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The Microbiome in Asthma: Role in pathogenesis, phenotype, and response to treatment

Ariangela J. Kozik, PhD[1] and **Yvonne J. Huang, MD**[1,*]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Michigan, Ann Arbor, MI, USA

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Introduction

Asthma was first described by Hippocrates as a disease of breathlessness, potentially caused by emotional distress[1]. The 17th century writings of Sir John Floyer describe bronchial constriction and the concepts of attacks and triggers[2]. In the 20th century, mounting evidence led to the characterization of asthma as an inflammatory condition[2]. Asthma symptoms were recognized as narrowing of the airways with distinctive sputum and swelling of the bronchial mucous membranes, triggered by a variety of circumstances or exposures that stimulate immune cells[2]. Despite many scientific advances, asthma remains a major public health concern both in the United States and globally. Asthma-related healthcare and socioeconomic costs remain substantial, costing an estimated $56 billion and 14 million work days missed each year in the U.S.[3]. Inadequate asthma treatment impacts quality of life and contributes to preventable deaths, especially among children and adolescents. Today, the field is once again at the threshold of a deeper understanding of asthma. Evolving paradigms link the origins of asthma to environmental exposures that shape immune responses, mediated by exogenous and endogenous stimuli including microbes. These same stimuli may modulate how asthma behaves once established, contributing to asthma's heterogeneity. The coupling of clinical insights with new investigative tools has generated new hypotheses and expanded the potential to understand better the different mechanisms underlying asthma and to inform new treatment strategies to revolutionize patient care.

There is no known singular cause of asthma. Existing data points to a combination of genetic risk and environmental factors that influence asthma susceptibility in children. For many, asthma onset in childhood and its persistence into adulthood is typically atopic in nature,

*Corresponding author: Yvonne J. Huang MD, 6301 MSRB3/SPC5642, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5642, Tel. (734) 936-5047; Fax: (734) 764-4556, yvjhuang@umich.edu.

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driven by type 2 immune responses to environmental allergens and microbes[4]. However, the mechanisms underlying asthma in other scenarios are often less clear. For example, gender influences asthma prevalence, which is higher in boys than girls in childhood but begins to reverse in adolescence[5]. Moreover, adult onset of asthma is common and linked in some cases to new environmental exposures, including viral respiratory illnesses, irritant exposures, and newly developed allergies or obesity[6]. A large knowledge gap exists on mechanisms of adult-onset asthma, which can range from clinically mild to severe.

Ultimately, continued progress in asthma research depends on recognition of the disease as a collection of heterogeneous presentations, as highlighted in a recent commission published in the *Lancet*[7]. Integration of cross-disciplinary approaches and scientific tools has generated new insights into the complexities of asthma pathogenesis in children, involving interactions amongst environmental factors, genetics, and trajectories of human microbiota establishment[8–11]. Similar integration of methods is generating new insights and hypotheses into the role of human microbiota in asthma phenotypes. The purpose of this review is to highlight the latest evidence in these areas and provide some perspective on next directions of research and potential impact on future patient care.

Overview of the human microbiome

The human body is home to a diverse array of microorganisms, revealed by culture-independent methods to comprise bacteria, viruses, and fungi that inhabit our internal and external surfaces. Studies have shown that the microbiota is individualized, dynamic, different between body sites, and both reflective of and sensitive to the environment[12]. There is ample evidence for the role of human microbiota in homeostasis, immunity, and metabolism[13]. In the interest of clarity, Table 1 defines some commonly used terms in microbiome investigation[14,15]that will be referred to in this review.

The microbiome is critical to metabolic and immune system programming from birth. Some evidence suggests that this relationship may be initiated in the womb. While there is not yet a consensus, some human studies suggest that maternal-fetal microbiota transfer may occur *in utero*[16,17]. Peri-natal and early life disturbances, such as maternal antibiotic use and mode of delivery, have been shown to alter the microbiome. Babies born vaginally have a distinct microbiome from those born via cesarean section, and these differences can persist weeks after birth[18,19]. Breastfeeding has been shown to directly impact the infant gut microbiome, protecting the infant from infections and encouraging maturation of the immune system[20]. Overall it has been widely shown that the presence and composition of human microbiota modulate immune tone and shape inflammatory responses, impacting later health outcomes[21,22]. Therefore, it is reasonable to conceptualize microbiota as a dynamic entity that at the very least mediates, if not potentially drives, mechanisms to promote either health or disease.

The microbiome in asthma pathogenesis

A wealth of evidence now exists implicating gut and respiratory dysbiosis in the pathogenesis of asthma in childhood, highlights of which are discussed here.

Gut microbiota

The gastrointestinal tract is colonized by a variety of microorganisms which most densely populate the colon. Bacterial members of the gut microbiota have been extensively studied, and their role in shaping both local and systemic immune responses is well established. In studies of childhood allergy and asthma, findings from different birth cohorts have consistently demonstrated a relationship between altered patterns of gut microbiota composition in the first years of life and the development of allergy and asthma[8–10]. In one of the largest prospective studies to date involving nearly 700 children, the gut microbiota configuration at 1 year of age was associated with asthma development at age 5[9]. These and other clinical findings are supported by work in mouse models that show age-dependent regulation of IgE production by the gut microbiota[23] and a potential direct role for specific bacteria, such as *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*, in mitigating asthma development during the first 100 days of life[8]. Table 2 summarizes several additional prominent taxa and evidence for links to asthma.

What are the mechanisms by which gut microbiota mediate asthma pathogenesis? The effects of short-chain fatty acids (SCFAs), produced by fermentation of fiber by specific gut bacteria, has received particular attention with supporting data from both murine models and human studies[24]. Altered levels of SCFAs have been linked to gut dysbiosis in children at-risk for asthma[8]. Important work in mouse models has delineated putative mechanisms by which fiber supplementation, via the generation of specific SCFAs, can shape naïve immune cell responses, including dendritic cell phenotype in the lungs[25]. Other mediators linked to gut microbial metabolism, such as histamine and tryptophan metabolites, have been implicated in mechanisms of asthma[24,26], but further studies are needed.

Respiratory microbiota

In pediatric studies the role of respiratory microbiota in asthma pathogenesis has largely focused on the nasopharyngeal (NP) niche. Not only is the nasopharynx easier to sample but it is also the most proximal point of contact between inhaled material and respiratory epithelia. While the composition of NP microbiota is overall very different from the lower respiratory tract (defined as below the glottis), there is some overlap, particularly in the setting of lung disease including asthma[27,28]. Thus study of the NP microbiome has the potential to inform biological pathways associated with asthma risk, as further detailed below[29,30].

Given the known strong association between childhood asthma and viral respiratory infections, in particular human rhinovirus and respiratory syncytial virus[31,32], recent data highlight the importance of interactions between bacteria and viruses in the nasopharynx. Analyses of NP samples from several pediatric cohorts have demonstrated important associations amongst bacterial microbiota composition, asthma risk, and/or frequency or severity of viral respiratory infections including bronchiolitis[29–31,33,34]. Notably, a consistent observation has been dynamic changes in NP microbiota composition early in life, followed by a settling into one of several microbiota patterns defined by relative dominance of one or more members. For example, as reported in one study[34], six bacterial genera generally define NP microbiota patterns in early childhood (*Moraxella*,

Streptococcus, *Corynebacterium*, *Alloiococcus*, *Haemophilus*, and *Staphylococcus*). However, frequency of viral respiratory infections and/or likelihood of developing persistent wheeze both have been strongly associated with the prevalence of *Haemophilus*, *Moraxella*, and/or *Streptococcus* in the nasopharynx[30,34].

Strikingly, the associations between a dysbiotic NP microbiota pattern and frequency of viral illness or asthma risk appear to be linked very early, within the first one or two months of life[38–40]. Moreover, in at least one study[34], a shift in NP bacterial microbiota composition towards *Moraxella* dominance was detected in the weeks preceding the clinical onset of viral illness. Finally, only in children who developed early sensitization to aeroallergens did a dysbiotic NP microbiota pattern associate with persistent wheeze in later childhood. Together, collective findings from studies of the NP microbiome suggest that, as seen in the gut, a 'critical window' of upper airway microbiota–immune interactions exists that may also influence asthma pathogenesis in children, although the mechanisms are not understood.

The microbiome in asthma phenotype

Respiratory microbiota

The relationships between microbial dysbiosis and asthma phenotype have predominantly been explored in studies of adults amongst whom the heterogeneity of asthma is well recognized. In contrast to the focus on upper airway sampling in pediatric studies, analyses of lower respiratory tract samples in adults have established asthma-associated differences in bronchial microbiota composition[35–38]. It is important to state upfront that many studies now have refuted the long-taught supposition that the lungs, even in health, are sterile or free from microorganisms[35,36,39]. Using a culture-independent approach to survey bacterial composition in bronchoscopic samples, Hilty et al. first showed that the bronchi of healthy individuals indeed harbor bacteria, but that the bacterial composition detected from the airways of both adults and children with asthma differed from that in healthy subjects[35]. Subsequent investigations confirmed that, although lower in microbial burden compared to the oral cavity[40], the lower respiratory tract harbors bacteria whose compositional configuration differs in asthmatic subjects[36–38,41–44]. Notably, this bronchial dysbiosis associated with asthma has been reported consistently across analyses of different specimen types (e.g. bronchoalveolar lavage, bronchial epithelial brushings, sputum), despite incomplete overlap in the identities of microbes detected[27].

Eosinophilic asthma is the best understood clinical phenotype, rooted in activation of type 2 immune responses that lead to airway infiltration by eosinophils that generally is responsive to corticosteroid treatments. Exposure to allergens stimulates type 2 inflammatory responses, as do other potentially concomitant factors[45,46]. For example, the diversity of bacterial content in allergenic environmental dust may modulate the degree of subsequent allergic sensitization[46]. In contrast there is a surprising lack of association found to date between asthma-associated lung bacterial dysbiosis and markers of type 2 airway inflammation or eosinophilic asthma[41,43,44]. This raises the question whether fungi, rather than bacteria, may play a greater role in perpetuating type 2 inflammation in the eosinophilic asthma phenotype[46,47]. Fungal proteases, such as that from *Aspergillus fumigatus*, can induce a

strong eosinophilic allergic airway response in mice[53] This correlates with clinical phenotypes characterized in certain geographic areas and described as severe asthma with fungal sensitization (SAFS)[46–49]. Given the estimates that more than 50,000 fungal spores/m^3 of air may be inhaled each day[50], this raises the question whether the links between fungal sensitization and allergic asthma may implicate dysbiosis related to airway mycobiota, which have yet to be well characterized.

The high prevalence in asthma of sensitization to aeroallergens leads one to query if atopic status, once established, might in itself be linked to alterations in airway microbiota composition. This was examined in a recent study comparing the bronchial bacterial microbiota of subjects with mild atopic asthma, atopy without asthma, and non-atopic healthy controls[27]. Significant differences were observed among these groups, including a pattern of bacterial dysbiosis strongly associated with atopy alone that was distinct from that observed in association with asthma. The findings suggest that the airway mucosal environment in allergen-sensitized subjects allows for establishment of a different microbiota configuration from that in nonsensitized subjects. However, what factors potentially drive microbiome differences between atopic subjects with or without asthma are unknown.

Neutrophilic asthma has generally been associated with more severe asthma and poor response to corticosteroid treatment[44,51]. Based on analyses of either sputum or samples obtained by bronchoscopy, studies from different cohorts have demonstrated that airway neutrophilia is associated with an altered bacterial microbiota composition[41,44,52]. Specifically, organisms belonging to the phylum Proteobacteria, such as *Haemophilus*, *Moraxella*, *Pseudomonas*, and *Klebsiella*, are proportionally enriched in neutrophilic asthma. In one study of severe asthma subjects with different sputum inflammatory phenotypes, those with neutrophilic asthma displayed significant differences in sputum bacterial diversity and composition[44]. Notably, no differences in airway bacterial composition were observed amongst the remaining phenotypes, including eosinophilic and pauci-granulocytic which together characterized the majority of subjects in this study[44]. In another study of severe asthma, significant associations between the proportional abundance of Proteobacteria members and epithelial expression of IL-17 pathway-related genes were observed[41]. Enrichment in Proteobacteria also correlated with less stable asthma control in this cohort. Findings from these and other studies together suggest that airway enrichment in potentially pathogenic members of the Proteobacteria, once established, may promote neutrophilic inflammation, possibly via activation of IL-17-driven pathways. Since airway neutrophilia tends to be observed in more severe asthma, it raises further questions regarding the role of corticosteroid therapy in potentially fostering an airway microenvironment conducive to the outgrowth of particular members.

Gut Microbiota

In contrast to investigations of other chronic medical conditions or of pediatric allergy and asthma, far less evidence exists currently on possible relationships between gut dysbiosis and asthma phenotype in adults. However, such relationships are plausible given known associations between altered gut microbiota patterns and allergic sensitization as well as

obese status. The potential for intestinal microbiota to modulate allergic airway inflammation has been demonstrated in murine models, mediated by SCFAs for example[25] and potentially modifiable by helminth co-infection[53]. In clinical studies, asthmatic adults have been found to harbor a higher burden of histamine-secreting bacteria in their gut than healthy subjects, suggesting a microbial source of histamine that affect manifestations of allergic asthma[26]. Intestinal microbiota differences also have been associated with sensitization to a greater number of aeroallergens and with differences in lung function amongst asthmatic adults[26,54]. These early findings invite a closer look into possible mechanisms by which the intestinal microbiota may influence features of asthma in adult populations.

The microbiome and asthma treatments

Current immunomodulatory treatments for asthma largely target mechanisms of type 2-related eosinophilic inflammation, such as corticosteroids and antibodies directed at specific cytokine mediators (e.g. IL-5). However, these strategies are not effective for patients without evidence of significant type 2 pathway activation and become limited for those who demonstrate persistent eosinophilic inflammation despite such treatments. Improved understanding of the biological drivers underlying different asthma phenotypes will advance more precise approaches to defining asthma in a given patient and determining best treatment options. Until then, the efficacy of current treatments in each patient should be considered alongside potential harms. For example, in addition to known clinical side effects of corticosteroids, emerging evidence suggests that use of inhaled corticosteroids even after just six weeks alters the bronchial microbiome[43]. While the long-term consequences of this remain unclear, prior work has shown that at least one member of the airway microbiota found to be enriched in steroid-resistant asthma may alter macrophage responses to corticosteroids[42].

Another therapeutic strategy of long-standing interest is macrolide antibiotics, which carry both antimicrobial and anti-inflammatory properties. While meta-analyses have failed to find overall evidence in support of their efficacy in asthma[55], individual large clinical trials have, such as recent demonstration that azithromycin reduces exacerbations in subjects with severe asthma[56]. However, concerns regarding the development of microbial resistance to macrolides persist, as increased carriage of macrolide resistance genes in the oropharyngeal microbiome has been shown[57]. Other microbiome-modifying effects of macrolides may exist. Better means of determining which asthmatic patients may benefit from macrolide treatment is needed, which may relate to harboring a higher burden or diversity of airway microbiota at baseline amongst those using corticosteroid[36].

Probiotic therapies offer a promising approach to therapeutic microbiome manipulation, and interest in probiotic therapies for allergic diseases continues to increase. There is ample evidence from mouse studies that link intestinal microbiota to immune tolerance[58,59]. The World Allergy Organization recognizes net benefit of probiotics for possible eczema prevention and recommends probiotic use in pregnant and lactating women, as well as in infants with high risk of allergy[60]. Studies regarding the use of probiotics for the treatment of asthma have been inconclusive. Pre-clinical studies have reported positive effects of

probiotics on manifestations of asthma. For example, *Lactobaccilus rhamnosus* GG has been shown to decrease airway inflammation in a mouse asthma model[61]. However, several clinical trials have found no evidence for a positive effect[62]. Similarly, clinical studies of probiotics for primary prevention of asthma have yet to show positive benefits[63]. Overall, there is not yet sufficient clinical evidence to support the use of probiotics to treat or prevent asthma. For further in-depth discussion on this topic, we recommend a recent review[63].

Outstanding questions and challenges

Reflection on the recent recommendations published in the Lancet[7] highlights, in our view, the significant impact that incorporation of microbiome-centered lines of investigation can have on asthma research. Importantly, this should not be pursued as an isolated discipline but rather integrated with other investigative methods to attain a more holistic understanding of asthma behaviors and the biological drivers of disease instability or progression. To this end we endorse the value in "complementary use of [both] reductionist and system-based approaches"[7], the latter already being pursued to better understand the complexities of microbiome-host interactions.

Existing evidence clearly implicates the gut and respiratory microbiota in shaping asthma pathogenesis in childhood, but their role in the march towards phenotypic differentiation in later life is less clear. Findings from adult studies also implicate these microbiome compartments in asthma phenotype, but mechanistic insights have been more difficult. One challenge is the absence of clinical studies with built-in capacity to investigate the interactions among dynamic lifestyle changes and exposures, immune responses to various stimuli, and of course functions conferred by microbiota in a given individual that may tune responses in these interactions (Figure 1). Secondly, model systems that better reflect human asthma behaviors could provide complementary mechanistic insights. Ultimately, in our view, these two challenges must be addressed if clinical strategies to manipulate microbiota or apply microbial products are to be successful in modifying trajectories of asthma in which the microbiome is demonstrated to play a strong role.

Finally, many clinically relevant questions remain for which we speculate, based on at least some evidence, that further understanding of the human microbiome's role will be informative.

1. *What timeframe is the critical window in which modulation of the microbiome may have sufficient influence to avert the development of asthma?* Recent evidence continues to push this critical window to very early life, at least soon after birth and even peri- or pre-natally. This speaks to much larger questions regarding societal and lifestyle habits.
2. *Are microbiota changes related to differing clinical features of asthma a driver or consequence of underlying mechanisms?* We submit that both are possible and likely differ by context. The strong associations observed to date between a "type 2-low" phenotype and differences in *bacterial* members of the lower airway microbiota suggest the possibility that potentially pathogenic members of the latter stimulate non-type 2 immune responses. This may reflect forms of severe

asthma characterized by significant airway neutrophilia. On the other hand, sensitization to and the detection of fungi in the airways are associated with strong type 2 inflammatory responses, suggestive that fungi can drive such responses. Could this explain eosinophilic severe asthma that may persist despite directed treatments?

3. *Could the microbiome affect responses to asthma treatment, or vice versa such that treatment-induced changes in the microbiome have important consequences*? Again, we speculate both are possible based on some existing evidence. Responsiveness to corticosteroid or macrolide treatment has been linked to characteristics of the airway microbiota present at baseline[36,42,43]. Changes in the airway immune environment after institution of such treatments also could provide a selection pressure on microbiota composition, as reflected in the very definition of "microbiome" as a habitat. Future work will also need to consider the role of other members of the microbiome beyond bacterial, although further methodologic advances are needed to make pursuing such in clinical studies more feasible, accessible and cost-efficient.

Most of the challenges outlined above will require better integration of clinical research and laboratory tools, the latter continually evolving in the – 'omic and bioinformatic space. However, combining advanced approaches (e.g. function-oriented 'omic' tools) with improved study designs or models, nested within a systems-level framework, will likely reveal connections that enable more rapid advancement towards microbiome-informed therapeutic or curative strategies for asthma.

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Key Messages:

- Collective evidence supports the ‘critical-window’ hypothesis that interactions between the immune system and the intestinal or airway microbiota in very early life influence asthma risk and pathogenesis.
- Growing evidence suggests that particular asthma phenotypes may be driven by or are reflective of alterations in the lower airway microbiome, which can be further shaped by asthma treatments.
- A large knowledge gap exists on mechanisms underlying adult-onset asthma, but changes in environmental exposures, lifestyle factors and immune response tendencies should be considered across the lifespan.
- To maintain progress towards more precise therapeutic strategies for asthma, better integration of phenotyping tools, including molecular and microbial methods, with appropriate study designs is needed along with longitudinal assessments.

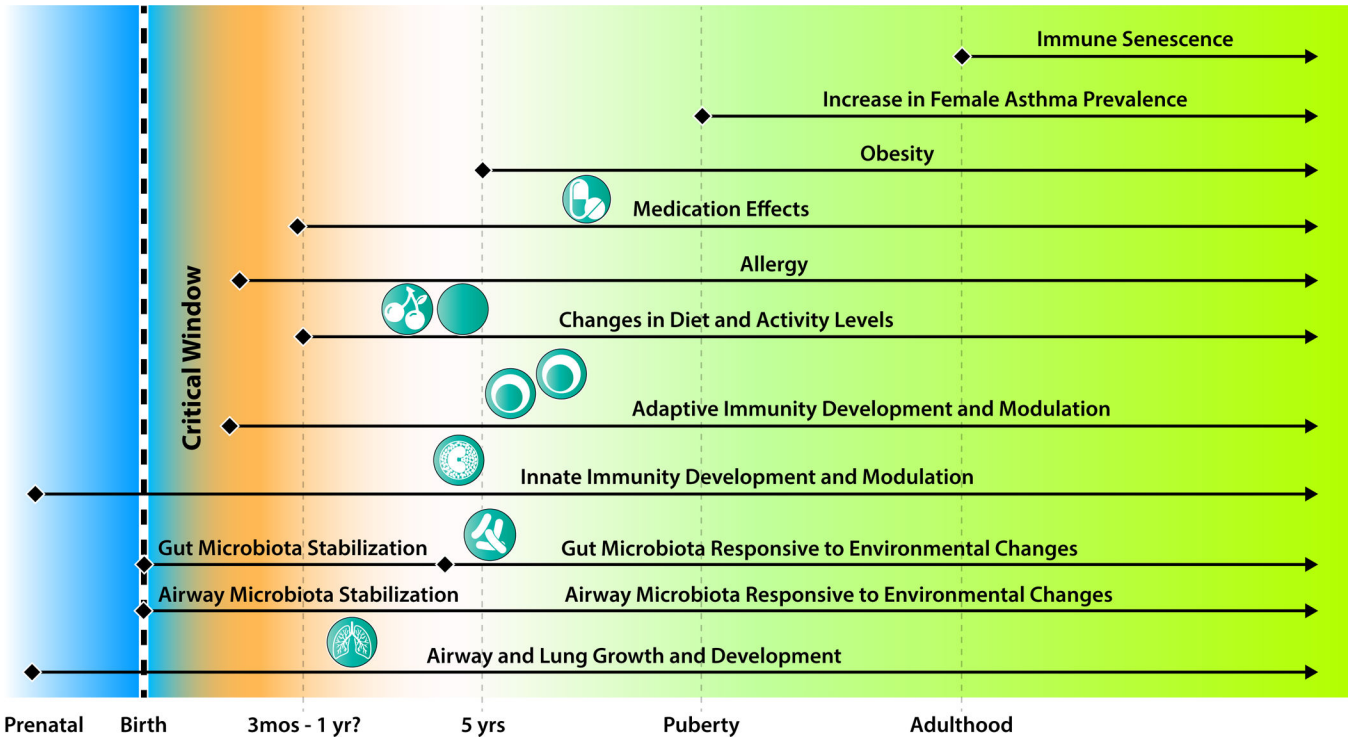

Figure 1.

Factors that can be critical influences on asthma pathogenesis and phenotype through effects on the gut and/or respiratory microbiomes. Mechanisms are understood for some but not all interactions.

Table 1

Term	Definition
Microbiota	The assemblage of all microorganisms present in a defined site or niche. Current usage often implies only bacteria.
Microbiome	The entire habitat, including the microbiota, their genomes (genes) and the surrounding site-specific conditions. Current usage often refers only to bacterial members of the 'biome'.
Mycobiota ***Mycobiome***	Variation on the above definitions referring specifically to fungi present in a habitat.
Metagenome ***Metagenomics***	Collection of genomes and genes from the members of a microbiota, characterized by the process of 'metagenomics' (i.e. shotgun DNA sequencing) to obtain information on potential functions of the microbiota
Dysbiosis	Descriptive for imbalance in a microbiome, such as lack of homeostasis in microbial composition or functions
Diversity	Multiple types of measures exist. A calculated index or measure reflecting the types, numbers and distribution of microbiota present within a sample or site (oc-diversity) or between different samples or sites (β-diversity).

Table 2.

Bacterial genera associated with asthma.

Bacterial Genus	Compartment	Link to Asthma
Bifidobacterium[9,14]	Gastrointestinal	Decrease abundance associated with risk for asthma in childhood
Dolosigranulum[30,34], *Corynebacterium* (C)[27,30,34]	Nasopharyngeal	Prevalence associated with lower risk of viral respiratory infections and asthma in children; (C) negatively associated with eosinophilic lung inflammation in adults
Faecalibacterium[8,9]	Gastrointestinal	Decreased abundance in children at risk for asthma
Haemophilus[43,34]	Nasopharyngeal	Increased abundance in early life associated with increased frequency of viral infections and likelihood of developing persistent wheeze
Moraxella[30,34]	Nasopharyngeal, Respiratory	Increased abundance in early life associated with increased frequency of viral infections and likelihood of developing persistent wheeze
Neisseria[27,30,34]	Respiratory	Increased abundance associated with asthma in adults
Rothia[8]	Gastrointestinal	Decreased abundance in children at risk for asthma
Streptococcus[34]	Nasopharyngeal, Respiratory	Increased abundance in early life associated with increased frequency of viral infections and likelihood of developing persistent wheeze
Veillonella[8]	Respiratory (R), Gastrointestinal (G)	(G) Decreased abundance in children at risk for asthma

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