

## The Microbiome and Epidemiology

## The respiratory microbiome: an underappreciated player in the human response to inhaled pollutants?

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## ABSTRACT

**Purpose:** Microbial communities in or on the body (i.e., the microbiome) are highly physiologically active and influence human health. Although environmental scientists are increasingly aware of the gut microbiome, the respiratory microbiome's role in the human response to inhaled pollutants is largely unknown. **Methods:** We reviewed the literature and present mechanisms by which the microbiome might mediate or modify human responses to inhaled pollutants.

**Results:** The respiratory microbiome has been shown to influence chronic lung disease exacerbations, and increasing evidence indicates a role in disease development. Research also suggests that the respiratory microbiome could plausibly metabolize inhaled pollutants or modulate host inflammatory responses to exposure. Because these responses depend on the microbes present, defining the composition of the resident microbiome and how microbial communities shift with exposure may help to explain variations in susceptibility to inhaled pollutants. Although more research is needed, significant measurement challenges remain for large epidemiologic studies of the respiratory microbiome.

**Conclusions:** The respiratory microbiome is likely an underexplored intermediate and potential cause of individual susceptibility to inhaled irritants/toxicants. Characterizing the microbiome's role in the human response to inhaled exposures could improve our understanding of the casual agents of exposure and suggest novel public health interventions.

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Inhaled irritants and toxicants represent important environmental exposures that are linked to death and disease. Health effects associated with these exposures include increased risks of lung cancer, heart and respiratory diseases, as well as metabolic disorders [1]. Given continuous exposures across the lifetimes of all people, it is estimated that 3.1 million deaths and 3.1% of disability-adjusted life years are lost globally per year because of exposures to outdoor particulate pollution. Exposures to air pollution from household combustion of solid fuels account for an additional 3.5 million deaths and 4.5% of disability-adjusted life years lost. Active and passive exposures to tobacco smoke further contribute 6.3 million deaths and 6.3% of disability-adjusted life years lost. Collectively, these impacts place the inhalation of air pollutants within the top 10 risk factors for the Global Burden of Disease [2].

Governmental regulations have successfully reduced outdoor air pollution concentrations and limited tobacco smoke exposures in the United States, with corresponding improvements in health [3–6]. Excess risk remains, however, even at levels of pollution below existing standards. In addition, not all individuals bear the same burden of disease from inhaled pollution exposures. Enhanced susceptibility has been reported among children, seniors, and persons with obesity, diabetes, coronary artery disease, and asthma [7,8]. Although these factors may be associated with a several-fold larger risk in any individual investigation, the characteristics conferring risk are not always consistent across studies. This suggests that traditional risk factors may be insufficient to fully identify those at enhanced risk.

In this article we hypothesize that microbial communities, especially those within the respiratory tract, may have an important, yet under-recognized, role in the human response to inhaled irritants/toxicants. Microbes, including bacteria, fungi, and viruses, reside on all human tissues exposed to the external environment. Collectively referred to as the microbiome, microbial communities in or on the body are highly physiologically

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active and known to influence the well-being of their host [9]. While most research is focused on relationships between the microbiome and health, environmental scientists have begun to pay increasing attention to the gut microbiome since microbes of the gut have been shown to metabolize environmental toxicants [10–12], stimulate host inflammatory response, and affect risk of host infection [9]. In spite of the clear physiological parallels, however, very little thought has been given to the role of the respiratory microbiome in the human response to inhaled irritants/toxicants. Here, we describe what is known about the respiratory microbiome, discuss how it and the gut microbiome might influence the human response to inhalation exposures, and encourage researchers to consider the respiratory microbiome as a mechanistic intermediate and potential cause of individual susceptibility to inhaled irritants/toxicants.

### What do we know about the respiratory microbiome?

For over 100 years, traditional wisdom was that in those without lung diseases, microbial communities resided only in the upper (i.e., mouth and nose) but not the lower (i.e., lungs) airways. More recently, however, the use of culture-independent, sequence-based techniques has clearly shown that the lungs are not sterile [13,14]. A summary of the current state of the science can be found in several excellent review articles [15–18] with brief highlights in the following paragraphs.

The origins of the microbial communities in the lungs include inspired air, which contains around 100 bacteria/m<sup>3</sup> [19], as well as those microaspirated and/or dispersed from the oropharynx [18,20]. With no physical barrier blocking bidirectional movement, the lungs also actively eliminate microbes via mucociliary clearance, cough, and innate and adaptive host immune responses. In health, alveolar macrophages, antibacterial surfactant, and other environmental conditions (e.g., temperature, pH, and nutrients) inhibit extensive bacterial growth, resulting in low colonization of the lungs as compared to other compartments. For example, it is estimated that there are approximately 1,000 times fewer microbes in the lungs than the mouth and 1 million to 1,000 million times fewer microbes than in the gut [13,21–24]. In spite of their low abundances, there are diverse and dynamic communities present. Bacterial species common to healthy lungs include *Streptococcus*, *Prevotella*, and *Veillonella* [14,20,22,23].

In diseased lungs, conditions often become more favorable for bacterial reproduction. Evidence of this growth is provided by a small, but growing, literature documenting different bacterial communities between healthy individuals and those with chronic respiratory diseases such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma [13,14,17,25–28]. For example, individuals with asthma or COPD have been reported to have higher abundances of Proteobacteria than healthy individuals [13,28]. This finding is important because this phylum includes known respiratory pathogens.

Interestingly, it appears as though the respiratory microbiome community structure may not just reflect the presence of a disease but may also correlate with disease severity. For example, differences in bacterial communities in the lungs have been associated with asthma severity [17,25,29,30] and with the frequency of exacerbations in patients with bronchiectasis [31]. There is also evidence that bacterial communities in the lungs are related to responsiveness to therapeutic interventions [27] and administration of probiotics has been shown to reduce the frequency of cystic fibrosis exacerbations [32]. Collectively, these findings suggest an important role for resident bacteria not only in disease development, as proposed by the hygiene hypothesis [33], but also for the initiation of exacerbations and potentially for treatments.

### How might the respiratory microbiome influence the human response to inhaled irritants/toxicants?

There is a growing understanding that our microbiota plays a critical role in the development and mediation of many human processes. As some of the first cells in the body encountering inhaled environmental toxicants, it is likely that the respiratory microbiome is both affected by these exposures and affects these exposures (Fig. 1). In the ideal world, the microbiome would serve as a protective shield for human host. However, it is also likely that the human host gets caught in the cross-hairs of the microbial response to inhaled pollutants and experience collateral damage from those interactions.

Inhaled irritants/toxicants deposit throughout the respiratory tract, with larger particles depositing more prominently in the upper airways (i.e., nose) and the smallest particles and gases reaching deep into the lower airways [34]. If these inhaled exposures induce direct oxidative stress or changes to growing conditions such as local alterations in pH, a likely result could be a shift in which microbes are present (i.e., the microbiome community structure). Disrupting the community structure of the microbiome could then result in changes in the functions it performs, with downstream consequences for human health. Specifically, we hypothesize that changes to microbial function will include alterations to the balance of antioxidant and proinflammatory conditions given that the microbiome is known to modulate the host immune response [13,16]. This is important for air pollution exposures since there is strong evidence from controlled and observational studies implicating oxidative stress and inflammation as key mechanisms in the pathogenesis of inhaled pollutants [35]. This conjecture is also consistent with findings that chronic inflammatory conditions such as asthma and diabetes [8,36–41], which themselves have been linked to the

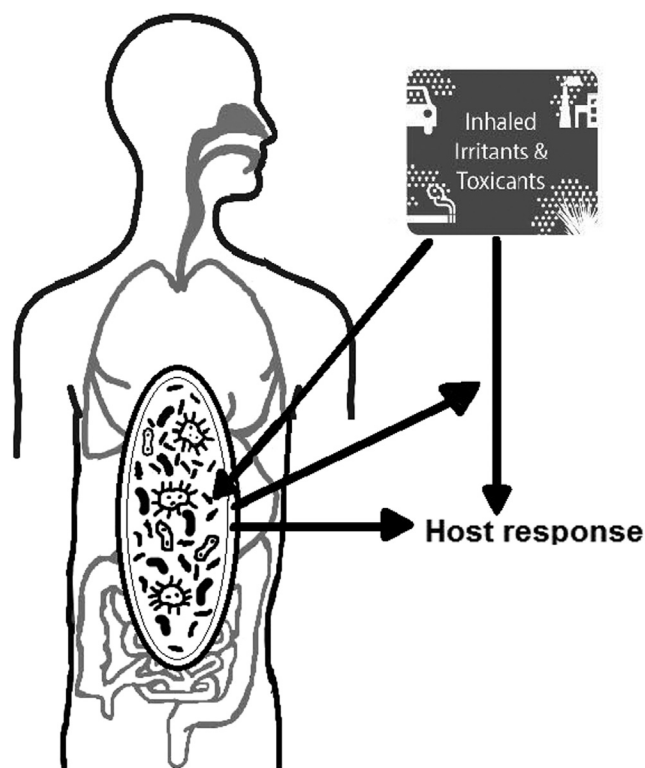


Fig. 1. Hypothesized interplay of inhaled irritants, the respiratory microbiome, and health.

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