Published in final edited form as:

Curr Opin Pulm Med. 2020 January ; 26(1): 27–32. doi:10.1097/MCP.0000000000000632.

Ecological Interactions in Asthma: from Environment to Microbiota and Immune Responses

Ariangela Kozik, PhD, Yvonne J. Huang, MD*

University of Michigan, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, 6301B MSRB3/SPC5642, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5642

Abstract

Purpose of Review—Asthma is a heterogeneous condition shaped not only by genetics but also host conditioning by environmental factors. Recognizing the ecological context of microbe-immune interactions across environments and body sites is a necessary step towards better understanding how human microbiota influence or drive the pathogenesis and pathophysiology of asthma in its various presentations.

Recent Findings—There is increasing evidence of a critical role for microbiota in asthma pathogenesis and outcomes across various body compartments, including the upper and lower airways and gut. We discuss recent studies from this area including: 1) development of a method to quantify microbial farm-effect in non-farm environments, 2) relationships between environmental microbial exposures and asthma prevalence across different geographies, 3) microbiome-mediated responses to ozone, and 4) microbiome-immune interactions within and across body compartments. Beyond bacteria, recent reports of asthma-associated differences in archaea and fungal organisms also are highlighted.

Summary—Collective evidence warrants application of an ecological framework to advance mechanistic insights into microbiota-immune interactions in asthma. This is necessary to achieve goals of developing successful therapeutic interventions targeting modification of microbiomes.

Keywords

asthma; microbiome; microbiota; exposures; environment

Introduction

Interest in the ‘microbiome’, defined as the collection of microorganisms (microbiota), their genomes and ecological interactions within a given environmental niche¹ is very relevant to asthma. The ecology of how microbes relate to one another, within a given environment (or microenvironment), and are influenced by changes in their environmental niche, is an important underlying premise of microbiome research². Ample evidence supports the framing of asthma as a disease shaped by both endogenous and environmental exposures, the latter including cross-talk between microbes and the immune system^{3,4}. In this context,

*corresponding author: yvjhuang@umich.edu, Tel: 734-936-5047.

Conflicts of Interest: none

several links have been observed between environmental risk factors, differences in human microbial exposures, altered patterns of human microbiota composition and asthma-associated immune responses. These interactions have now been examined in relation to the microbiota in different mucosal body compartments (nasal, lower airway, intestinal). Appreciating the ecological context of such interactions is a necessary step towards better understanding how human microbiota contribute to the pathogenesis and pathophysiology of asthma in its various phenotypes.

The clinical heterogeneity of asthma is well recognized⁵. However, the pathways underpinning the different asthma phenotypes still are incompletely understood but very likely are multifactorial⁶. The role of microbial exposures and of inter-individual differences in microbiota composition have been intensely studied to understand how these factors, within a complex ecosystem, mediate manifestations of asthma^{7–10}. Here, we discuss recent studies from this rapidly evolving area, that have substantively contributed new insights and hypotheses regarding microbiome-host interactions in asthma.

Environmental exposures and asthma risk

Investigation of the relationships between environmental microbial exposures and asthma risk has been rooted in the hygiene hypothesis, which postulates that exposure to microbes and microbial products in early childhood can diminish the risk of asthma and allergies¹¹. The hypothesis rests also on the observation of increasing prevalence of asthma and allergic disease parallel to the process of industrialization and urbanization. The establishment of a self-tolerant and functional immune system is a critical process in early life, wherein immunomodulation occurs on a scale that can have lifelong influence^{12–14}. In general, this is thought to be the period from birth to 3 years of age, with mounting evidence of an early ‘critical window’ (the first 100 days)^{14,15}. However, much remains to be understood mechanistically about how environmental exposures in early life (or across the lifespan) influence asthma risk and outcomes.

In the Urban Environment and Childhood Asthma (URECA) study, investigators observed that cumulative allergen exposure (specifically, cockroach, mouse and cat) - over the first 3 years of life was associated with allergic sensitization, which in turn associated with recurrent wheeze¹⁶. However, the study found unexpectedly an inverse relationship between allergen exposure within the first year of life and recurrent wheeze at age 3. In house dust samples collected in the first year of life, bacteria from the families of *Prevotellaceae*, *Lachnospiraceae* and *Ruminococcaceae* were associated with protection against atopic wheeze¹⁶. Importantly, the study found that the bacterial content of house dust modified the impact of the allergen content on the development of wheeze. Interestingly, children who developed neither atopy nor wheeze were exposed to the highest levels of allergens combined with the highest levels of the protective bacteria. This suggests that the indoor microbiome (in early-life) may mitigate the impact of allergen exposure on the immune system.

In a separate intervention study¹⁷, infants at high risk for asthma (family history, less exposure to pets) received either oral supplementation with *Lactobacillus rhamnosus* GG

(LGG) or placebo in the first six months of life, and the effects of LGG on gut bacterial community composition and metabolites examined. The investigators reported LGG-associated “rescue” of deficits that were observed in the gut microbiome of placebo-treated infants. These deficits included a delayed developmental trajectory of gut microbiota composition, increased glycolysis and depletion in anti-inflammatory lipids¹⁷. However, the effects of LGG were not sustained beyond the treatment period of six months. In discussing their findings, the investigators speculate that although probiotic supplementation may rescue deficits in how the gut microbiome assembles its composition and metabolic capacity in early life, it may not fully replace the influences of exposure to environmental microbes in driving expansion of the functional repertoire of gut microbiota.

Recent studies have further examined different geographic or ‘built’ environments, shedding light on differences in microbial exposures and relationships to asthma pathogenesis^{18–20}. A recent study of the transcriptomic activity of indoor (house dust) fungal communities showed an association between dampness conditions (modeled *in vitro*) and upregulation of fungal metabolic processes such as increased expression of allergen-encoding genes²⁰. In a seminal earlier study, Stein and colleagues²¹ examined the relationships between house dust bacterial content and asthma prevalence in children from U.S. Amish compared to Hutterite populations, known to differ in their rates of asthma and allergy (higher in Hutterites who apply industrialized farming practices)^{22,23}. House dust from Amish homes contained higher endotoxin levels, and analysis of a single pooled mattress dust sample from each population showed differences in bacterial composition. Parallel analyses of blood innate immune cell populations and their functional phenotype revealed significant differences between the groups²¹, and complementary animal studies demonstrated protection from experimentally induced asthma in mice exposed to Amish house dust. This work delineated mechanistic links that recapitulated evidence for a ‘farm’ effect protective against allergic asthma.

In a different geographic context, Kirjavainen and colleagues analyzed the microbial content of house dust collected from farm and non-farm homes in Finnish birth cohorts and introduced the farm home-resembling microbiota index (“FaRMI”), the first reported measure developed to characterize house dust as ‘farm-like’ or not²⁴. In general, a high FaRMI index was negatively associated with *Streptococcaceae*, and positively associated with *Sphingobacteria*, *Clostridia*, and *Alphaproteobacteria*. The study demonstrated an asthma-protective effect of farm-like indoor microbiota in non-farm homes; a high FaRMI index at the age of two months was associated with decreased risk of asthma by the age of six years. The environmental features of non-farm homes associated with a high FaRMI index were walking inside with shoes worn outdoors, presence of two or more older siblings, elevated indoor moisture, and increased age of the house. Strikingly, these environmental/lifestyle factors were not themselves associated with asthma protection in this study, suggesting that the microbial features associated with a high FaRMI index were more important in protection against asthma. A high FaRMI index was also associated with suppression of microbe-induced type 1 cytokines, providing evidence for an immune-protective/tolerance effect of farm-like microbes.

Focusing on the urban indoor environment, a recent study investigated the ‘aerobiome’ in the bedrooms of asthma patients in Chicago²⁵. The study found significantly different indoor

air microbes in rural, suburban, and urban homes, and reported a small number of prevalent bacteria forming a ‘core’ microbiome comprised of both human-associated organisms and outdoor bacteria. Additionally, houses that were physically closer to each other had similar microbiota, suggesting that a common source of indoor bacteria or common external factors promote the assembly of similar microbial communities. Although some evidence suggests that the latter is likely²⁶, more studies are needed. Richardson et al.²⁵ also described the influence of outdoor air exposure on the urban indoor microbiome, reporting that indoor *Alternaria* load was positively associated with open windows and increased indoor air bacterial diversity. Homes that kept windows open, had nearby flowering plants, and owned dogs also had increased bacterial diversity. Given this web of environmental influences, moving forward it will be important for studies of asthma to consider the ecological context of the various environments in which asthmatic patients reside, work and spend significant amounts of other time.

Asthma and associated microbiome features across mucosal compartments

Samples from different mucosal compartments (intestinal, upper and lower airways) have been studied to test hypotheses of whether and how altered human microbiota characteristics shape the clinical and immunologic features of asthma. The concept of a “common mucosal immune response”²⁷ serves as an underlying premise in support of now widely reported, asthma-associated differences in microbiota-immune interactions, both within and outside of the respiratory tract²⁸.

The gut microbiome, typically referring to analysis of fecal samples, has been extensively studied as it harbors the highest microbial biomass, serving as a constant trigger to maintain immune homeostasis²⁹. Until recently, bacterial members of a microbiome have been the primary focus of studies for reasons that include better established tools (molecular, analytic and reference knowledge base) to profile and understand bacterial ecology. However, there is increasing interest in non-bacterial members of the microbiota and their potential role in asthma pathogenesis^{30–32}. For example, a recent study³⁰ of bronchoalveolar lavage (BAL) and endobronchial brush (EB) samples showed significant differences in the fungal microbiota of asthmatic subjects with type 2-high versus type 2-low asthma phenotype irrespective of inhaled corticosteroid use which did not differ between the two subgroups. The investigators also showed evidence of bacterial-fungal relationships within the lower airway.

Another non-bacterial group present in microbiomes are archaea, a domain of life related to, but a distinct lineage from bacteria. Much is unknown about archaea in humans and their functional interactions. A recent study³¹ investigated the abundance of *Methanosphaera stadtmanae* and *Methanobrevibacter smithii*, two common gut archaea, in 472 fecal samples collected from children between 6–10 years of age in the KOALA cohort and examined whether the prevalence of these two species associated with asthma or allergy risk. The presence of *M. stadtmanae* was associated with lower asthma risk, which decreased over the three categories of *M. stadtmanae* abundance (absent, low, and high). Previous studies have

shown immunogenic activity in the gut and lung by *M. stadtmanae* in both human cells and mice^{33–35}. *M. stadtmanae* is common in farm environments and may contribute to immune tolerance. While this targeted study was limited by its cross-sectional design and the low overall abundance of *M. stadtmanae*, this is the first reported epidemiological association between a gut archaeal species and lower asthma risk in school-age children.

Recent studies in mice generated novel insights implicating an important role for gut bacteria in mechanisms by which exposure to ozone (O₃) affects pathophysiologic traits of asthma^{36–38}. Tashiro et al. examined the hypothesis that microbiota contribute to O₃-induced lung function responses in obese mice. Specifically, using leptin knockout (db/db) mice), they observed the following: (1) O₃ induced airway hyperresponsiveness (AHR) in obese mice, (2) antibiotic treatment attenuated O₃-induced AHR, and (3) transfer of colonic contents from obese mice into germ-free mice led to greater O₃-induced AHR than was seen in those who received colonic contents from non-obese mice³⁸. In another study, Cho et al. found that male mice exhibited greater O₃-induced AHR than female mice but that antibiotic treatment (oral cocktail of ampicillin, metronidazole, neomycin and vancomycin) abolished this sex-based difference, implicating involvement of microbiota³⁶. Interestingly, exposing female mice to a male microbiome reproduced the male-associated pattern of O₃-induced AHR. Although sex differences in the baseline (untreated) gut microbiome of mice were identified, the mechanisms by which gut bacteria mediate differential responses to O₃ remain unclear.

Nasopharyngeal (NP) microbiota patterns also have been examined in relation to asthma outcomes, particularly in children as these samples are more readily obtained. The composition of bacterial microbiota found in the upper respiratory tract differs greatly from that in the lower respiratory tract³⁹, as further discussed below. However, studies of NP samples (typically swabs) have revealed striking associations between different bacterial patterns, acute viral illnesses, and asthma^{15,40,41}. For example, a *Haemophilus*-dominant NP microbiome was associated with delayed clearance of respiratory syncytial virus in a multicenter study of infants with bronchiolitis⁴⁰. Longitudinal studies in infant cohorts have observed NP bacterial patterns that, in the setting of acute viral infections, associate subsequently with either transient or chronic wheeze phenotypes¹⁵. Intriguingly, the relationships appear to be modified by existing allergic sensitization¹⁵. In a multicenter study of asthmatic children living in U.S. inner cities, a *Moraxella*-dominant nasal microbiota associated with increased exacerbation risk, while a *Staphylococcus*- or *Corynebacterium*-dominated profile associated with reduced respiratory illness and exacerbation events⁴¹.

Although topographically complex, the respiratory tract can be sampled by different means and technologies, which may reflect different local tissue responses to stimuli that converge in shaping asthma. A recent study³⁹ examined paired nasal brush, induced sputum, and EB samples collected from three groups of adults: atopic mild asthmatic, atopic non-asthmatic, and non-atopic healthy subjects. In addition to bacterial microbiota comparisons between sample types and groups, relationships to immune markers profiled from EB and BAL were examined³⁹. The composition of microbiota differed significantly by sample type, with nasal brush being most distinct. However, similarities between EB and induced sputum were

greatest in the asthmatic group, who also shared more bacteria in common between nasal and EB samples, including members of the *Moraxella* genus. Nasal relative abundance of *Moraxella* was inversely related to that of *Corynebacterium*, and these two nasal bacteria showed significant positive and negative relationships, respectively, with markers of eosinophilic inflammation in BAL and other biomarkers. The findings³⁹ represent important efforts toward defining microbiota-immune relationships in asthma from different airway compartments within individuals.

Conclusions and Future Directions

The human body is an ecosystem consisting of multiple specialized ‘compartments’ and unique microenvironments, varying in their dynamic responses to exposures and perturbing stimuli. The latter include inhaled and ingested material such as pollutants, particulate matter, microbes, allergens, food and medications. Evidence continues to accumulate that microbiota have an important role in mediating asthma pathogenesis and shaping the asthma phenotype. Thus, an ecological framework is necessary to advance and understand mechanistic insights into how these interactions shape asthma. The web of microbiota-immune interactions almost certainly is multi-directional and has the capacity to profoundly shape host biology depending on context (Figure 1).

Considering the contribution of environmental factors to asthma development demands viewing an individual’s biological responses and microbiome as a function of concomitant and cumulative exposures (the ‘exposome’)⁴². It is crucial to develop innovative ways to measure environmental influences present in study populations, so that factors shaping indoor and host microbiota characteristics can be properly assessed. Just as important is capturing information on relevant endogenous factors, such as individual-specific health conditions or medication usage, that also can influence or even confound interpretation of microbiome-immune relationships. In addition, to achieve goals of therapeutic modulation of the microbiome to affect asthma outcomes, a more precise understanding of each individual’s microbiota and what components impact its capacity for dynamic, sustained responses to perturbing stimuli is needed². Currently, collective evidence from studies of probiotic, prebiotic, and synbiotic use for the treatment or prevention of asthma has not been sufficient to suggest clinical utility⁴³. However, some studies have shown positive effect on reducing risk of atopic sensitization and eczema⁴⁴. The ambivalent results to date expose the need for a more granular, ecosystem-informed understanding of asthma pathophysiology⁴⁵. They also highlight ongoing knowledge gaps about the functional activities of microbiota and factors that exert sustained influence on microbiome composition and function. As such, microbiome-targeting therapies likely will need to be ‘tuned’ to individual or population-specific characteristics (exposures, diet, age, sex).

In summary, a better understanding of the ecological mechanisms involved in microbial-immune interactions in asthma requires greater knowledge of the following: (1) the context of environmental exposures and lifestyle factors relevant to an individual or at a population level; (2) well-designed longitudinal studies that allow for examination of causal links in the human context, validation of evidence from animal models and vice versa; (3) the comparative contribution of microbiome-immune interactions in different body

compartments (gut vs. nasal vs. lower airway) to biological and clinical asthma phenotypes. Further incorporation of tools to generate different levels of biological data (i.e. transcriptomic, epigenomic, metabolomic, proteomic) for integrative analysis can provide deeper insight into molecular-level interactions, as discussed in a recent review⁴⁶. Challenges remain for researchers in all aspects of the above to execute this in human studies. Nonetheless, with rapidly evolving progress in investigative techniques, there is great potential to net significant scientific and future clinical gains through an ecosystem-wide understanding of asthma.

Acknowledgments

Financial support and sponsorship: Support for this work was provided by NIH grants T32HL007749 (A.J.K), R01AI129958 (Y.J.H.) and R03HL138310 (Y.J.H.)

References

1. Marchesi JR & Ravel J The vocabulary of microbiome research: a proposal. *Microbiome* 3, 31 (2015). [PubMed: 26229597]
2. Gilbert JA & Lynch SV Community ecology as a framework for human microbiome research. *Nature Medicine* 25, 884 (2019).
3. Sbihi H, Boutin RC, Cutler C, et al. Thinking bigger: How early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease. *Allergy* (2019). doi:10.1111/all.13812 • * Highlights the need for and the challenges of integrating indoor and outdoor microbiomes exposures into early-life studies of asthma.
4. Carr TF, Alkatib R & Kraft M Microbiome in Mechanisms of Asthma. *Clin. Chest Med.* 40, 87–96 (2019). [PubMed: 30691719]
5. Scherzer R & Grayson MH Heterogeneity and the origins of asthma. *Ann. Allergy Asthma Immunol.* 121, 400–405 (2018). [PubMed: 29928982]
6. Kozik AJ & Huang YJ The microbiome in asthma: Role in pathogenesis, phenotype, and response to treatment. *Ann. Allergy Asthma Immunol.* 122, 270–275 (2019). [PubMed: 30552986]
7. Murrison LB, Brandt EB, Myers JB & Hershey GKK Environmental exposures and mechanisms in allergy and asthma development. *J Clin Invest* 129, 1504–1515 (2019). [PubMed: 30741719]
8. O'Connor GT, Lynch SV, Bloomberg GR, et al. Early-life home environment and risk of asthma among inner-city children. *Journal of Allergy and Clinical Immunology* 141, 1468–1475 (2018). [PubMed: 28939248]
9. Kader R, Kennedy K & Portnoy JM Indoor Environmental Interventions and their Effect on Asthma Outcomes. *Curr Allergy Asthma Rep* 18, 17 (2018). [PubMed: 29470668] • ** Critical discussion of a study demonstrating that the greater burden of asthma morbidity among the African-American population can be explained by socioeconomic and environmental inequities rather than race-based biological or genetic 'proxy' associations with important factors that influence health outcomes (health literacy, exposures, environment, stress). Highlights the importance of adjusting research and patient care to examine and intervene in the social and environmental factors that shape asthma.
10. Matsui EC, Adamson AS & Peng RD Time's up to adopt a biopsychosocial model to address racial and ethnic disparities in asthma outcomes. *Journal of Allergy and Clinical Immunology* 143, 2024–2025 (2019). [PubMed: 30940518]
11. Liu AH Revisiting the hygiene hypothesis for allergy and asthma. *J. Allergy Clin. Immunol.* 136, 860–865 (2015). [PubMed: 26449798]
12. Altman MC, Whalen E, Togias A, et al. Allergen-induced activation of natural killer cells represents an early-life immune response in the development of allergic asthma. *Journal of Allergy and Clinical Immunology* 142, 1856–1866 (2018). [PubMed: 29518416]

13. Renz H, Holt PG, Inouye M, et al. An exposome perspective: Early-life events and immune development in a changing world. *Journal of Allergy and Clinical Immunology* 140, 24–40 (2017). [PubMed: 28673401]
14. Arrieta M-C, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 7, 307ra152 (2015).
15. Teo SM, Tang HHF, Mok D, et al. Airway Microbiota Dynamics Uncover a Critical Window for Interplay of Pathogenic Bacteria and Allergy in Childhood Respiratory Disease. *Cell Host & Microbe* 24, 341–352.e5 (2018). [PubMed: 30212648]
16. Lynch SV, Wood RA, Boushey H, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J. Allergy Clin. Immunol.* 134, 593–601.e12 (2014). [PubMed: 24908147]
17. Durack J, Kimes NE, Lin DL, et al. Delayed gut microbiota development in high-risk for asthma infants is temporarily modifiable by *Lactobacillus* supplementation. *Nature Communications* 9, 707 (2018). • The potential for therapeutic microbiome modification is promising, yet this work shows that these strategies must be informed by an understanding of the environmental context.
18. Martikainen M-V, Rönkkö TJ, Schaub B, et al. Integrating farm and air pollution studies in search for immunoregulatory mechanisms operating in protective and high-risk environments. *Pediatric Allergy and Immunology* 29, 815–822 (2018). [PubMed: 30152886]
19. Dannemiller KC Moving towards a Robust Definition for a “Healthy” Indoor Microbiome. *mSystems* 4, e00074–19 (2019). [PubMed: 31120023]
20. Hegarty B, Dannemiller KC & Peccia J Gene expression of indoor fungal communities under damp building conditions: Implications for human health. *Indoor Air* 28, 548–558 (2018). [PubMed: 29500849]
21. Stein MM, Hrusch CL, Gozdz J, et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *New England Journal of Medicine* 375, 411–421 (2016). [PubMed: 27518660]
22. Motika CA, Papachristou C, Abney M, Lester LA & Ober C Rising prevalence of asthma is sex-specific in a US farming population. *Journal of Allergy and Clinical Immunology* 128, 774–779 (2011). [PubMed: 21840584]
23. Holbreich M, Genuneit J, Weber J, et al. Amish children living in northern Indiana have a very low prevalence of allergic sensitization. *Journal of Allergy and Clinical Immunology* 129, 1671–1673 (2012). [PubMed: 22513133]
24. Kirjavainen PV, Karvonen AM, Adams RI, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nat. Med.* (2019). doi:10.1038/s41591-019-0469-4 • **This study presented the first reported measure for determining the degree of ‘farm-like’ microbial content in a particular environment. Standardizing and understanding the components of the long-discussed ‘farm-effect’ in theory may allow for comparisons of this index across studies and is essential for future efforts to engineer asthma-protective environments. This work also highlights the need for more research into the role of the non-bacterial microbiota in asthma.
25. Richardson M, Gottel N, Gilbert JA, et al. Concurrent measurement of microbiome and allergens in the air of bedrooms of allergy disease patients in the Chicago area. *Microbiome* 7, 82 (2019). [PubMed: 31159879] • ** This study presents a promising method for robust indoor air microbial sampling and analysis. This work highlights the importance of research into understanding indoor/outdoor microbiome assembly and the implications for asthma risk.
26. Wilkins D, Leung MH & Lee PK Indoor air bacterial communities in Hong Kong households assemble independently of occupant skin microbiomes. *Environmental Microbiology* 18, 1754–1763 (2016). [PubMed: 25923292]
27. Mestecky J The common mucosal immune system and current strategies for induction of immune responses in external secretions. *J. Clin. Immunol.* 7, 265–276 (1987). [PubMed: 3301884]
28. Huang YJ & Boushey HA The microbiome in asthma. *J. Allergy Clin. Immunol.* 135, 25–30 (2015). [PubMed: 25567040]
29. Hansen R, Gerasimidis K & Turner S Asthma causation and the gastrointestinal microbiome and metabolome: Might there be a signal, or is it just noise? *Journal of Allergy and Clinical Immunology* 144, 401–403 (2019). [PubMed: 31078572]

30. Sharma A, Laxman B, Naureckas ET, et al. Associations between fungal and bacterial microbiota of airways and asthma endotypes. *Journal of Allergy and Clinical Immunology* (2019). doi:10.1016/j.jaci.2019.06.025 • ** This large single-center study showed associations of fungal signatures and bacterial-fungal interactions with asthma inflammatory phenotype, highlighting a need for more research on fungal contributions to the airway microbiome in asthma and atopy.
31. Barnett DJM, Mommers M, Penders J, et al. Intestinal archaea inversely associated with childhood asthma. *Journal of Allergy and Clinical Immunology* 143, 2305–2307 (2019). [PubMed: 30796982]
32. Busse WW, Lemanske RF & Gern JE The Role of Viral Respiratory Infections in Asthma and Asthma Exacerbations. *Lancet* 376, 826–834 (2010). [PubMed: 20816549]
33. Lecours PB, Duchaine C, Taillefer M, et al. Immunogenic Properties of Archaeal Species Found in Bioaerosols. *PLOS ONE* 6, e23326 (2011). [PubMed: 21858070]
34. Bang C, Weidenbach K, Gutschmann T, et al. The Intestinal Archaea *Methanospiraeta stadtmanae* and *Methanobrevibacter smithii* Activate Human Dendritic Cells. *PLOS ONE* 9, e99411 (2014). [PubMed: 24915454]
35. Lurie-Weinberger MN & Gophna U Archaea in and on the Human Body: Health Implications and Future Directions. *PLOS Pathogens* 11, e1004833 (2015). [PubMed: 26066650]
36. Cho Y, Abu-Ali G, Tashiro H, et al. Sex Differences in Pulmonary Responses to Ozone in Mice. Role of the Microbiome. *Am. J. Respir. Cell Mol. Biol.* 60, 198–208 (2019). [PubMed: 30240285]
37. Cho Y, Abu-Ali G, Tashiro H, et al. The Microbiome Regulates Pulmonary Responses to Ozone in Mice. *Am J Respir Cell Mol Biol* 59, 346–354 (2018). [PubMed: 29529379]
38. Tashiro H, Cho Y, Kasahara DI, et al. Microbiota contribute to obesity-related increases in the pulmonary response to ozone. *Am J Respir Cell Mol Biol* (2019). doi:10.1165/rcmb.2019-0144OC
39. Durack J, Huang YJ, Nariya S, et al. Bacterial biogeography of adult airways in atopic asthma. *Microbiome* 6, 104 (2018). [PubMed: 29885665] • *This study from a multi-center cohort represents a rare effort to compare microbiota patterns from different airway compartments and examine relationships to immunologic features in mild atopic asthma.
40. Mansbach JM, Hasegawa K, Piedra PA, et al. *Haemophilus*-Dominant Nasopharyngeal Microbiota Is Associated With Delayed Clearance of Respiratory Syncytial Virus in Infants Hospitalized for Bronchiolitis. *J Infect Dis* 219, 1804–1808 (2019). [PubMed: 30590603]
41. McCauley K, Durack J, Valladares R, et al. Distinct nasal airway bacterial microbiotas differentially relate to exacerbation in pediatric patients with asthma. *Journal of Allergy and Clinical Immunology* (2019). doi:10.1016/j.jaci.2019.05.035
42. Cecchi L, D'Amato G & Annesi-Maesano I External exposome and allergic respiratory and skin diseases. *Journal of Allergy and Clinical Immunology* 141, 846–857 (2018). [PubMed: 29519451]
43. Ver Heul A, Planer J & Kau AL The Human Microbiota and Asthma. *Clinic Rev Allerg Immunol* (2018). doi:10.1007/s12016-018-8719-7
44. West CE, Dzidic M, Prescott SL & Jenmalm MC Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. *Allergol Int* 66, 529–538 (2017). [PubMed: 28865967]
45. Shukla SD, Shastri MD, Chong WC, et al. Microbiome-focused asthma management strategies. *Current Opinion in Pharmacology* 46, 143–9 (2019). [PubMed: 31357048] • *Discussion of the potential and challenges of developing microbiome targeted therapeutic strategies for asthma.
46. Tyler SR & Bunyavanich S Leveraging -omics for asthma endotyping. *Journal of Allergy and Clinical Immunology* 144, 13–23 (2019). [PubMed: 31277743] • *Discusses the powerful potential of integrating -omics techniques and analyses to advance definition of asthma endotypes.

Key Points

- The human microbiome operates in a complex ecosystem and is shaped by environmental and lifestyle factors that must be considered to understand its role in asthma pathogenesis.
- How microbiota influence asthma risk or asthma phenotype must consider the context of their behaviors, including the microenvironment and cumulative biological exposures.
- Improved understanding is needed of the comparative contribution of microbiome-immune interactions across different body compartments to asthma.

Figure 1. Ecological interactions shape host and microbial biology.

The human body is a complex ecosystem that experiences concurrent microbial and non-microbial exposures from external/built environments, other animals, diet, medication, and pollutants. The human ecosystem is also impacted by concomitant inflammatory and/or immune disorders. An ecological framework is necessary to advance mechanistic insights into these multi-directional interactions and how they shape asthma