels of immunoglobulins, IL-17, leukotrienes, and EPO activity, and reduce the gene expression of TLR4, CCL11, AKT, NLRP3, NF-κB, MyD88, and MUC5AC. Additionally, probiotics increase IL-38 gene expression. Prebiotics specifically influence PI3K gene expression and contribute to the control of airway inflammation [69].

Bacterial metabolites can also be beneficial. In a study conducted on mice, SCFA produced in the gut, particularly butyrate and propionate, suppress allergic airway inflammation by promoting tolerogenic dendritic cells and supporting the expansion of regulatory T cells [1,70].

Postbiotics - non-viable microorganisms or their bioactive fragments—are increasingly investigated as an adjunctive therapy in pediatric asthma. A systematic review including 2,419 children across 18 RCTs found that six trials used bacterial lysates, primarily OM-85 BV and PMBL®, at doses of 3.5-7 mg/day [71].

Clinical studies indicate that postbiotic therapy can reduce respiratory morbidity. For example, in one RCT of 75 preschool children, OM-85 BV administered for 10 days per month over three months significantly decreased wheezing episodes and acute respiratory tract infections (ARTIs) [72].In a randomized controlled trial with 49 children suffering from allergic asthma, 12 weeks of PMBL® treatment led to elevated counts of regulatory T cells (Treg), cytotoxic T cells ($CD8^+$), and natural killer (NK) cells, alongside a reduction in T-cell activation markers ($CD3^+CD69^+$ and $CD3^+CD25^+$), indicating an immunomodulatory effect that could help explain the observed decrease in asthma exacerbations and respiratory infections [73].

Nevertheless, challenges remain, including substantial heterogeneity in dosing regimens and formulations across studies, and the lack of standardization complicates direct comparisons of outcomes [71].

Fecal microbiota transplantation (FMT) involves transferring stool from a healthy donor to a recipient to restore gut microbial balance. Recent experimental findings have prompted clinical interest in microbiota-based therapies for asthma. While probiotics have shown some benefits, FMT may offer a more effective means of restoring gut microbial balance, as it introduces a diverse microbial community capable of establishing long-term colonization. Unlike probiotics, which transiently inhabit the gut, FMT can induce lasting changes in intestinal microbiota composition, as evidenced by sequencing studies showing donor-like

profiles in recipients weeks after transplantation.

Although the mechanisms underlying FMT's potential benefits in asthma remain unclear, it likely acts by reestablishing microbial diversity and colonization resistance. Advances in culture-independent molecular techniques now enable precise characterization of microbial changes before and after FMT, providing valuable insights into its therapeutic effects.

Despite limited data, FMT represents a promising, low-cost, and biologically grounded strategy for asthma management. Future research should focus on elucidating the gut–lung axis, defining how FMT modifies gut microbiota in asthmatic patients, and conducting controlled clinical trials to assess its efficacy and safety [74].

These findings highlight the key role of gut microbiota modulation in controlling airway inflammation and immune signaling, supporting the gut-lung axis as a therapeutic target in asthma.

4. Discussion

The findings summarized in this review highlight the central role of the human microbiome, particularly the gut and respiratory microbiota, in shaping immune maturation and determining the risk, phenotype, and severity of bronchial asthma. A consistent pattern emerges across studies: disturbances of microbial communities early in life, especially within the first 100 days, have long-term immunological consequences that influence susceptibility to allergic disease and chronic airway inflammation.

A major theme across the literature is the concept of "critical windows" of immune and microbial development. During infancy, the microbiome is highly modifiable and influenced by delivery mode, breastfeeding, antibiotic exposure, environmental biodiversity, and early-life respiratory infections. Disruptions in this period impair the establishment of immune tolerance, resulting in altered differentiation of T-cells, reduced regulatory T-cell function, and enhanced Th2 or Th17 skewing. Several studies show that cesarean delivery and reduced gut microbial diversity at one year significantly increase asthma and allergic sensitization risk by school age, particularly when specific dysbiotic patterns persist. These findings emphasize that transient early-life deviations may not be harmful unless they lead to long-term microbial imbalance.

The relationship between microbiome composition and specific asthma phenotypes further underscores the mechanistic links between microbial ecosystems and immune pathways. Th2-high asthma, characterized by eosinophilic inflammation and IgE-mediated responses, often arises from early deficits in *Bifidobacterium, Lactobacillus*, and SCFA-producing bacteria. In contrast, Th2-low and neutrophilic asthma is associated with increased

Proteobacteria (e.g., *Haemophilus, Moraxella, Neisseria*) in the airways, which activate IL-17–related pathways, promote neutrophilic inflammation, and contribute to steroid resistance. These observations suggest that microbiome signatures could be used to differentiate clinical endotypes and potentially personalize asthma management.

Therapeutic strategies aimed at modifying the microbiome show promise, yet findings remain heterogeneous. Probiotics, particularly *Lactobacillus* and *Bifidobacterium* strains, have demonstrated immunomodulatory effects and improvements in asthma control in some pediatric studies. However, large randomized trials show inconsistent results regarding long-term prevention of asthma or eczema, likely due to differences in strains, dosing, timing, and host-specific factors. Similarly, postbiotics - such as bacterial lysates - consistently reduce respiratory infections and may lower asthma exacerbations, but optimal formulations and regimens remain undefined.

FMT, although still experimental in asthma, represents a compelling therapeutic avenue due to its capacity to induce long-lasting microbial restructuring. Its potential role in modifying the gut–lung axis warrants investigation through controlled clinical trials.

Despite substantial progress, several limitations in the literature remain. Many studies are observational, which limits our ability to determine whether the relationships identified are truly causal rather than merely correlated. Microbial profiles often vary across populations and are influenced by diet, geography, socioeconomic status, and methodological differences in sequencing and data analysis. Furthermore, microbial interactions with viral infections - major triggers of asthma development and exacerbation - are complex and incompletely understood. Another challenge is that microbiome interventions appear most effective when administered during early-life windows, raising ethical and practical issues for preventive strategies.

Future research should focus on mechanistic studies that combine microbiome analyses with metabolomics and detailed immune profiling to better understand how specific microbes or their metabolites influence asthma development. Large, multi-center, long-term studies will be crucial for confirming which microbial markers can reliably predict asthma risk. In addition, personalized microbiome-based therapies - such as targeted probiotics, synbiotics, or advanced microbial mixtures designed for individual patients, offer a promising direction for future treatment strategies.

In conclusion, the microbiome plays a foundational role in immune education and asthma pathogenesis. Early-life microbial disturbances contribute to the development of distinct asthma phenotypes and modulate disease severity, while microbiome-targeted interventions remain a promising but still evolving therapeutic field. A deeper understanding of the gut-lung

axis and host-microbiota interactions may ultimately enable personalized prevention and treatment strategies for asthma.

5. Conclusions

The evidence presented in this review clearly demonstrates that the microbiome - intestinal, respiratory, and cutaneous - plays a crucial role in both the development and progression of bronchial asthma. Early life constitutes a critical "immunological window", during which the composition of the microbiota can shape immune responses for years to come. Dysbiosis resulting from cesarean delivery, antibiotic exposure, formula feeding, or low environmental biodiversity increases the risk of developing asthma and allergies, influences disease phenotype, and affects its severity.

Studies show that specific microbial signatures are associated with the characteristic inflammatory trajectories of asthma: a deficiency of SCFA-producing bacteria promotes the development of Th2-high asthma, while an excess of Proteobacteria in the airways correlates with the Th2-low phenotype, more severe disease manifestations, and corticosteroid resistance. Moreover, early disturbances of the gut microbiome lead to long-term changes in the gut-lung axis, affecting T-cell maturation, dendritic cell function, and epithelial barrier integrity.

Growing evidence confirms that the microbiota not only determines the risk of developing asthma but also influences its long-term course - including the frequency of exacerbations, treatment response, and symptom dynamics. In this context, the microbiome is emerging as an important predictive biomarker and a promising therapeutic target.

Microbiome-modulating interventions - such as probiotics, prebiotics, postbiotics, and potentially fecal microbiota transplantation, show potential in reducing asthma symptoms and exacerbations, although study results remain inconsistent and effectiveness varies depending on the strains used, dosage, patient age, and asthma phenotype. The most consistent benefits are associated with bacteria that produce short-chain fatty acids, which enhance immunological tolerance mechanisms.

In summary, current scientific evidence suggests that the microbiome is a fundamental regulator of the development and course of bronchial asthma. The development of microbiome-targeted therapies, based on precisely selected probiotic strains, postbiotic preparations, or microbiota reconstruction techniques, has the potential to transform modern strategies for asthma prevention and treatment. To fully harness this potential, further well-designed clinical studies are needed to deepen our understanding of gut–lung axis interactions and to determine optimal therapeutic approaches.

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Author contributions

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Conflict of interest

The authors declare there are no conflicts of interest.

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