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REVIEW ARTICLE

The possible role of particulate matter on the respiratory microbiome: evidence from in vivo to clinical studies

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Abstract

Environmental pollution, which contains ambient particulate matter, has been shown to have a significant impact on human health and longevity over the past 30 years. Recent studies clearly showed that exposure to particulate matter directly caused adverse effects on the respiratory system via various mechanisms including the accumulation of free radical peroxidation, the imbalance of intercellular calcium regulation, and inflammation, resulting in respiratory diseases. Recent evidence showed the importance of the role of the respiratory microbiome on lung immunity and lung development. In addition, previous studies have confirmed that several chronic respiratory diseases were associated with an alteration in the respiratory microbiome. However, there is still a lack of knowledge with regard to the changes in the respiratory microbiome with regard to the role of particulate matter exposure in respiratory diseases. Therefore, this review aims to summarize and discuss all the in vivo to clinical evidence which investigated the effect of particulate matter exposure on the respiratory microbiome and respiratory diseases. Any contradictory findings are incorporated and discussed. A summary of all these pieces of evidence may offer an insight into a therapeutic approach for the respiratory diseases related to particulate matter exposure and respiratory microbiome.

Keywords Particulate matter · Microbiome · Respiratory diseases · Air pollution · Lung

Introduction

Particulate matter (PM) is one of the global crisis air pollutants associated with the increase in acute and chronic mortality (Chen and Hoek 2020; Lepeule et al. 2012; Liu et al. 2019). PM can be categorized by aerodynamic diameters including: (1) PM10 or coarse PM, which has an aerodynamic diameter equal to or less than 10 µm; (2) PM2.5 or fine PM, which has an aerodynamic diameter equal to or less than 2.5 µm; and (3) PM0.1 or ultrafine PM, which has an aerodynamic diameter equal to or less than 0.1 µm (Donaldson et al. 2001; U.S. EPA 2021). PM0.1 is the smallest particle, which can penetrate most extensively and deeply, and pass directly into the circulation, also being retained in the body for long periods of time (Ophir et al. 2019). PM also contains metals (such as lead, iron, zinc), solvents [such as volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs)], and microbes (such as bacteria, fungus, and viruses), which cause many additional adverse health problems (Anderson et al. 2012). Inhalation is the major route of PM uptake, the PM then primarily affecting the respiratory system as the

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one initially exposed. Recent studies clearly showed that PM directly caused several effects on the respiratory system via various mechanisms including the accumulation of free radicals and an increase in their peroxidation, the imbalance of intercellular calcium regulation, and inflammation (Leikauf et al. 2020). All of those mechanisms can induce respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and lung cancer (Doiron et al. 2019; Hamra et al. 2014; Orellano et al. 2017; Yang et al. 2020).

Previous evidence showed that the respiratory microbiome plays a role on the immunity and development of the lungs (Dickson and Huffnagle 2015; Marsland et al. 2013). Therefore, the imbalance of the respiratory microbiome may cause the pathogenesis of several respiratory diseases. In accordance with this suggestion, several studies confirmed that many chronic respiratory diseases such as asthma, COPD, cystic fibrosis, and lung cancer were associated with a reduction in the diversity of the respiratory microbiome (Dy and Sethi 2016; Hosgood et al. 2019). Significantly, the *Proteobacteria* phylum and pathogenic genera such as *Haemophilus, Streptococcus,* and *Moraxella* were found to be overrepresented in the lungs of patients with COPD and asthma (Dy and Sethi 2016; Sokolowska et al. 2018).

Although there is much evidence to support the role of the respiratory microbiome in the pathogenesis of respiratory diseases, there is still a lack of knowledge regarding its role in the pathogenesis of respiratory diseases which were related to PM exposure. Therefore, this review aims to summarize and discuss all the in vivo to clinical evidence, which showed the effect of PM exposure on the respiratory microbiome related to respiratory diseases. A summary of all this information may provide insight into a therapeutic approach for the pathogenesis of respiratory diseases related to PM exposure and the respiratory microbiome.

Literature review methodology

In this review, the effect of particulate matter on the respiratory microbiome was reported in eight in vivo and ten clinical studies. The search carried out on the PubMed database included the search terms “particulate matter” and “respiratory microbiome”. Only original research articles related to the search criteria were included and published in English in the period 2016 to 2022.

Changes in the respiratory microbiome in relation to physiological and pathological conditions

The respiratory microbiome is characterized by the presence of bacteria, fungi, and other microorganisms in the respiratory tract. Although the respiratory microbiome is colonized during infancy, several factors from the host and environment including birth mode, feeding type, medication, smoking, or infection could cause changes in the composition of the respiratory microbiome (Bogaert et al. 2011, 2004b; Bosch et al. 2016, 2017). The respiratory microbiome can be examined from the nasal cavity to the lungs and is frequently divided into two parts: the upper respiratory tract (URT) and lower respiratory tract (LRT). The respiratory microbiome of the URT comprising the nasal cavity, the nasopharynx and oropharynx, and the portion of the larynx above the vocal cords, while the respiratory microbiome in the LRT comprises the trachea, bronchi, bronchioles, and alveoli. The URT microbiome varies as a consequence of maternal origin and environmental exposure. The LRT microbiome varies as a result of micro-aspiration and translocation of microbes from the URT, and the upper gastrointestinal tract (Bassis et al. 2015; Dickson and Huffnagle 2015). The major phyla of respiratory microbiome in both URT and LRT were *Firmicutes, Bacteroidetes*, and *Proteobacteria* (Morris et al. 2013). However, the density, diversity, and characteristics of respiratory microbiome were found to differ between the URT and LRT (Man et al. 2017). The nasal cavity is lined with skin and is dominated by a lipophilic microbiome including *Staphylococcus* spp., *Propionibacterium* spp., and *Corynebacterium* spp. The microbiome of nasopharynx was found to be more diverse than the nasal cavity containing overlap microbiomes from the nasal cavity such as *Moraxella* spp., *Staphylococcus* spp., and *Corynebacterium* spp. Meanwhile the different microbiome between nasopharynx and nasal cavity was *Haemophilus* spp. and *Streptococcus* spp. (Bosch et al. 2016; Man et al. 2017) The oropharynx showed the highest density and diverse microbiome with the dominant colonizers being streptococcal species, *Neisseria* spp., *Rothia* spp. and anaerobes, including *Veillonella* spp. and *Prevotella* spp. (Man et al. 2017). While the LRT microbiome was directly transferred from URTs, especially oropharynx, the composition of microbiome was commonly found in oropharynx including *Haemophilus* spp., *Staphylococcus* spp., and *Streptococcus* spp. (Man et al. 2017).

The respiratory microbiome was found to play a role in protecting the respiratory tract from pathogen colonization and in the development of the respiratory tract and immunity (Bäumler and Sperandio 2016; Bogaert et al. 2004a; Olszak et al. 2012). In normal situations, host–microorganism interaction was the most important mechanism in keeping the balance of respiratory health. The resident respiratory microbiome activated immune cells and released a signal to regulatory cells including alveolar macrophages and regulatory T cells (Sommariva et al. 2020; Zheng et al. 2020). To balance the microbes in the respiratory microbiome, the host responds by releasing antimicrobial peptides and secretory immunoglobulin A (sIgA) (Hapfelmeier et al. 2010;

Sommariva et al. 2020). These interactions regulate inflammation and the induction of microbial tolerance and contribute to the normal development and the maintenance of respiratory microbiome communities. Furthermore, there was a microbial inter-compartment cross talk between the respiratory and gastrointestinal tracts, known as the "gut–lung axis (GLA)" (Marsland et al. 2015). In this GLA, short-chain fatty acids, produced by the gut microbiome, could notify antigen-presenting cells in the lungs and cause the activation of lung inflammatory responses (McAleer and Kolls 2018). The GLA was found to be complex and unclear, and the mesenteric lymphatic system might be an important system for the translocation of bacteria, biomarkers, and metabolites into the GLA (Bingula et al. 2017; Marsland et al. 2015; McAleer and Kolls 2018).

It has been hypothesized that the respiratory microbiome might be associated with respiratory disease. Differences between the respiratory microbiome in healthy individuals and chronic pulmonary patients have been found (Dickson et al. 2015). In addition, an increase in potential respiratory pathogens such as *S. pneumoniae, H. influenzae*, and *M. catarrhalis* and a decrease in microbial diversity have been observed in association with respiratory tract infection (Laufer et al. 2011; Pettigrew et al. 2012). In asthmatic children, many studies reported the reduction in microbial diversity (Koppen et al. 2015; Kozyrskyj et al. 2007). Furthermore, the pathogenesis of each respiratory disease, such as architectural distortion of the lung in COPD, local immunologic response in the lungs, antibiotic use, biofilm formation, osmotic changes, and thickened mucus in cystic fibrosis, also influenced the respiratory microbiome and led to alterations in the microbial communities (O'Dwyer et al. 2016). Although there is much evidence to support the role of the respiratory microbiome in the pathogenesis of respiratory disease, there is still a lack of knowledge regarding the role of the respiratory microbiome on the pathogenesis of respiratory diseases related to PM exposure. Therefore, the following paragraph summarizes and discusses all the in vivo and clinical evidence concerning the effect of PM exposure on the respiratory microbiome.

Effects of acute exposure to particulate matter on respiratory microbiomes: reports from in vivo studies

Two studies have reported the effects of acute exposure to particulate matter on respiratory microbiomes. The first study investigated the impact of various concentrations of PM2.5 exposure on the lung microbiome in a mice model (Li et al. 2020). Interestingly, only exposure to medium (5.4 mg/kg) and high concentrations of PM2.5 (16.2 mg/kg), but not to a low concentration of PM2.5 (1.8 mg/kg) caused changes in the respiratory microbiome as indicated by increased α-diversity, *Bacteroidetes, Cyanobacteria, and Firmicutes*, and a decrease in *Proteobacteria* in the lungs (Li et al. 2020). The second study investigated the acute effect of PM on the lung microbiome via exposure to total suspended particles (TSP) into the broilers (Shen et al. 2022). Both doses of TSP exposure (4 and 8 mg/m^3) increased α-diversity, β-diversity, *Epsilonbacteraeota, Tenericutes*, *Firmicutes* and decreased *Bacteroidetes, Acidobacteria, Planctomycetes,* and *Gemmatimonadetes* in the lung tissue of broilers (Shen et al. 2022). Both findings suggested that acute exposure to PM increased microbial α-diversity and perturbed the bacterial profile, major profile changes being in *Firmicutes* and *Bacteroidetes. Firmicutes* increased in both studies, but *Bacteroidetes* increased in the lungs of mice and decreased in those of broilers. The differences between the changes in the respiratory microbiomes in broilers and mice may depend on the species. The dominant phyla in broiler's lungs in order of prevalence were found to be *Firmicutes, Bacteroidetes*, and *Proteobacteria,* respectively (Shen et al. 2022), while the major phylum in the mouse lungs was *Proteobacteria*, followed by *Bacteroidetes, Cyanobacteria, and Firmicutes,* respectively (Chen et al. 2020). This could explain that the difference in the dominant respiratory microbiome between species may depend on the source of PM. The source of PM from indoor farms might input microbes as a result of aerosolization of animal feces, feedstuff, skin, and feather fragments (Dai et al. 2020); therefore, the microbial composition from indoor PM could differ from the standardized PM.

Both studies reported the effects of acute exposure to particulate matter on lung inflammation and lung metabolites. In the mice model, all doses of exposure to PM2.5 (1.8, 5.4, 16.2 mg/kg) caused lung inflammation as indicated by increased inflammatory cell infiltration into the lungs and an increase in inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, IL-17, and tumor necrosis factor alpha (TNF-α) in both bronchoalveolar lavage fluid (BALF) and serum (Li et al. 2020). In addition, only exposure to medium (5.4 mg/kg) and high concentrations of PM2.5 (16.2 mg/kg) decreased lung metabolites such as valine, L-isoleucine, acetic acid, caproic acid, fumaric acid, and valeric acid (Li et al. 2020). In broilers, both doses of TSP exposure (4 and 8 mg/m^3) also increased inflammatory cytokines (IL-8) in the lungs, indicating lung inflammation (Shen et al. 2022). Both doses of TSP exposure also increased some lung metabolites (mostly in the carnitine category) and decreased some lung metabolites (crenolanib, dibutyl phthalate) in broilers (Shen et al. 2022). All of these findings demonstrated that acute exposure to PM altered the composition of the lung microbiome, affecting pulmonary inflammation and pulmonary metabolism. All of these findings are summarized in Table 1. The possible mechanisms involved in the induction of lung

pathology as a result of acute PM exposure are summarized in Fig. 1.

Effects of chronic exposure to particulate matter on respiratory microbiomes: reports from in vivo studies

Five studies reported on the effects of chronic exposure to particulate matter on respiratory microbiomes (Table 2). Two studies investigated PM2.5 exposure via intratracheal instillation, and the other three studies investigated PM2.5 exposure via inhalation. In the case of PM2.5 exposure via intratracheal instillation, 200 μg of PM 2.5 exposure for 3 weeks increased β-diversity, but decreased α-diversity in a mouse model (Chen et al. 2020). In addition, the alterations in bacterial profiles were observed in BALF, as indicated by decreasing *Streptococcus* and *Prevotella* and an increase in *Lachnoanaerobaculum, Peptoniphilus, and Actinomyces*. These changes in the respiratory microbiomes also caused changes in the lung morphometry as indicated by increased inflammatory cell infiltration around the bronchi of mice exposed to PM2.5 for 3 weeks (Chen et al. 2020). Interestingly, exposure to PM2.5 for 4 weeks via intratracheal instillation did not affect the changes in the microbial diversity in BALF of SCID mice (Yang and Xiao 2018). However, PM2.5 exposure resulted in increases in the *Cyanobacteria phyla, Streptococcaceae family, and Carnobacterium genus* and decreased *Bifidobacterium, Propionibacterium, and Campyrobacter* in BALF of SCID mice (Yang and Xiao 2018). Four weeks of PM exposure also caused changes in the lung morphometry as indicated by an increase in lung cancer tumors, tumor nodules, expression of IL-1β, matrix metalloproteinase-1 (MMP1), and vascular endothelial growth factor (VEGF) (Yang and Xiao 2018).

With regard to PM2.5 exposure via inhalation, the study into ambient exposure to PM2.5 for 8 weeks showed a rise in β-diversity and changes in microbial profiles in BALF of mice as indicated by an increase in some microbiomes profiles (*Proteobacteria, Tenericutes, Planctomycetes*, and *Acidobacteria*) and a decrease in others (*Firmicutes, Bacteroidetes, Actinobacteria, Chloroflexi, and Euryarchaeota*) (Ran et al. 2021). In addition, 8 weeks of exposure to ambient PM2.5 caused severe changes in the lung morphometry in a mouse model as indicated by bronchopneumonia, interstitial pneumonitis, thickening of the alveolae, and pulmonary edema (Ran et al. 2021). These changes were associated with an increment in inflammatory markers in the lung, as indicated by increases in IL-6, IL-1β, TNF-α, mast cell protease-1(Mcpt-1), and immunity-related GTPase (IRGM) (Ran et al. 2021). In addition, the changes in lung morphometry in PM2.5-treated mice were related to the imbalance of pulmonary metabolism which were related to an imbalance in energy consumption, including in the pyruvate pathway, glutamine pathway, lipid metabolism, and choline metabolism (Ran et al. 2021).

All of these findings suggested that the route of administration, dose, and duration of exposure to PM2.5 affected the changes of the respiratory microbiome such as microbiome diversity and microbiome profiles in the respiratory system. Moreover, the differences in the route of administration, dose, and duration of exposure to PM2.5 also caused a dose–response relationship of respiratory parameters. Intratracheal instillation, low dose (200 μg/2 day/week or 20 μl/twice/week), and short term (3–4 weeks) of PM2.5 exposure altered some immune responses and some pathological changes in the lung. However, by inhalation, high dose (226.50 mg/m^3, 8 h/day, 7 days/week), and long term (8 weeks) of PM2.5 exposure aggravated these pulmonary immune responses and pathological conditions.

In addition to the study regarding only the exposure to PM2.5, a study into chronic exposure to PM10, PM 2.5, and PM1 from biomass fuel (BMF) for 4 weeks also showed alterations in the respiratory microbiome in rats, specifically increased α-diversity, *Clostridiaceae, Ruminococcaceae, Hyphomonadaceae,* and *Veillonellaceae* (Li et al. 2017). Chronic exposure to BMF also stimulated the lung immune responses as indicated by increased levels of IgA, IgG, and macrophages in the BALF of rats (Li et al. 2017). In addition, chronic exposure to motor vehicle exhaust (MVE), which contained PM10, PM 2.5 and PM1, increased α-diversity, *Clostridiaceae*, *Brocadiaceae*, *Hyphomonadaceae Planococcaceae*, *Hyphomicrobiaceae*, and *Veillonellaceae* in the BALF of rats (Li et al. 2017). However, decreases in the bacterial profiles of *Aerococcaceae*, *Pseudomonadaceae*, *Comamonadaceae*, *Oxalobacteraceae*, and *Caulobacteraceae* were observed in the BALF of rats exposed to MVE (Li et al. 2017). In addition, only IgA was increased in the BALF of rats exposed to MVE (Li et al. 2017). All of these findings suggested that the exposure to BMF and MVE generated different respiratory microbiomes and consequently caused different respiratory immune responses. A possible explanation of the different responses of the respiratory microbiome and respiratory immune response between exposure to BMF and MVE could be due to the differences in sources and concentration of PM between BMF and MVE. In addition, BMF exposure contained higher PM (PM10, PM2.5, and PM1) and gas concentrations (NO1, NOx, and CO) than MVE. Therefore, the respiratory immune responses in the BMF exposed-group were higher than in the MVE exposed-group.

It has been found that the change of microbiome is affected by several factors, such as environmental stimuli and diet consumption (Ahn and Hayes 2021; Leeming et al. 2019). Several studies confirmed that consumption of a high-fat diet altered the gut microbiota and consequently

Table 1 Effects of acute exposure to particulate matter on respiratory microbiomes: reports from in vivo studies

Specimen/models	Particulate matter (type/route of administration dose/duration)	Major findings						Interpretation	References
		Respiratory microbiomes				Respiratory parameters			
		Diversity		profiles		Lung morphometry	Immune response	Others		
		α	β	Increase	Decrease				
BALF from 6-week-old male C57BL/6N mice	PM2.5 powder/intratracheal instillation/1.8, 5.4, 16.2 mg/kg/on day 1, day 4, and day 7	↑	N/A	1.8 mg/kg: ↔ 5.4 mg/kg: Phyla: *Bacteroidetes* *Cyanobacteria* *Firmicutes* 16.2 mg/kg Phyla: *Bacteroidetes* *Cyanobacteria* *Firmicutes*	1.8 mg/kg: ↔ 5.4 mg/kg: ↔ 16.2 mg/kg Phyla: *Proteobacteria*	1.8 mg/kg: ↑inflammatory cell infiltration into the peribronchiolar region, mainly neutrophils 5.4 mg/kg: ↑↑ inflammatory cell infiltration 16.2 mg/kg ↑↑ inflammatory cell infiltration ↑ alveolar septal thickening and fibrosis ↑ alveolar contraction and number of goblet cells	1.8 mg/kg: ↑ IL-1β, IL-6, IL-8, IL-17, and TNF-α only in BALF 5.4 and 16.2 mg/kg: ↑ IL-1β, IL-6, IL-8, IL-17, and TNF-α in both BALF and serum	Lung metabolite 1.8 mg/kg: ↔ 5.4 and 16.2 mg/kg: ↓ valine, acetic acid, L-isoleucine, valeric acid, caproic acid, fumaric acid	PM2.5 exposure significantly altered the lung microbiome composition, the levels of several metabolites involved in diverse metabolic pathways, and lung morphology in a dose-dependent manner	Li et al. (2020)
Lung tissue from broilers	TSP from broiler house/inhalation/4, 8 mg/m^3, /7-d exposure of 2 h/day for 3 days	↑	↑	4 and 8 mg/m^3: Phyla: *Epsilonbacteraeota* *Tenericutes* *Firmicutes*	4 and 8 mg/m^3: Phyla: *Bacteroidetes* *Acidobacteria* *Planctomycetes* *Gemmatimonadetes*	N/A	8 mg/m^3: ↑ lung IL-1β 4 and 8 mg/m^3: ↑ lung IL-8	4 and 8 mg/m^3: lung metabolite: ↑ mostly in carnitine category ↓ crenolanib, dibutyl phthalate	PMs led to the disruption of the microbial community and caused changes in the metabolites of the broiler lung	Shen et al. (2022)

BALF bronchoalveolar lavage fluid, *FcRn* neonatal Fc receptor, *IL* interleukin, *MΦ* macrophages, *MMP1* matrix metalloproteinase-1, *MOMA-2* macrophage antibody-2, *pIgR* polymeric IgA receptor, *PM* particulate matter, *ROS–RNS* reactive oxygen species and reactive nitrogen species, *SCID* severe combined immunodeficiency, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *TP* total protein, *TSP* total suspended particulate, *VEGF* vascular endothelial growth fact

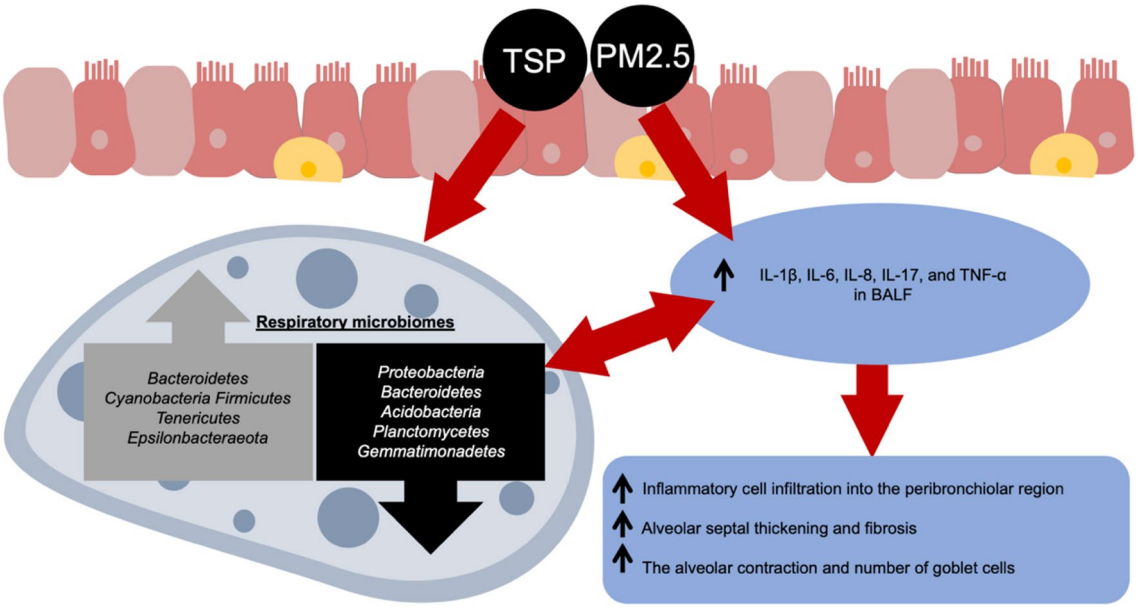

Fig. 1 Acute effects of PM2.5 and TSP on pulmonary parameters and respiratory microbiomes. Once PM2.5 and TSP have built up in the respiratory tract, TSP and PM2.5 have a bi-directional effect on the microbiomes at the phyla level, causing both increases and decreases. TSP and PM2.5 also caused elevation of the inflammatory markers in BALF. There is a correlation between pulmonary inflammatory markers and respiratory microbiomes. Increased inflammatory processes led to morphologic alterations including cell infiltration, septal thickening, and fibrosis. *BALF* bronchoalveolar lavage fluid, *IL* interleukin, *PM2.5* particulate matter 2.5, *TNF* tumor necrosis factor, *TSP* total suspended particulate

caused inflammation in several organs (Mulders et al. 2018; Silva Figueiredo et al. 2017; Wypych et al. 2017). However, only one study investigated the comparative effect of PM exposure between mice consuming whether a high-fat diet (HFD) or low-fat diet (LFD) (Daniel et al. 2021). Daniel and colleagues found that 30 days of PM exposure from diesel exhaust did not cause any changes in the respiratory microbiomes of LFD-fed mice (Daniel et al. 2021). Interestingly, 30 days of PM exposure from diesel exhaust decreased *Firmicutes* and *Bacteroidetes* in BALF of HFD-fed mice (Daniel et al. 2021). Although PM exposure activated lung immune responses and the changes in lung morphology in both LFD- and HFD-fed mice, PM exposure aggravated systemic neutrophils, systemic lymphocytes, lung nitrotyrosine, lung monocytes, and macrophages in HFD-fed mice. The findings of this study suggested that PM exposure altered the respiratory microbiome and consequently aggravated lung immune responses, leading to changes in the lung morphology in HFD-fed mice.

In the gut–lung axis, the gastrointestinal system is connected to the respiratory system by the mesenteric lymphatic system, which leads to the translocation of the microbiome, metabolites, and mediators between both systems (Enaud et al. 2020). Therefore, we speculated that this aggravative effect of the respiratory microbiome and lung immune responses in HFD-fed rats with PM exposure may be caused by the translocation of microbiomes, metabolites, and mediators from the gastrointestinal system.

All of these findings demonstrate that chronic exposure to PM altered the composition of the lung microbiome, which leads to pulmonary inflammation and lung morphometry. Furthermore, chronic PM exposure also aggravates these changes in the HFD-fed condition. The possible mechanisms of chronic PM exposure inducing these pathologies are summarized in Fig. 2.

Effects of particulate matter on respiratory microbiomes: reports from clinical studies

Ten studies reported on the effects of PM exposure on the respiratory microbiome. Three studies performed their research on children and infants, which demonstrated a reduction in microbial diversity and changes in the respiratory microbiome following PM exposure (Gisler et al. 2021; Li et al. 2021; Wu et al. 2021). In elementary school children, ambient PM exposure caused changes in the respiratory microbiome, as indicated by a reduction in α-diversity, an increase in some bacterial profiles (*Proteobacteria*, *Streptococcus*, *Gemella*), and a decrease in others (*Fusobacteria* and *Actinomyces*) (Li et al. 2021; Wu et al. 2021). In infants, the ambient PM exposure caused the changes in the respiratory microbiome, as indicated by a reduction in β-diversity

Table 2 Effects of chronic exposure to particulate matter on respiratory microbiomes: reports from in vivo studies

Specimen/models	Particulate matter (type/ route of administration dose/ duration)	Major findings							Interpretation	References
		Respiratory microbiomes				Respiratory parameters				
		Diversity		profiles		Lung morphometry	Immune response	Others		
		α	β	Increase	Decrease					
BALF from 6-week-old males BALB/c mice	PM2.5 powder/ intratracheal instillation/total 200 μg/2 days/week for 3 weeks	↓	↑	Genus: *Lachnoanaerobaculum* *Peptoniphilus* *Actinomyces*	Phyla: *Bacteroidetes* *Fusobacteria* *Genus: Streptococcus* *Prevotella*	↑ Inflammatory cell infiltration around the bronchi	N/A	N/A	PM2.5 exposure was associated with a decrease in lung microbiota diversity and altered bacterial profiles	Chen et al. (2020)
BALF from male CB17-SCID mice	PM2.5 solution / tracheal instillation/20 μl (PM 2.5 10 mg/ml)/ per time/twice per week for 4 weeks	N/A	N/A	*Phylum* *Cyanobacteria* *Family: Streptococcaceae* *Genus* *Carnobacterium*	Genus: *Bifidobacterium* *Propionibacterium* *Campylobacter*	↑ Lung cancer tumor, tumor nodule, expression of MMP1, IL-1β, and VEGF	N/A	↑ angiogenesis factor in blood, TP in BALF	PM2.5 perturbed micro-ecosystem of the upper respiratory tract of tumor-bearing mice	Yang and Xiao (2018)
BALF from 4- to 5-week-old female BALB/c mice	Ambient PM2.5/ inhalation/~ 226.50 mg/ m^3/8 h/day, 7 days/ week for 8 weeks	↔	↑	Phyla: *Proteobacteria* *Tenericutes* *Planctomycetes* *Acidobacteria*	Phyla: *Firmicutes,* *Bacteroidetes,* *Actinobacteria,* *Chloroflexi,* *Euryarchaeota,*	Bronchopneumonia, interstitial pneumonitis, thickening of the alveolar, and pulmonary edema	Blood: ↑ IL-6, IL-1β, TNF-α, Mcpt-1 and IRGM	Blood metabolites: ↑ TP, GLB, UA, TC, TG, HbA1c, pyruvate, amino acid, lipid, choline metabolism ↓ CK, albumin, glutamine BALF metabolite: ↓ choline, TMAO, creatine, betaine, citrate, pyruvate, glutamine	PM 2.5 exposure changed respiratory microbiomes, which was associated with activation of both local and systemic inflammation, and further exacerbated metabolic alterations	Ran et al. (2021)

Table 2 (continued)

Specimen/models	Particulate matter (type/ route of administration dose/ duration)	Major findings							Interpretation	References
		Respiratory microbiomes				Respiratory parameters				
		Diversity		profiles		Lung morphometry	Immune response	Others		
		α	β	Increase	Decrease					
BALF from 7–9 week-old males Sprague Dawley rats	PM10, 2.5 and 1 from biomass fuel/ inhalation/30 g/ exposure—1 h/ day, 5 days/week in 4 weeks	↑	N/A	Family: *Clostridiaceae, Ruminococcaceae Hyphomonadaceae Veillonellaceae*	↔	↔Mean linear intercepts, ratio of wall area to total bronchial area in lung sections	↑ MΦ, IgA and IgG in BALF ↔neutrophils, lymphocytes, eosinophils, IgM in BALF	N/A	PMs from biomass fuel exposure changed respiratory microbiomes, which was associated with the stimulation of macrophages, IgA, and IgG in the lung without morphology change	Li et al. (2017)
BALF from 7–9 week-old males Sprague Dawley rats	PM10, 2.5 and 1 from motor vehicle exhaust/inhalation/ N/A—2 h/day, 5 days/week for 4 weeks	↑	N/A	Phyla: *Proteobacteria* Family *Clostridiaceae Brocadiaceae Hyphomonadaceae Planococcaceae Hyphomicrobiaceae Veillonellaceae*	Phyla: *Aerococcaceae Pseudomonadaceae Comamonadaceae Oxalobacteraceae Caulobacteraceae*	↔Mean linear intercepts, ratio of wall area to total bronchial area in lung sections	↑ IgA in BALF ↔MΦ, neutrophils, lymphocytes, eosinophils, IgG, IgM in BALF	N/A	PMs from motor vehicle exposure changed respiratory microbiomes, changes associated with the stimulation of only IgA in the lung without other immune responses or morphology changes	Li et al. (2017)

Table 2 (continued)

Specimen/models	Particulate matter (type/ route of administration dose/ duration)	Major findings							Interpretation	References
		Respiratory microbiomes				Respiratory parameters				
		Diversity		profiles		Lung morphometry	Immune response	Others		
		α	β	Increase	Decrease					
BALF from 4–6 weeks-old male C57Bl/6 mice on a low-fat diet (LFD: 10% fat) or high-fat diet (HFD: 45% fat) consumption	diesel exhaust particles/oropharyngeal aspiration/35 µg/ twice a week for 30 days	N/A	N/A	↔	LFD: ↔ HFD: Phyla: *Firmicutes* *Bacteroidetes*	LFD & HFD: peribronchial inflammation surrounding the bronchioles, collagen deposition surrounding the bronchioles	Blood LFD: ↑ MΦ neutrophils, lymphocyte, monocyte HFD: ↑ MΦ, monocyte ↑↑ neutrophils, lymphocyte BALF: LFD & HFD: ↑ IgA, IgG, pIgR expression, Lung tissue LFD: ↑ TNF-α, IL-10, ROS–RNS, nitrotyrosine, MOMA-2 HFD: ↑ TNF-α, IL-10, ROS–RNS ↑↑ nitrotyrosine, MOMA-2	Lung LFD & HFD: ↑ TLR2, TLR4, t NF-κB p65, mucus production LFD: ↑ Muc4 HFD: ↑↑ Muc4	Diesel exhaust particles were associated with the activation of inflammation and bacterial alterations which was exacerbated by concurrent consumption of an HFD	Daniel et al. (2021)

BALF bronchoalveolar lavage fluid, *CK* creatine kinase, *GLB* globulin, *HbA1c* Glycated hemoglobin, *IL* interleukin, *IRGM* immunity-related GTPase M, *MΦ* macrophages, *MOMA*-2 monocyte and macrophage, *Mcpt-1* mast cell protease-1, *PM* particulate matter, *TC* total cholesterol, *TG* triglyceride, *TMAO* trimethylamine N-oxide, *TNF* tumor necrosis factor, *TP* total protein, *UA* uric acid

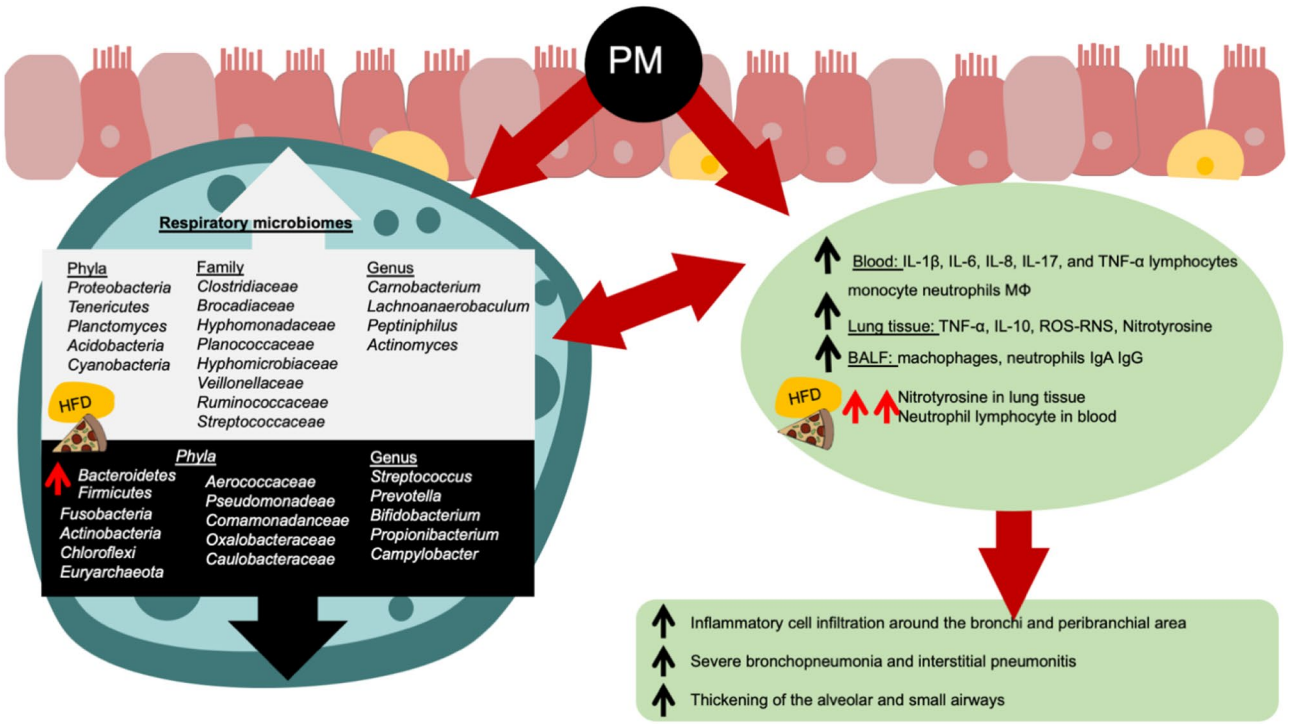

Fig. 2 Chronic effects of PM2.5 exposure on pulmonary parameters and respiratory microbiomes. PM2.5 exposure influences the microbiomes in both an upward and a downward direction. In addition, PM2.5 exposure increased inflammatory markers in both blood and BALF. Consumption of an HFD aggravated the increase of respiratory microbial profiles (*Bacteroidetes* and *Firmicutes*), which consequently aggravated white blood cells and nitrotyrosine in BALF. All of this cause an increase in inflammatory processes which led to morphological alterations such as cell infiltration, alveolar thickening, and pneumonitis. *BALF* bronchoalveolar lavage fluid, *IL* interleukin, *BALF* bronchoalveolar lavage fluid, *HFD* high-fat diet, *Ig* Immunoglobulin, *IL* interleukin, *MΦ* macrophages, *ROS–RNS* reactive oxygen species and reactive nitrogen species, *PM* particulate matter, *TNF* tumor necrosis factor, *TSP* total suspended particulate

and *Corynebacteriaceae* (Gisler et al. 2021). PM exposure not only caused respiratory microbiome changes, but also increased lung inflammation and reduced lung function in elementary school children, as indicated by increased lung inflammatory response including fractional exhaled nitric oxide (FeNO) and increased TNF-α, reduced forced expiratory volume (FEV), and diminished forced vital capacity (FVC) (Li et al. 2021; Wu et al. 2021).

In contrast to the studies in children and infants, the studies into the respiratory microbiome in adults showed divergent findings. A study on vendors in an open-air market reported changes in the respiratory microbiome of an increase in α-diversity, β-diversity, bacterial phyla (*Firmicutes, Fusobacteria, Actinobacter),* and many types of bacterial genus after acute exposure to ambient PM (Qin et al. 2019). In healthy subjects, Rylance and colleagues reported non-significant diversity changes, but presented differences in lung microbiome profiles with an increase in *Neisseria* and *Streptococcus*, and a decrease in *Tropheryma* in BALF of non-smoking adults (Rylance et al. 2016). However, Mariani and colleagues reported that short-term exposure to PM decreased α- diversity in healthy subjects (Mariani et al. 2021). In addition, these changes in microbial diversity were only associated with PM2.5 exposure, but not with PM10 exposure (Mariani et al. 2021). In contrast to short-term exposure, long-term exposure to both PM2.5 and PM10 increased *Lachnospiraceae* and *Ruminococcaceae*, while decreasing *Prevotellaceae*, *Veillonellaceae*, *Porphyromonadaceae*, *Fusobacteriaceae*, *Paraprevollaceae,* and *Flavobacteriaceae* in throat swabs of healthy subjects (Li et al. 2019). Furthermore, these changes in microbial profiles were associated with the reduction of lung function in healthy subjects, as indicated by decreased FVC and peak expiratory flow rate (PEFR) (Li et al. 2019). The findings from healthy subjects suggested that PM exposure caused changes in the respiratory microbiome with consequential stimulation of lung inflammation and impaired lung function.

Several studies demonstrated that PM exposure also affected the respiratory microbiome in patients with respiratory disorders (Hosgood et al. 2019; Mariani et al. 2021; Smit et al. 2017; Wang et al. 2019). In allergic rhinitis, only exposure to PM2.5, but not PM10 increased α-diversity in allergic rhinitis subjects (Mariani et al. 2021). In addition, exposure to PM2.5 also increased α-diversity in participants with chronic obstructive pulmonary disease (COPD) risk (Wang et al. 2019). In non-smoking female lung cancer

patients, PM exposure also increased α-diversity without any change in microbial profiles (Hosgood et al. 2019). Furthermore, a study into hospitalized community-acquired pneumonia patients showed an increase in *S. pneumoniae* and a decrease in *Lactobacillus* samples taken from oropharyngeal swabs (Smit et al. 2017). All of these clinical findings suggested PM exposure was related to the changes in the respiratory microbiome in both the normal flora and the potential pathogens, both of which may decline pulmonary function in patients.

Although clinical findings showed PM exposure was related to the changes in the respiratory microbiome, the microbial diversity and the microbial profiles in each study were different. A possible elucidation of this different response of respiratory microbiome could be due to the differences in the source of the PM (ambient pollutant, indoor pollutant, or fuel combustion), the host (infants, children, adult, healthy, or patient), site of sample collection (saliva, buccal, nasal, or BALF), and the type of study design (case–control, cross-sectional, or cohort).

Different sources of PM were found to affect microbial profiles in different ways. The major sources of outdoor PM were from transportation, biomass burning, construction, and industrial usage, the major source of indoor PM being from household fuel combustion. According to this information, microbes associated with outdoor PM mainly came from the soil, water, and marine sources, while microbes associated with indoor PM were found to be specific microbes related to a specific place or source (Cao et al. 2014). For example, household smoky coal, which represents a major indoor PM source, was associated with *Fusobacterium*, whereas a biomass fuel, which represents a major outdoor PM source, was associated with *Petrobacteria* (Hosgood et al. 2019; Rylance et al. 2016).

The host was also the other factors that affected the respiratory microbiome. The determinants of lung bacterial colonization in children were related to the mode of delivery and feeding type (Bosch et al. 2017, 2016). Furthermore, children were more susceptible to respiratory effects than adults, due to their lungs being less well developed in comparison to adults (Burtscher and Schuepp 2012). In addition, the respiratory airways of children are smaller in diameter and shorter in length, and there is a higher respiratory demand, which may cause high exposure to PM. In adults, healthy individuals and respiratory disease patients also had different microbial communities. Subjects with lung cancer and allergic rhinitis had lower microbial diversity compared with healthy matched controls (Hosgood et al. 2019; Mariani et al. 2021). A possible elucidation of these changes may relate to medication. Medication, especially antibiotics or steroids, was one of the factors that had an impact in the case of respiratory disease patients (Bosch et al. 2017): patients taking medication may have a lower microbial diversity in comparison with healthy subjects.

The site of sample collection was also important; the characteristics and quantity of normal flora differed depending on the site of the respiratory tract. The nasal cavity was the first point of contact to PM; therefore, it had a higher chance of being disrupted by all types of PM. Furthermore, the method of specimen collection was also important. The collection of LRTs samples could be performed by BALF and from sputum; however, even though sputum collection was less invasive it had higher chance of contamination by URTs material which may affect the results (Wang et al. 2019).

Although several pieces of evidence confirmed that PM exposure could cause changes in the respiratory microbiome, the mechanism regarding this effect is still unclear. One of the most common mechanisms related to inflammation, PM directly activated immunity, disrupted the balance of normal flora, and finally caused the changes of respiratory microbiome. PM exposure itself activates the inflammatory process and recruits alveolar macrophages to eliminate PM. Then alveolar macrophages have a reduced capacity to engulf bacteria, which results in the rapid growth of *Streptococcus pneumoniae* and results in an increase in the abundance of *Streptococcus* (Rylance et al. 2015). Another mechanism associated with PM exposure that affected the respiratory microbiome was via the indirect effect of epithelial cell damage, which lost the permeability properties as a result of an increase in the inflammatory process (Jungnickel et al. 2015). After a change in airway permeability, the airway defense mechanism was found to be disrupted, and it consequently released more antimicrobial peptides and mucus which caused an imbalance in the host–microbiome interaction (Hiemstra et al. 2015). Even though several studies showed an association between PM exposure and the microbial community, respiratory metabolism, and inflammation, findings were inconclusive regarding the determination of the causal pathway of these findings due to limitations of the studies. Therefore, additional studies are needed to investigate more fully the mechanisms of PM induction changes of respiratory microbiome. All of the findings of these studies are summarized in Table 3.

Conclusion

Both acute and chronic PM exposure can affect the respiratory microbiome. Changes in microbial diversity and abundance have been associated with respiratory disease; therefore, it may be helpful in the future to use the respiratory microbiome as a predictor of respiratory diseases. PM exposure also caused pulmonary inflammation and pulmonary

Table 3 Effects of particulate matter on respiratory microbiomes: reports from *clinical* studies

Subjects	Particulate matter (concentration, duration)	Study design	Major findings					Interpretation	References
			Respiratory microbiomes				Respiratory parameters		
			Diversity		Microbiota profiles				
			α	β	Increase	Decrease			
Buccal mucosa from 65 healthy elementary school students aged 5– 12	Ambient PM2.5 (~38.87 μg/m3/ day, 4 days before health measurement)	Cross-sectional	↓	N/A	Phyla: *Proteobacteria*	Phyla: *Fusobacteria*	Lung function: ↓ FVC, FEV1 (lag 0–2 days) Inflammatory response: ↑ TNF-α in saliva (lag 0–2 days), FeNO (lag 0–2 days)	Short-term exposure to PM2.5 altered colonization of microbiota, increased airway inflammation, and impaired lung function in children	Wu et al. (2021)
Buccal mucosa for 3 follow up periods from 62 elementary school students	Ambient UFP (12,745 N/cm3, consecutive 4 days)	Cohort	↓	N/A	Genus: *Streptococcus Gemella*	Genus: *Actinomyces*	Lung function: ↓ FEV1 (lag 0–96 h), FVC (lag 0–48 h to lag 0–96 h) Inflammatory response: ↑ TNF-α in all lags, FeNO (lag 0–24 h to lag 0–96 h)	UFP exposure was associated with reduced microbe diversity in the oral cavity, reduced lung function, and increased airway inflammation levels among children	Li et al. (2021)
Nasal swab at 5th week of life to the 1st year of life from 47 healthy infants	Ambient PM2.5 (~17.1 μg/ m3, 1-week exposure before each nasal swab)	Cohort	↔	↓	↔	Phyla: *Corynebacteriaceae*	N/A	Low-to-moderate exposure to air pollution may impact the nasal microbiota during the first year of life	Gisler et al. (2021)

Table 3 (continued)

Subjects	Particulate matter (concentration, duration)	Study design	Major findings					Interpretation	References
			Respiratory microbiomes				Respiratory parameters		
			Diversity		Microbiota profiles				
			α	β	Increase	Decrease			
Pharyngeal swab from 83 vendors in an open-air farmer's market	Pre-smog; Ambient PM 2.5 (80 µg/m3,2 days before smog) - Post smog; Ambient PM2.5 (217 µg/m3, within 24 h after smog)	Cross-sectional	↑	↑	Phyla: *Firmicutes, Fusobacteria Actinobacteria* Genus: *Leptotrichia, Corynebacterium, Veillonella, Dolosigranulum, unidentified_Chloroplast, Moraxella, Gemella, Actinomyces, Granulicatella, Haemophilus,*	↔	N/A	Short-term exposure to smog altered the composition of the pharyngeal microbiota	Qin et al. (2019)
BALF from Healthy, non-smoking, adults	Indoor PM from history of a domestic source of PM exposure and the percentage of black carbon in alveolar MΦ	Cross-sectional	↔	↔	Genus: *Neisseria Streptococcus*	Genus: *Tropheryma*	N/A	The difference levels of particulate exposure in macrophage carbon content showed differences in the lung microbiome profile	Rylance et al. (2016)
Nasal swab from healthy subjects	Ambient PM2.5 (22.9 µg/m3/6 days preceding nasal sampling) Ambient PM10 (14.9 µg/m3/6 days preceding nasal sampling	Cross-sectional	PM2.5 ↓ PM10 ↔	N/A	N/A	N/A	Plasmatic EV: PM10 ↓ LTA +, LPS +, CD14 + EVs PM2.5 ↔	PM exposure differently affected bacterial nasal microbiome composition and EV release in healthy people compared to AR	Mariani et al. (2021)

Table 3 (continued)

Subjects	Particulate matter (concentration, duration)	Study design	Major findings					Interpretation	References
			Respiratory microbiomes				Respiratory parameters		
			Diversity		Microbiota profiles				
			α	β	Increase	Decrease			
Throat swab 3 times with 7–8 days from 114 healthy non-smoking	Ambient PM2.5 and PM10 for last 2 years in high, medium, and low polluted region before health measurements	Cross-sectional	N/A	N/A	Phyla: *Actinobacterin* Class: *Clostridia Actinobacteria* Order: *Clostridiales* Family: *Lachnospiraceae Ruminococcaceae*	Phyla: *Bacteroidetes* Class: *Bacteroidia* Order: *Bacteroidales* Family: *Prevotellaceae, Veillonellaceae, Porphyromonadaceae, Fusobacteriaceae Paraprevollaceae Flavobacteriaceae* Genus: *Prevotella, Veillonella, Fusobacterium, Campylobacter Capnocytophaga*	Lung function: ↓ FVC ↓ PEFR	Living in polluted regions altered oropharyngeal microbiota and decreased lung function in healthy people	Li et al. (2019)
Nasal swab from patients with allergic rhinitis	Ambient PM2.5 (22.9 μg/m3/6 days preceding nasal sampling) Ambient PM10 (14.9 μg/m3/6 days preceding nasal sampling)	Cross-sectional	PM2.5 ↑ PM10 ↔	N/A	N/A	N/A	Plasmatic EV: ↔	PM exposure differently affected EV release and bacterial nasal microbiome composition in HS compared to AR	Mariani et al. (2021)
Sputum from COPD risk participants	Ambient PM2.5 (N/A/14 days before the sputum collection date)	Cross-sectional	↑	N/A	N/A	N/A	N/A	Airway microbiome diversity was influenced by PM2.5 exposure	Wang et al. (2019)

Table 3 (continued)

Subjects	Particulate matter (concentration, duration)	Study design	Major findings					Interpretation	References
			Respiratory microbiomes				Respiratory parameters		
			Diversity		Microbiota profiles				
			α	β	Increase	Decrease			
Buccal cell from 45 never-smoking females with lung cancer and 45 never-smoking female controls	Indoor PM from history of smoky coal use compared to clean fuel	Case–control study	↑	↔	↔	↔	N/A	Increasing α- diversity was associated with smoky coal use compared to clean fuel use	Hosgood et al. (2019)
Oropharyngeal swab from 126 hospitalized community-acquired pneumonia patients	Spatial location of home address distance between farm and home address (< 1 km and ≥ 1 km)	Cross-sectional	N/A	N/A	Species: *S. pneumoniae*	Species: *Lactobacillus*	N/A	Exposure to air pollutants may contribute to dysbiosis of upper respiratory tract microbiota in susceptible individuals	Smit et al. (2017)

COPD chronic obstructive pulmonary disease, *FeNO* fractional exhaled nitric oxide, *FEV* forced expiratory volume, *FVC* forced vital capacity, *PEFR* peak expiratory flow rate, *TNF* tumor necrosis factor

metabolism, which may interact or enhance with the respiratory microbiome to progress into respiratory diseases. Further studies should investigate the association between PM exposure, the respiratory microbiome, and various pulmonary parameters to understand more about the pathophysiology of respiratory diseases following exposure to air pollutants.

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Data availability Data will be made available on request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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