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Review

Air pollution and endocrine disruptors induce human microbiome imbalances: A systematic review of recent evidence and possible biological mechanisms

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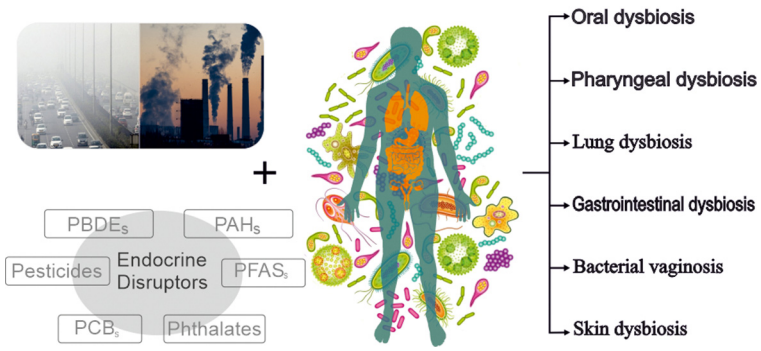
HIGHLIGHTS

- Environmental pollution could affect diversity of resident microbiota.
- Environmental pollution could affect abundance of resident microbiota.
- Studies suggest air pollution increases the abundance of *streptococcus*.
- Studies suggest air pollution increases the abundance of *veillionellales*.
- Scarcity of studies precludes observing consistent trends for other microbiota.

GRAPHICAL ABSTRACT



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ABSTRACT

A rich body of literature indicates that environmental factors interact with the human microbiome and influence its composition and functions contributing to the pathogenesis of diseases in distal sites of the body. This systematic review examines the scientific evidence on the effect of environmental toxicants, air pollutants and endocrine disruptors (EDCs), on compositional and diversity of human microbiota. Articles from PubMed, Embase, WoS and Google Scholar where included if they focused on human populations or the SHIME® model, and assessed the effects of air pollutants and EDCs on human microbiome. Non-human studies, not written in English and not displaying original research were excluded. The Newcastle-Ottawa Scale was used to assess the quality of individual studies. Results were extracted and presented in tables. 31 studies were selected, including 24 related to air pollutants, 5 related to EDCs, and 2 related to EDC using the SHIME® model. 19 studies focussed on the respiratory system (19), gut (8), skin (2), vaginal (1) and mammary (1) microbiomes. No sufficient number of studies are available to observe a consistent trend for most of the microbiota, except for *streptococcus* and *veillionellales* for which 9 out of 10, and 3 out of 4 studies suggest an increase of abundance with exposure to air pollution. A limitation of the evidence reviewed is the scarcity of existing studies assessing microbiomes from individual systems. Growing evidence suggests that exposure to environmental contaminants could change the diversity and abundance of resident microbiota, e.g. in the upper and lower respiratory, gastrointestinal, and female reproductive system. Microbial dysbiosis might lead to colonization of pathogens and outgrowth of

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pathobionts facilitating infectious diseases. It also might prime metabolic dysfunctions disrupting the production of beneficial metabolites. Further studies should elucidate the role of environmental pollutants in the development of dysbiosis and dysregulation of microbiota-related immunological processes.

Contents

1. Introduction

The Anthropocene epoch is characterized by a rapid population growth and industrialization resulting in an exponential increase of pollutants released into the environment. Emissions of air pollutants, from combustion sources, industrial processes, abrasion of surfaces and resuspension of dust causes widespread exposure to airborne toxicants with the potential to affect human health (Kampa and Castanas, 2008).

Epidemiological studies have identified effects of airborne pollution on the respiratory (Tobias et al., 2014; Xue et al., 2018), cardiovascular (COMEAP, 2018; Dehbi et al., 2017; Samoli et al., 2016), metabolic (Pope et al., 2015), neurological (Peters et al., 2019; Power et al., 2016) and reproductive system (Kihal-Talantikite et al., 2017). Some of the pollutants, such as nitrogen oxides (NOx), volatile organic compounds (VOCs) (Bolden et al., 2018), and ozone (O_3) are also well known for interfering with the endocrine system, and thus are also classified as endocrine disruptors (EDCs) (Rudel and Perovich, 2009). Particulate matter ($PM_{2.5}$ and PM_{10}) is also identified as an EDC (Huang et al., 2017), generally due to the array of organic chemicals adsorbed on its surface (e.g. plastic components such as phthalates, bisphenol, parabens, triclosan, alkylphenols, organobromine flame retardants, fluorosurfactants polyaromatic hydrocarbons, pesticides, herbicides, and some metals) (Darbre, 2018; Teil et al., 2016), and in some cases because of the core chemical composition of the PM itself (e.g. metal particles (Sanderson et al., 2016), polyaromatic hydrocarbons (Delgado-Saborit et al., 2009, 2010, 2013). Even more, emerging evidence is suggesting that air pollutants and other EDCs, such as phthalates, polychlorinated dibenzodioxins/furans, polyaromatic hydrocarbons (PAHs), pesticides, herbicides, and some metals, might affect the human microbiome (Valles and Francino, 2018), impacting on the lung (Li et al., 2019) and gut (Alderete et al., 2018) microbiomes.

The human microbiome (HM) consists of various microbiota that exists in tissues or biofluids such as skin, digestive system, biliary tract, external ear, mucous membranes, urogenital tract, etc. (Ursell et al., 2012). HM comprises of 10–100 trillion microbial cells, including bacteria, archaea, fungi, protists, and viruses (Peterson et al., 2009). The composition of the nasal cavity and nasopharynx microbiome differs from the skin, and oral cavity microbiome and is commonly composed of *Propionibacteria, Corynebacteria, Staphylococcus, Streptococcus, Dolosigranulum* and *Moraxella*; while oral cavity and oropharynx microbiome composition consists mainly of *Prevotella, Veillonella, Streptococcus, Haemophilus, Fusobacterium, Neisseria, Rothia* and *Corynebacteria* (Huffnagle et al., 2017; Shekhar et al., 2018). The lung microbiome is mainly composed of *Prevotella, Streptococcus, Veillonella, Neisseria, Haemo*philus, and *Fusobacterium* (Mathieu et al., 2018; Twigg et al., 2013). The composition of human skin microbiome is elevated on *Propionibacterium* for skin in contact with lipophilic environments; *Staphylococcus* and *Corynebacterium* species are abundant in skin in contact with moist, whereas infant skin has a high level of *Firmicutes* (Byrd et al., 2018; Capone et al., 2011). Finally, the gut microbiome contains mainly bacteria within the phyla *Fusobacteria, Actinobacteria, Firmicutes, Proteobacteria*, and *Bacteroidetes* (Rinninella et al., 2019).

The human microbiota is created on a delicate dynamic balance between symbiotic microbial cells and host organs, which play an essential role in the functioning and the physiological development of digestion, immune response, growth, and brain development (Pflughoeft and Versalovic, 2012). Whilst some changes in the microbiome might occur due to evolutionary changes, natural selection and genetics, others result as a consequence of exposure to environmental pollutants, diet variation, among others, which can also alter microbial composition and populations (Arumugam et al., 2011). Organophosphates (OPs), polybrominated diphenyl ethers (PBDEs), and bisphenol A (BPA) are among those environmental toxicants known to act as EDCs.

One of the most critical EDCs are the OPs, which trigger acute and chronic toxicity by inhibiting the activity of acetylcholinesterase (AChE) and results in the increase of cytokines production, and lipid peroxidation (Rock and Patisaul, 2018). Besides the alteration in AChE, there is some evidence that OPs exposure might affect human microbiomes and alter the oral and gut microbiomes, reducing the oral bacterial genus *Streptococcus* significantly (Stanaway et al., 2017). Correspondingly, exposure to OPs increased the abundance of *Methanobacteriales* in human gut microbiota, which is linked to higher body weight and larger waist circumference (Ahn et al., 2011). PBDEs are a significant part of environmental pollutant EDCs found in flame-retardants, electrical equipment, construction supplies, and furniture (Siddiqi et al., 2003). PBDE-28 was associated with a decrease in the microbiome diversity of *Lactobacillus*, which is essential for early life (Lu et al., 2015). Previous studies have suggested that modification in gut microbiota and diversity in early life could lead to the development of atopic disease immune phenotype (Kong et al., 2012; Stiemsma et al., 2014). BPA is another EDCs, which has similar structure to the estrogen and has high affinity for binding to estrogen receptors BPA, therefore altering the production of estrogen and other hormones (Rosenfeld, 2017).

The interactions between HM and exposure to pollutants play a vital role in human health and maintaining homeostasis. However, there is still a profound gap on the effect of exposure to environmental toxicants, such as air pollutants and EDCs, on the HM and the consequences of those effects on essential mechanisms where HM are involved. We have examined the existing scientific evidence through a systematic review to summarize the current available knowledge on the effect of environmental toxicants, such as air pollutants and EDCs, on human microbiota, identify research perceptions, current gaps, and future research.

2. Methods

We performed a systematic review of human microbiome alterations attributed to exposure to EDCs, pesticides in particular, and air pollutants, in compliance with PRISMA standards (PRISMA checklist in Supplementary Methods, File 1). The protocol was not registered.

2.1. Data sources and literature search strategy

We have queried the academic databases, including PubMed, Embase, and Web of Science Database for all English-language human studies published between February 22nd, 2000, to March 9th, 2021. The search strings are provided in the supplementary methods (File 2). We have filtered human studies.

It is of note that Google Scholar was searched on a regular basis in order to identify additional relevant citations and fill any possible gap. Moreover, we manually searched the reference lists from relevant original and review articles.

2.2. Eligibility criteria & study selection

First, we defined the scope of the study and made a clear research question. Second, we have selected those papers that addressed our question and objectives. Papers with not related outcomes, papers with repeated contents, literature reviews or non original articles were excluded from the references. Articles with clearly stated and focused objectives within the scope of our research were included in this review.

2.2.1. Inclusion and exclusion criteria

Studies were included in the review, providing they fulfill the following criteria:

1) Articles with study design including cohort, case-control, cross-sectional were considered, as well as those that reported results from a specific in vitro designed based on a dynamic model called Simulator of the Human Intestinal Microbial Ecosystem (SHIME®).
2) Exposure status to EDCs or air pollutants, has been clearly stated.
3) Alterations in any human microbial communities, including gut, lung, oral microbiomes, to name but a few, were recognized through microbial bioassay techniques, particularly 16S rRNA gene analysis, place counts, microbial diversity analysis, associated enzyme activities, etc.

Studies were excluded if 1) sufficient data on the interaction of EDCs with the microbiota were not provided; 2) the articles were not written in English; 3) were non-human studies; or 4) were non-original studies.

2.2.2. Screening and article selection

All articles captured by the literature search in the mentioned databases were imported into Rayyan, the systematic review web application to make decisions based on the defined criteria. After resolving duplicates, two independent reviewers (SEM and AA) screened the publications by title and abstract and conflicts were solved by a third reviewer (LG). Then the full text of retrieved studies was uploaded on Rayyan, and the second stage of screening was performed by the two independent reviewers (SEM and AA). Controversies at this stage were resolved by the third reviewer (LG). A flow diagram illustrates the result of this process that presented in Fig. 1.

2.3. Data extraction and quality control

A predefined informative form was prepared in excel datasheet for extracting information from the selected studies. Data was collected in a methodical manner by two reviewers (SEM and AA) independently, and the two additional reviewers (SP and JMDS) checked and incorporated them. The following information was entered in the form: First author & publication year, study type, study population, exposure, target microbiome and results. In the cases that the information extracted from the papers was not clear, the authors discussed to reach consensus. Two independent reviewers (SEM and JMDS) used the Newcastle-Ottawa Scale (NOS) to assess and rate the quality of individual studies based on the quality control protocol described in the supplementary methods (Supplementary Materials, File 6). Three independent reviewers (SEM, AA and SP) assessed the risk of bias for each included study using the NTP/OHAT risk of bias rating tool. A forth reviewer (JMDS) revised the risk assessment and settle any differences between two of the independent reviewers (Supplementary Materials, File 7).

3. Results and discussion

Upon revision of the literature, 31 studies were selected, including 24 and 5 studies focused on the effect of air pollutants and EDCs on human microbiome, respectively, and 2 studies examining the effect of EDCs using the SHIME® model. 19 studies focussed on the respiratory system, 8 on the gut (including 6 in human populations and 2 based in SHIME® model), 2 on the skin, 1 on vaginal and 1 on the mammary microbiomes.

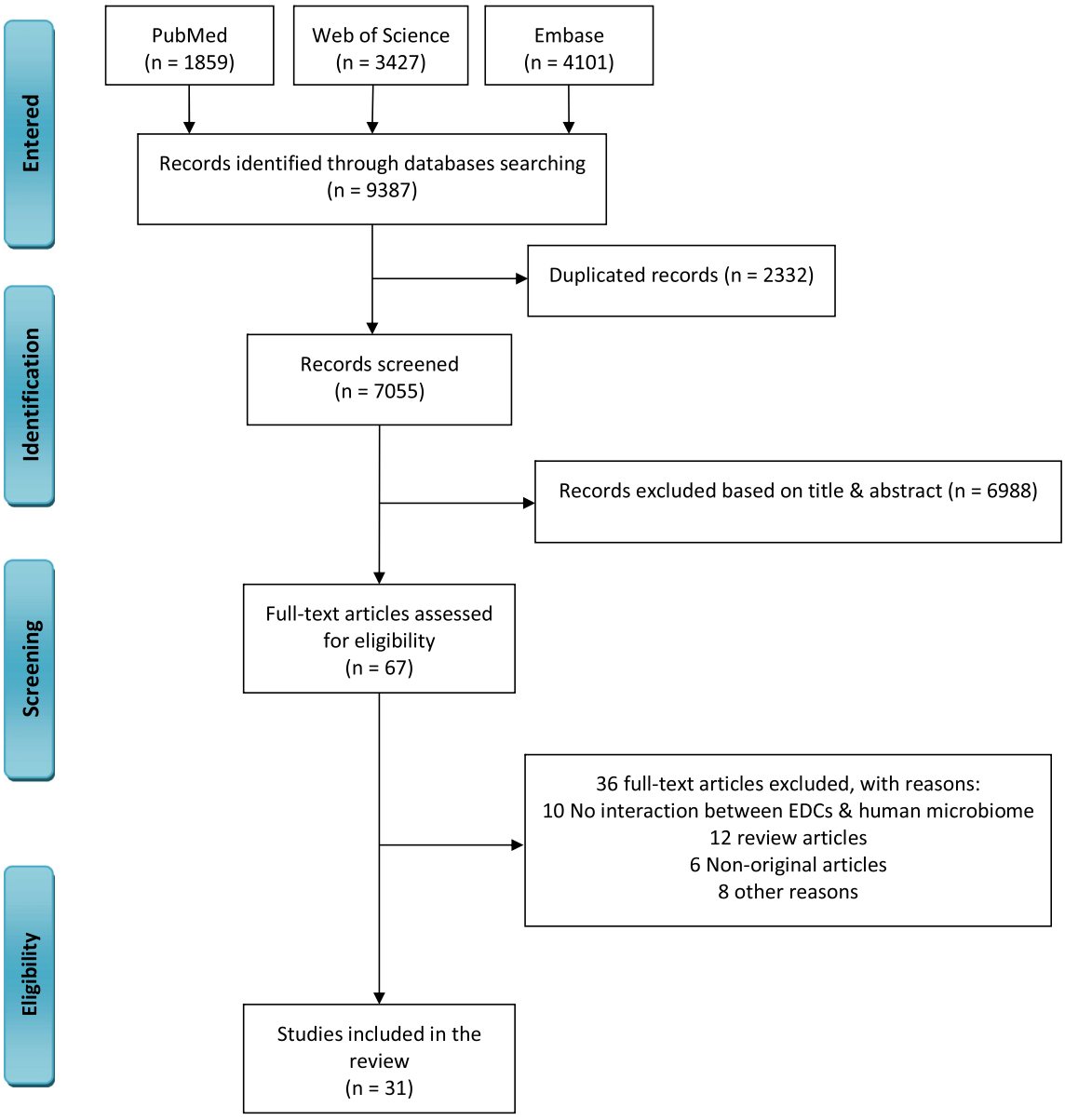

Fig. 1. Flow diagram of study selection based on the PRISMA statement.

An overview of the selected articles regarding the exposure of humans to pollutants and its effect on the microbiome can be found in Table 1 for human studies and Table 2 for SHIME® model studies. The articles categorized based on the site of effects are presented in detail in Supplementary File 3. The effect observed by scientific classification of the microbiome under study is detailed in Table S1, S2 and S3 (Supplementary Materials, File 4), and the results summarized by site of effects are presented in Fig. S1 (Supplementary Materials, File 5). The results of the NOS quality assessment of individual studies can be found in Supplementary Materials, File 6, whilst the results of the PNT/OHAT bias risk assessment is found in Supplementary Materials, File 7).

3.1. Environmental exposure and dysbiosis

The colonization of human microbiota commences after birth and takes about two to three years to develop into an adult-like microbiome. Underlying factors, including diet, medications, and environmental exposures might affect the infant microbiome development and subsequently in the modulation of the immune system. Furthermore, increasing evidence confirms that microbiota dysbiosis in the gut at early life could bring about the development of many respiratory diseases as the gut microbiome influences the immune cell maturation and resistance to pathogens (Sokolowska et al., 2018). Therefore, it is expected that exposure to environmental contaminants during childhood alters early-life microbial composition which in turn modulates the newborn immune system and puts life-long health at serious risks (Tamburini et al., 2016).

Evidence disentangling the interplay between environmental exposures and human microbiome and related health consequences is growing quickly. The symbiotic balance between the colonized microbiota in healthy individuals and the host, termed eubiosis, is highly fragile and susceptible to indigenous and exogenous factors, including the host genetic background, diet, environmental contaminants, antibiotics, and infectious agents all of which may impose harmful effects on the composition and function of the microbiome termed dysbiosis (Levy et al., 2017). Microbial dysbiosis can lead to disease worsening or enhanced vulnerability to new disorders. Under exposure to environmental

Table 1
Summary of results of effects of air pollutants and endocrine disruptors on the human microbioma from human studies.

Author	Study type	Study population	Exposure	Microbiome	Results
Stanaway et al., 2017	Longitudinal cohort	65 Hispanic adult farmworkers and 52 non-farmworkers from USA	Organophosphate insecticide: azinphos-methyl	Oral	Decrease *Streptococcus, Micrococcineae, Halomonas,Haemophilus, Actinomycineae, Granulicatella*, and *Gemella* in exposed workers.
Hu et al., 2020a	Longitudinal	97 healthy adults from China	Ambient O_3	Oral	Ambient O_3 was positively associated with α-diversity of oral microbiome, but the exposure-response curves only yielded positive associations in the range 60 μg/m^3 to 75 μg/m^3. With an interquartile range increase in ambient daily O_3, the abundance of *Proteobacteria* decreased by 3.1% and *Firmicutes* increased by 3.3%, whilst the *Proteobacteria:Firmicutes* ratio decreased by 0.9%.
Vallès et al., 2019	Cross-sectional	303 adults from the United Arab Emirates	Incense burning	Oral	Exposure to incense burning was associated with higher microbial diversity and overall microbial compositional changes in adults. Incense use was associated with significant depletion of the dominant taxon *Streptococcus*, even in occasional users.
Wu et al., 2021	Longitudinal panel	62 children from China	Short-term $PM_{2.5}$	Oral	Short-term $PM_{2.5}$ exposure was associated with decreased diversity in buccal mucosa bacterial community in healthy children. *Proteobacteria* and *Fusobacteria* had a higher and lower (respectively) relative abundance in the high exposure group compared to the low $PM_{2.5}$ exposure group.
Hu et al., 2020b	Cross-sectional	30 asthmatic and 30 healthy children from China	PAHs (atmospheric and urine)	Orophyrangeal	High and low molecular weight PAHs concentrations measured in ambient air where correlated with *Micrococcus* (*Actinobacteria*) and *Bacillus* abundance in throat samples of asthmatic children, respectively. The level of 1-OHPyrene in urine was also positively correlated with throat *Prevotella-7* abundance.
Smit et al., 2017	Cross-sectional	126 patients hospitalized with community-acquired pneumonia in The Netherlands	PM and endotoxins (from poultry farms)	Orophyrangeal	Oropharyngeal microbiota of patients with Community-Acquired Pneumonia living within 1 km of a poultry farm showed an increased abundance of *Streptococcus pneumoniae*.
Zhao et al., 2020a	Cross-sectional	22 adult patients with asthma from China	$PM_{2.5}$, SO_2, NO_2, O_3	Orophyrangeal	The composition and community structure of the oropharyngeal microbiome in adults with asthma are significantly different depending on air pollution exposure. NO_2 was the only environmental factor that significantly affected the microbial community structure of the oropharynx. The different genera associated with NO_2 were *Rothia*, *Actinomyces*, *Fusobacterium* and *Leptotrichia*. The altered taxa related to $PM_{2.5}$ were *Cupriavidus* and *Acinetobacter*. *Actinobacillus* and *Prevotella* showed a highly positive correlation with O_3.
Qin et al., 2019	Cross-sectional	83 adult outdoor farmer market vendors from China	PM_{10} and $PM_{2.5}$ (smog with $PM_{2.5}$ and PM_{10} levels up to 200 and 300 mg/m^3)	Pharyngeal	Exposure to smog altered the composition of the pharyngeal microbiota increasing the genera *Leptotrichia, Corynebacterium, Veillonella, Dolosigranulum, Moraxella, Gemella, Actinomyces, Granulicatella, Streptococcus, Staphylococcus* and *Haemophilus*. It decreased the genus *Prevotella* and *Neisseria*.
Carrión et al., 2019	Cluster-randomized-controlled trials	130 children with pneumonia and 130 healthy controls from Ghana	Household air pollution	Nasopharyngeal	Children living in households with wood burning stove had a higher mean number of microbial species than the children with dual-burner liquefied petroleum gas. This difference was driven by increased bacterial rather than viral species presence. Results were pronounced in pneumonia cases and attenuated in healthy controls. Higher prevalence of bacterial species were *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*.
Vanker et al., 2019	Birth cohort	982 mother-infant pairs from South Africa	Indoor air pollution (PM_{10}, CO, NO_2, benzene, toluene)	Nasopharyngeal	Mother: Antenatal exposure to NO_2 above ambient standards was associated with increased maternal nasopharyngeal carriage of

(continued on next page)

Table 1 (*continued*)

Author	Study type	Study population	Exposure	Microbiome	Results
					M. catarrhalis. Benzene exposure was associated with maternal *H. influenzae* carriage. Infant: PM_{10} was associated with an increased risk of *H. influenzae* at 6 months and *M. catarrhalis* at 12 months. NO_2 increased the risk of gram-negative *bacilli* carriage at 12 months, while CO increased the risk of *S. pneumoniae* carriage at 6 months
Zhao et al., 2020b	Cross-sectional	8 college students from China	Air pollutants ($PM_{2.5}$, SO_2, NO_2, and O_3)	Nasopharyngeal	Phyla *Acidobacteria*, *Gemmatimonadetes*, and genus *Symbiobacterium* were positively associated with $PM_{2.5}$. Genera *Streptococcus* and *Prevotella* were positively correlated with O_3 exposure occurring 30 days prior to collection.
Mariani et al., 2018	Cross-sectional	40 Healthy adults from Italy	PM_{10} and $PM_{2.5}$	Nasal	Inverse association between PM_{10} and $PM_{2.5}$ levels and α-diversity indices (Chao1, Shannon and PD_whole_tree). Higher abundance of *Actinobacteria*, *Proteobacteria* and *Firmicutes* with increased PM_{10} and $PM_{2.5}$ concentrations. *Moraxellaceae* showed a positive association with PM_{10} and $PM_{2.5}$
Padhye et al., 2021	Cross-sectional	132 patients with chronic rhinosinusitis (n=111) and healthy controls (n=21) from USA	$PM_{2.5}$	Nasal	For all patients, higher levels of $PM_{2.5}$ were negatively correlated with lower relative abundance (RA) of *Corynebacterium*. The RA of bacterial phyla, other bacterial genera, or alpha diversity indices were not correlated with $PM_{2.5}$ levels.
Wang et al., 2019	Cohort	115 healthy and at risk for COPD adults in China	$PM_{2.5}$	Airway	14% to 39% of the variance on the OTUs of *Fusobacterium*, *Actinobacillus*, *Oribacterium*, *Peptostreptococcus*, *Leptotrichiaceae* and *Catonella* was explained by variations on the $PM_{2.5}$ concentrations up to 14 days earlier.
Li et al., 2021	Longitudinal panel	62 children from China	Ultrafine particle (UFP)	Oral	Short term UFP exposure was associated with reduced diversity in buccal microflora. UFP exposure was also associated with increased *Streptococcus*, *Gemella*, and decreased *Actinomyces*.
Li et al., 2019	Cross-sectional	114 university students from China	$PM_{2.5}$ and PM_{10}	Respiratory tract	The relative abundance of *Bacteroidetes* and *Fusobacteria* were significantly lower, whilst *Firmicutes*, *Proteobacteria* and *Actinobacteria* higher in participants from polluted regions. In the highest polluted region, the abundance of *Prevotellaceae*, *Veillonellaceae*, *Porphyromonadaceae*, *Fusobacteriaceae*, *Paraprevollaceae* and *Flavobacteriaceae* was the lowest, whereas the abundance of *Lachnospiraceae* and *Ruminococcaceae* was the highest. The abundance of the most dominant *Bacteroidales* became significantly lower and that of *Clostridiales* significantly higher with increasing pollution.
Rylance et al., 2016	Cross-sectional	44 adults from Malawi	Household Air Pollution	Lung	Adults exposed to higher levels of particulates have higher abundances of Streptococcus and Neisseria (pathogenic) and lower abundance of *Tropheryma* within their lung microbiome. *Petrobacter* (uncommon environmental bacterium) abundance was higher in people using biomass fuel for household cooking and lighting, compared with exclusive use of electricity.
Hosgood et al., 2014	Case- Control	16 never smoking females with and without lung cancer in China	Polycyclic Aromatic Hydrocarbon household air pollution from burning coal	Oral and lung	Sputum samples had on average 488.25 species-level OTUs in the flora of cases who used smoky coal (PAHrich) compared with 352.5 OTUs among cases who used smokeless coal (PAH-poor).
Hosgood et al., 2019	Case- Control	90 never smoking females with and without lung cancer in China	Household air pollution: Fuel types used in the home (smoky coal, smokeless coal, others)	Respiratory tract	Increasing alpha diversity (observed species, PD whole tree, Shannon) was associated with smoky coal use compared to clean fuel use. No differences in alpha diversity were observed when comparing smokeless coal users and clean fuel users. Increased *Fusobacteriia* and decreased *Betaproteobacteria* in those using of smoky coal
Geller et al., 2018	Cross-sectional	854 female adults from USA	Phthalate metabolites	Vaginal	Concentrations of MnBP, ΣDEHP metabolites, and urinary creatinine were highest among women with bacterial Vaginosis

Table 1 (*continued*)

Author	Study type	Study population	Exposure	Microbiome	Results
Roslund et al., 2019	Cross-sectional	53 daycare children from Finland	Polycyclic aromatic hydrocarbons (PAHs) levels in soil and air	Skin	Elevated concentrations of PAH in soil was associated with altered *Actinobacteria, Bacteoridetes* and *Proteobacteria* communities on children's skin. The relative abundance of genus Mycobacterium on skin increased with higher surface soil levels of PAHs.
Wu et al., 2020a, 2020b	Cross-sectional	20 young and healthy Chinese women	Air Quality index (PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO)	Skin (face)	Long-term exposure to airborne pollutants could lead to significant alterations with an increase in both the abundance and diversity of facial bacterial microbiome. Increased abundance of *Staphylococcus, Haemophilus, Enhydrobacter, Prevotella*, and *Veillonella*.
Lee et al., 2011	Cross-sectional	83 female adults from Korea	Organochlorine pesticides	Gut	Serum organochlorine pesticides concentrations were positively correlated with feces levels of *Methanobacteriales*
Iszatt et al., 2019	Birth cohort	267 1 month old infant pairs from Norway	28 chemicals including PCBs, PBDEs, PFAS, and organochlorine pesticides	Gut	Environmental toxicants in breast milk, notably PBDE-28, PFOA, PFOS, and dioxin-like PCB-167, influence infant gut microbial composition. – Higher concentrations of PBDE-28 and the PFOS in breastmilk was associated with less microbiome diversity. – sub-OTUs of Lactobacillus were lower in abundance in samples from infants with relative "high" vs. "low" toxicant exposure. – PBDE-28 exposure decreased the Shannon diversity by 4%, and lowered the abundance of *Veillonella*, propionic, and acetic acids – PBDEs, PFOS exposure diminished the α--diversity – PCB-167 exposure was associated with greater β-diversity – PCB-105 correlated with abundance of *Clostridium perfringens*
Alderete et al., 2018	Cohort	43 adults from USA	Traffic-related air pollution (TRAP): nitrogen oxides	Gut	Freeway TRAP was correlated with decreased *Bacteroidaceae, Tissierellaceae* and *Corynebacteriaceae*, whilst increased *Coriobacteriaceae*
Zheng et al., 2020b	Panel study	11 asthmatic and 10 healthy children from China	Air Quality index (PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO) during clean and smog days	Gut	The composition of intestinal microbiome changed between clean and smog days among all children. During smog days, *Bifidobacteriaceae, Erysipelotrichaceae*, and *Clostridium* sensu stricto 1 decreased, and *Streptococcaceae, Porphyromonadaceae, Rikenellaceae, Bacteroidales S24–7* group, and *Bacteroides* increased in asthmatic children, while *Fusicatenibacter* decreased and *Rikenellaceae* and *Terrisporobacter* increased in healthy children. Abundance of *Firmicutes* negatively associated with concentration of $PM_{2.5}$, PM_{10}, NO_2, and SO_2
Fouladi et al., 2020	School-based cohort	101 young adults from USA	Air pollution (NO_2, PM_{10}, $PM_{2.5}$, O_3, total NOx)	Gut	Higher exposure to 24-h O_3 was associated with lower Shannon diversity index, higher *Bacteroides caecimuris*. Higher NO_2 exposure was associated with fewer taxa, including higher *Firmicutes*. The percent variation in gut bacterial composition that was explained by air pollution exposure was up to 11.2% for O_3 concentrations.
Liu et al., 2019	Cross-sectional	6627 adults from China	Air pollution ($PM_{2.5}$, PM_1, SO_2, NO_2, O_3, CO)	Gut	Both PM2.5 and PM1 were negatively associated with alpha diversity indices of the gut microbiota. The relative abundance of most *Firmicutes, Proteobacteria* and *Verrucomicrobia* bacteria were negatively associated with PM concentrations.
Tang et al., 2019	Cross-sectional	29 breastfeeding Chinese women	Hexa-chlorocyclohexane (HCH)	Mammary	High concentrations of hexachlorocyclohexane (HCH) were found in colostrum and predominantly *Proteobacteria* (67.6%) and *Firmicutes* (25.1%) were identified. The microbial diversity at the genus level differed between samples with different HCH levels. Two- or more fold changes were observed for Proteus at higher versus lower levels of exposure for alpha and beta isomers. In the gamma isomer *Enterococcus* were halved whilst Pseudomonas were 1.7 fold increased with high vs low g-HCH.

Table 2
Summary of results of effects of endocrine disruptors on the human microbioma from SHIME® Model.

Author	Feces sample	EDC	Exposure	Results
Joly et al., 2013	Healthy humans	Chlorpyrifos (CPF)	1 mg/day during 30 days	Exposure to CPF was associated with a strong increase over time in the numbers of *Enterococcus* spp. and a moderate increase in the numbers of *Bacteroides* spp. In contrast, the *Lactobacillus* spp. after 30 days was lower than at before the exposure and after 15 days. The effect of CPF exposure on *Bifidobacterium* spp. was less marked, with a decrease of about 1 log10 after 30 days relative to day 0 and day 15.
Reygner et al., 2016	Healthy humans	Chlorpyrifos (CPF) dissolved in rapeseed oil	1 mg/day in 10 ml oil for 4 weeks.	– Exposure to CPF was associated with a) Decrease in the colonic *bifidobacterial* population at day 15 and an increase in the colonic *E. coli* count at day 30. b) A rise in the total bacterial count, which reflected an increase in *Bacteroides* spp., *Clostridium* spp. and *enterobacterial* populations at day 15 and 30 c) A decline in the *bifidobacterial* count at day 300. – The exposure altered the total bacteria diversity in the different vessels by day 15, whereas the effect on the *bifidobacterial* population in the transverse and descending colon reactors was only apparent on day 30.

pollutants, human microbiome communities undergo dramatic changes that may lead to a wide range of abnormalities. In the following sections, potential biological mechanisms as consequences of the interaction between environmental stressors (i.e., air pollutants and EDCs) and human microbiota along with subsequent physiological outcomes are discussed in a systemic approach.

3.2. Potential mechanisms triggered by exposure to air pollutants

3.2.1. Oral/respiratory microbiome

Pulmonary microbiota consists of microorganisms, including bacteria, viruses, fungi, and archaea accompanied by their metabolites and genomes. The diversity and abundance of these microorganisms varies throughout the upper and lower airway tracts. Microbial colonization initiates immediately after birth; none withstanding, this process is extremely dynamic as the microbial composition experience underlying changes in response to environmental factors interconnected to individual genetic predisposition (Chotirmall et al., 2017). One of the main functions of healthy niche-specific microbial communities is establishing the state of symbiosis and restraining the colonization of pathogens and outgrowth of pathobionts (pathogenic commensals) caused by the disruption of healthy microbial composition. On the contrary, pathogens adopt various strategies to evade commensal-mediated resistance to colonization. As a consequence, maintaining the sensitive equilibrium between pathogens or resident pathobionts and the niche-specific microbiome is significant to control related infections and diseases (Kamada et al., 2013). Bacteria are part of the frontline response within the respiratory tract as they encounter and deal with inhalable media at the first stage.

There is a body of evidence suggesting that exposure to indoor and outdoor air contaminants exerts negative influences over the respiratory tract microbiota that may raise the risk of infectious diseases such as pneumonia (Rylance et al., 2016; Smit et al., 2017) and lung cancer (Hosgood et al., 2019; Hosgood et al., 2014).

3.2.1.1. Air pollution as a carrier of microbiota. Since air pollution is capable of carrying microbiota, including pathogens into the human body, a possible pathway via which the human microbiome undergoes compositional changes in gastrointestinal and respiratory tracts is the airborne transmission of contaminants, especially inhalable PM (Ji et al., 2019; Qin et al., 2019). Applying metagenomic methods for analyzing the microbial composition of Beijing's PM pollutants showed that the most plentiful microorganisms in PM during severe smog periods would be bacteria, some of which are pathogen or opportunist pathogens which are responsible for respiratory diseases (Cao et al., 2014). As evidenced by the significant diversified microbial composition of pharyngeal, Qin et al. reported that PM-attached pathogens could be inhaled by healthy individuals and results in the dysbiotic pharyngeal microbiome. They reported an increased abundance of 38 phyla, including *Firmicutes*, *Fusobacteria*, and *Actinobacteria* and 559 genera, including major respiratory pathogens *Streptococcus*, *Haemophilus*, *Moraxella*, and *Staphylococcus* after smog event. Their results suggests that exposure to smog with high levels of PM considerably alter pharyngeal microbiota (Qin et al., 2019). Critical alterations of pharyngeal flora could cause respiratory tract diseases to develop (Esposito and Principi, 2018; Teo et al., 2015) as an overwhelming majority of microbes, inducing pneumonia comes from the upper airway (Wu and Segal, 2018). Qin and colleagues revealed that 142 new genera in post-smog pharyngeal microbiota originate from different sources such as feces, sewage sludge, soil, and water resources (Qin et al., 2019). Such unexpected differences of microbiota between pre-and post smog episodes imply that PM might provide a central core for adsorption and transportation of microorganisms from different exogenous sources to the human airway tract.

In agreement with this suggestion, Rylance et al., observed *Petrobacter*, an uncommon bacterial genus associated with fossil fuels, in lung lavage of Malawian people using biomass fuels for cooking and lighting (Rylance et al., 2016). This unusual observation might suggest that PM is capable of translocating microbiota from the environment into the human body.

Further research is needed to provide compelling evidence on the capability of air pollutants to alter the human microbiome via carrier and translocation of microorganisms.

3.2.1.2. Air pollution, microbiome dysbiosis and coronavirus outbreaks. The likely physical mechanism (air pollutant microbe-carrier) could partially account for the increased mortality because of viral outbreaks, including SARS-Coronavirus during 2003 (Cui et al., 2003) and COVID-19 (Eric et al., 2020). A recent argument concerning the current COVID −19 epidemic suggests a positive association between long-term exposure to PM and COVID −19 related deaths in the U.S. (Wu et al., 2020a) and northern Italy (Eric et al., 2020; Piazzalunga-Expert, 2020). Scarce studies, however, subscribe to this view that although a variety of microorganisms exist in the ambient aerosol, PM-attached microbes from exogenous sources are different from those inhabited in the organs of the human body (Wang et al., 2019). Even if it was true, microbiota disequilibrium might occur once exposure to PM-enriched air pollution introduces new species into niche-specific communities of bacteria (e.g. respiratory microbiota) and negatively affect the microbial ecology and microbiota succession rate. Perturbations in microecology inflict changes to the microbial diversity, which may lead to the dominance of respiratory pathobionts, the commensal organisms that are found in a limited number within respiratory routes under normal conditions. Pathobionts are potential pathogens; however, in a balanced microbiome, they are not able to function as harmful organisms leading to disease. In fact, alterations in microbial composition and subsequent dysbiosis may influence the interactions between resident

microbiota, including indigenous pathobionts, with the host immune systems resulting in the development of respiratory infections and cancers.

3.2.1.3. Air pollution, microbiome dysbiosis and respiratory tract aerosol deposition. Inhalation of PM leads to the deposition of particles >10 μm (in diameter) in URT, whereas bacteria- and virus-containing PM with fewer diameters may reach LRT resulting in dysbiosis of the microbiome, especially in lower airways (Man et al., 2017). Dysbiotic airway flora, in turn, causes pathogenic microbes to increases leading to lung infections such as pneumonia (Mao et al., 2018). On the other hand, microbiota dysbiosis causes inflammation-inducing bacteria to increase resulting in lung carcinogenesis (Jin et al., 2019a, 2019b). Air pollution-induced dysbiosis in the respiratory airways' microbiome is investigated through the evaluation of taxonomic composition and is quantified via the measurement of α- and β- diversity, that is the number [richness], distribution [evenness], and relative abundance of various microbial taxa. Increasing α-diversity associated with the presence of livestock in home (Hosgood et al., 2019) and dysbiotic oropharyngeal microbiota composition associated with living near poultry farms (Smit et al., 2017). These results suggest that, to some extent, the translocation of microbes from the residential environment to the respiratory airways might result in enhanced growth of pathobionts. This was observed for *Fusobacterium* (Hosgood et al., 2019), *Streptococcus* (Hosgood et al., 2014; Rylance et al., 2016; Smit et al., 2017), *Moraxella* (Mariani et al., 2018), *Granulicatella* (Hosgood et al., 2014), and *Neisseria* (Rylance et al., 2016) in respiratory airways. Mariani et al. reported an inverse correlation between α-diversity and the abundance of a majority taxa of nasal bacterial with PM_{10} and $PM_{2.5}$ levels that induced dysbiosis in the nasal microbiota (Mariani et al., 2018). Evidence asserts that a decrease in bacterial diversity contributes to severe URT infections like acute otitis media (Pettigrew et al., 2012) and mucosal inflammation in chronic rhinosinusitis (Abreu et al., 2012). At the genus level, a positive relationship was observed between the levels of PM and *Moraxella* (Mariani et al., 2018). This genus possesses human pathogenic species such as *Moraxella catarrhalis* which declines the antiviral defense ability of bronchial epithelial cells, a potential risk factor for respiratory infections (Heinrich et al., 2016). Under exposure to high-level-PM smog, the relative abundance of species *M. catarrhalis* and *Haemophilus influenzae* in pharyngeal microbiota experienced an increase of 24% and 150%, respectively. *H. influenzae* is among the source of the most important causes of child morbidity and mortality, including but not limited to pneumonia (Walker et al., 2013). Findings from evaluating the oropharyngeal microbiome of healthy individuals in areas with different levels of air quality in northeastern china supports this notion that living in heavily polluted region can bring about microbial dysbiosis through altering the relative abundances of respiratory microbiota tract in all taxonomic levels, including Phylum, Class, Order, Family, and Genus (Li et al., 2019). Significant differences between α-diversity indices and the profiles of pharyngeal microbiota of healthy individual before and after exposure to smog with high concentration of PM demonstrated that microbiota- air pollution interactions exert fundamental influences leading to dysbiosis in upper and lower airway's microbiota (Qin et al., 2019).

3.2.1.4. Indoor air pollution, microbiome dysbiosis and lung cancer. Hosgood et al. (2014) reported that exposure to household air pollution enriches pathogenic bacterial OTUs in the lower airway (i.e. sputum samples) of never-smoking female lung cancer cases (Hosgood et al., 2014). Such finding provides an essential clue to establish an etiologic association between respiratory tract microbial imbalances and diseases attributed to air pollutants. To elucidate this relationship, they put forward a potential mechanism in which chronic lung inflammation is a link between lung cancer and pathogenic genera (e.g. *Granulicatella*, *Abiotrophia*, and *Streptococcus*) enriched via exposure to the smoke of household coal burning (Hosgood et al., 2014). Since the microbiota has an underlying role in the development of the innate and adaptive immune systems and immune homeostasis, they exert a determining effect over the immunologic reactions to different situations. Nuclear transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) and Signal transducer and activator of transcription 3 (STAT3) play a mediatory role in this regard (Elinav et al., 2013).

Similar to Hosgood et al.'s (2014) study, the significant abundance of pathogenic bacteria *Neisseria* and *Streptococcus* has been reported in bronchoalveolar lavage samples from Malawian adults exposed to high household PM (Rylance et al., 2016). *Streptococcus* and *Neisseria* are the pathogens involved in bacterial pneumonia and meningitis, respectively.

3.2.1.5. Air pollution, microbiome dysbiosis and pneumonia. Elevated airborne dust concentrations were associated with for bacterial pneumonia in Niger (Jusot et al., 2017). Short- and long- term exposure to air pollution associates positively and significantly with the hospitalization of children and the elderly due to pneumonia (Neupane et al., 2010; Nhung et al., 2017). Among children, the pollutant-specific excess risk percentage per 10 $\mu g/m^3$ increment of pollutants was 1.5% (95% CI: 0.6%–2.4%) for PM_{10} and 1.8% (95% CI: 0.5%–3.1%) for $PM_{2.5}$ (Nhung et al., 2017). Likewise, a strong association between long-term exposure to higher concentrations of $PM_{2.5}$ (OR=2.26, 95% CI: 1.20–4.24) and nitrogen oxide (OR=2.3, 95% CI: 1.25–4.21) with hospitalization for CAP was observed over the 5th–95th percentile range increase of exposure (Neupane et al., 2010).

Residential proximity to places such as livestock and poultry farms, which are important sources of PM emissions, may increase the risk of pneumonia in residents.

Inducing air pollution- derived pneumonia infection in the lower respiratory tract (LRT) may be mediated by alterations in the microbiome residing in the upper airway tract, including anterior nares, nasal passages, paranasal sinuses, the nasopharynx, and oropharynx (Wu and Segal, 2018). Smit and colleagues suggested an 11% increase in the risk of CAP in individuals living near poultry farms may have an association with changes in the community composition of oropharyngeal microbiota (Smit et al., 2017).As shown in Fig. 2, such microbial imbalance may result in a decrement in the colonization resistance, a mechanism for the protection of normal upper respiratory tract (URT) flora against incursion by new and pathogenic microbiota (de Steenhuijsen Piters et al., 2015). This may in turn diminish the control over pathogenic commensals leading to the overrepresentation of *S. pneumoniae* and eventually the incremental risk of respiratory tract infection.

3.2.1.6. Air pollution, microbiome dysbiosis and meningitis. Exposure to elevated airborne dust concentrations was identified as a significant risk factor for bacterial meningitis in Niger (Jusot et al., 2017). In industrialized countries, exposure to high concentrations of PM_{10} was also associated with increased incidence of meningitis (Michele et al., 2006).

3.2.1.7. Role of inflammation and oxidative stress as mediators in the relationship among air pollution, microbiome dysbiosis and pneumonia. The putative role of PM in the modulation of innate immune responses is implicated in the imbalanced respiratory microbiota. Phagocytosis and release of pro-inflammatory mediators such as reactive oxygen species (ROS) are two pathways for PM removal from the lung by alveolar macrophages, the resident phagocytes of lower airways. High PM loading of alveolar macrophages as a potential result of living in the vicinity of PM emission sources increases cytokines interleukins 6 (IL-6) and IL-8 and impairs phagocytosis of pathogens such as *S. pneumoniae* and *Mycobacterium tuberculosis* (Rylance et al., 2015). Besides, PM-derived oxidative stress enhances the adhesion of *S. pneumoniae* to human airway epithelial cells which is taken into account as a prerequisite for infection (Mushtaq et al., 2011) (Fig. 2). Such compelling evidence emphasizes the possible relevance on a mechanistic link between exposure to high levels of air pollutants, PM in particular, and pneumonia incidence.

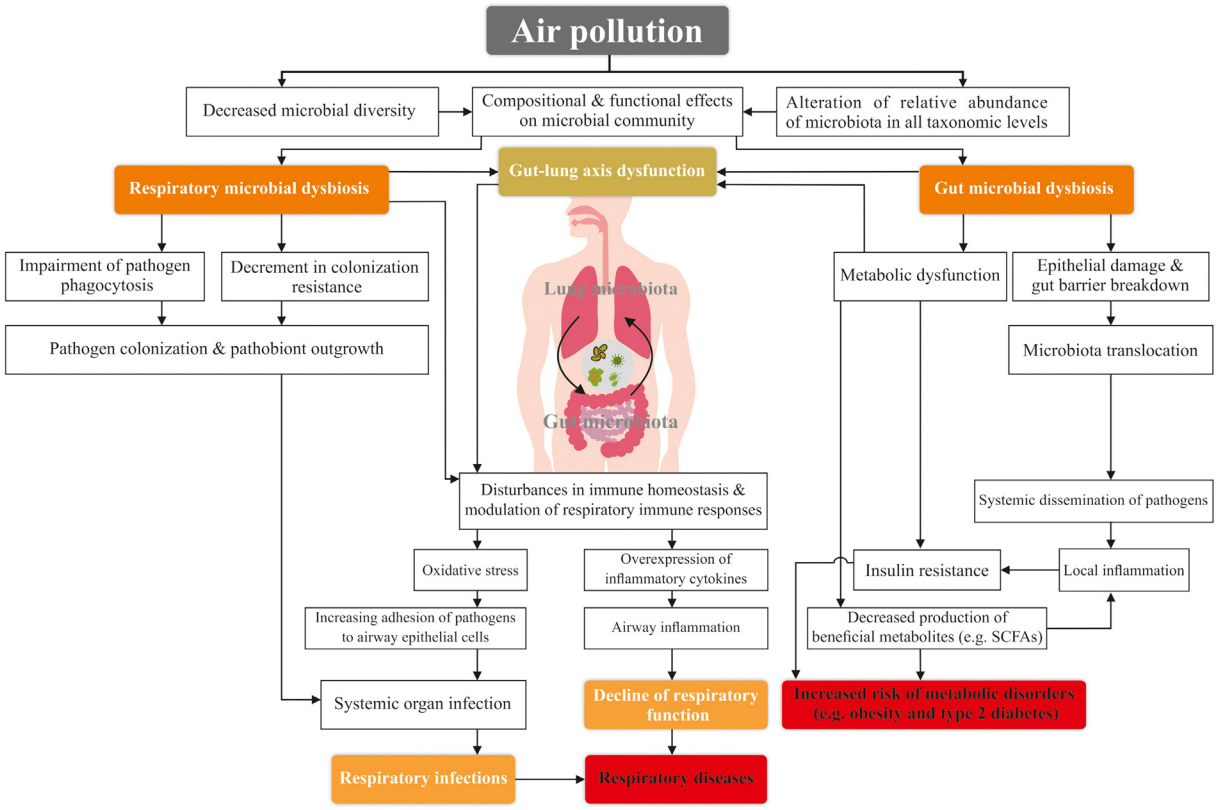

Fig. 2. The interactions between air pollutants and the human microbiota.

Commensal microbiota might play a role in immunomodulation and protection for inflammatory conditions. This is the case of *Streptococcus salivarius, which* modulates the IL-8 response against the pathogen *Streptococcus pyogenes* (Shekhar et al., 2018). Therefore, a decrease in commensal microbiota with an immunomodulatory role, e.g. a protective role from inflammatory conditions, might increase the toxic effect of air pollution by increasing the inflammatory driven responses elicited upon exposure to air pollutants (Bauer et al., 2012) (Fig. 2). On the other hand, increased abundance of such commensal microbiota might lead to inflammatory conditions, such as that observed with increased abundance of *Prevotella* leading to higher mucosal inflammation mediated by T helper cell type 17 (Larsen, 2017).

3.2.1.8. Air pollution, microbiome dysbiosis and chronic respiratory diseases (CRDs). On the other hand, emerging evidence implies that variations in the diversity or abundance of the pulmonary microbiome may contribute to the pathogenesis and risk of several chronic respiratory diseases (CRDs) such as asthma, cystic fibrosis, bronchiectasis, and COPD (Budden et al., 2019; Mammen et al., 2020). Regarding the interplay between lung microbiota and cancer, growing evidence affirms that changes in airways' microbiome play a significant role in the global development of lung cancer. Generally, α-diversity is meaningfully lower in tumor lung tissues compared with that in non-malignant ones, an association which is the case in other respiratory disorders (Mao et al., 2018).

Hosgood et al. (2014) observed bacterial composition differences in the sputum of never-smoking lung cancer cases compared to controls from Xuanwei (rural China) varied by cancer status and the coal type burned in the homes of the subjects (Hosgood et al., 2014). For further investigation on the possible relationship between household air pollution-induced dysbiotic respiratory system and lung cancer, they expanded the sample size with an additional 90 never-smoking women in the same rural area. According to the results obtained from this case-control study, the risk of lung cancer was inversely associated with α-diversity in sputum samples of cases (n=45) (Hosgood et al., 2019). This finding of dissimilarities in the microbiome diversity of LRT between lung cancer females and controls was consistent with their previous study (Hosgood et al., 2014). Of note, increased risk of lung cancer was also observed among participants with the lowered relative abundance of phylum *Fusobacteria,* while the increased abundance of class *Fusobacteriia* was associated with using smoky coal compared with clean fuels (Hosgood et al., 2019). Reduction of *Fusobacteria* abundance was also reported in the oropharyngeal microbiome of healthy residents of a highly polluted area in China in comparison with moderately and low polluted regions (Li et al., 2019). *Fusobacterium* spp. is a commensal bacterium to the oral cavity belongs to *Fusobacteriia* contributing to carcinogenesis mechanisms (Gholizadeh et al., 2017).

3.2.1.9. Air pollution, microbiome dysbiosis and respiratory function. The scope of influence of PM exposure on the human respiratory tract is not only confined to infections and lung cancers but also a dysbiotic airway microbiome would result in the decline of respiratory function. Through a cohort study, Wang et al. investigated the potential associations among three factors, including respiratory microbiota, PM concentration, and respiratory function (Wang et al., 2019). The results demonstrated that FEV_1/FVC, an essential ratio for the measurement of respiratory function and a major diagnostic criterion of COPD, has a positive association with sputum bacteria load. Further, it was explored that the respiratory microbiota profile is interconnected to respiratory function factors. On the other side, it was observed that PM exposure exerts profound influence on airway microbiota. The authors hypothesized that PM components may change the micro-environment inside LRT leading to the disruption of airway microbiota.

3.2.1.10. Summary of potential mechanisms by exposure to air pollution on the respiratory tract microbiome. On the ground of the aforementioned

epidemiological evidence, the airway microbiome profile could be assessed as a general biomarker for the status of respiratory tract (Wang et al., 2019). Having a dynamic nature, the human airway ecosystem can be disrupted via short- and long- term exposure to air contaminants, especially PM. As depicted in Fig. 2, changes in microbial diversity or abundance of airway tract may bring about the chronic colonization of pathogens and pathobionts that derives the pathogenesis of respiratory diseases, including CRDs. Long-term colonization of pathogenic microbiota, however, depends upon factors such as the host's immunological profile and pulmonary microenvironment as well as the species colonized (Huffnagle et al., 2017). Given that the respiratory immune system is known as an essential player of inter-talk between the host and transient microbiota (Chotirmall et al., 2017), air pollutants could impair immunological responses through inducing dysbiosis in the airway microbiota (Fig. 2).

Fig. 2. shows the interactions between air pollutants and the human microbiota. Exposure to air pollutants leads to undesirable changes in diversity, abundance, composition, and function of the airways and gut microbiomes. Such microbial imbalances might elicit subsequent negative changes, most importantly pathogen colonization, metabolic dysfunction, and disturbances in the immune responses. Under disruption of the homeostasis, the formation of oxidative and inflammatory cascades occurs along with systemic infection leading to a wide range of human diseases.

Microbiota may influence the body's ability to respond to environmental exposures, whilst environmental conditions might influence the composition and function of microbiota. This might be the case of *Bacteriodites*, found in the oral and lung microbiome. *Bacteriodites* can metabolize and degrade high molecular weight organic compounds (Bauer et al., 2006), such as PAHs. Many of the studies reviewed suggests that air pollution reduce the population of *Bacteriodites* in the respiratory tract. Qin et al. (2019) observed a reduction of *Bacteriodites* in vendors in an open-air farmer's market in China exposed to 2-day severe smog episode (Qin et al., 2019). Likewise, a reduction of *Prevotella*, a genus within the *bacteriodites* phylum, was observed in healthy young adults exposed to air pollution in China (Li et al., 2019). The lower abundance of *Bacteriodites* might result in a system less able to detoxify harmful toxicants associated with air pollution, such as PAHs, and hence more vulnerable to the toxic effects of such environmental toxicants.

3.2.2. Gut microbiome

Metabolic disorders such as vitamin D deficiency (Mousavi et al., 2019), obesity (Barrea et al., 2017), and type 2 diabetes (T2D) (Liu et al., 2013) have been linked to air pollution exposure. On the other hand, alterations in gut microbial composition have been observed during obesity (Ley et al., 2006) and T2D (Ross et al., 2015). Therefore, the gut microbiome could be a missing etiological link playing a key role in the association of these metabolic disorders and exposure to air pollution.

An examination of gut microbiota of obese adolescents exposed to traffic-related air pollution (TRAP) revealed how air pollution correlates with obesity and T2D, and that a strong correlation exists between elevated TRAP exposure and decreased abundance of *Bacteroidaceae* and increased abundance of *Coriobacteriaceae* (Alderete et al., 2018). The relative abundance of these taxa has been associated with metabolic dysfunctions and intestinal inflammation. *Bacteroidaceae* depletion in obese children (Riva et al., 2017) and *Coriobacteriaceae*-linked insulin resistance (a risk factor for T2D) among obese pregnant women (Gomez-Arango et al., 2016) are two notable examples of this association. Moreover, Alderete et al. reported a significant correlation between *Bacteroidaceae* with fasting glucose, a risk factor for T2D (Alderete et al., 2018). Increased abundance of *Firmicutes* and *Actinobacteria* with decreased abundance of *Bacteroidetes* has been associated with obesity in insulin-resistant subjects (Ley et al., 2006; Moreno-Indias et al., 2016; Turnbaugh et al., 2009; Turnbaugh et al., 2006). Also, very low levels of *Bacteroidaceae* are found in obese children (Riva et al., 2017) and morbidly obese adults who have high insulin resistance (Moreno-Indias et al., 2016). Increased abundance of *Prevotellaceae* is found in vegetarian diet and associated with chronic inflammatory conditions (Ley, 2016; Ley et al., 2006). *Prevotellaceae* and *Bacteroidaceae* are antagonist, so there is prevalence of one group when they coexist in the gut. An inverse association between *Bacteroidetes* and *Prevotella* has been reported with obesity and type 2 diabetes (Fugmann et al., 2015; Furet et al., 2010; Gomez-Arango et al., 2016). Obese pregnant women have also a predominance of *Firmicutes* over *Bacteroidetes*. Abundance of *Firmicutes* species has been associated with an increased expression of key enzymes involved in polysaccharide digestion, generating more energy from the same diet (Cani, 2013).

It is well-known that the gut microbiome is a critical player in the metabolic processes and immune reactions through the exchanges of metabolites and genes between the host and the resident microbial communities (Nicholson et al., 2012; Palau-Rodriguez et al., 2015). Moreover, the microbiota participates in maintaining the intestinal barrier between the flora in the circulatory system and the intestinal lumen. Thus any disturbances in the gastrointestinal tract (GIT) microbial composition and/or function may hurt gut barrier integrity leading to microbiota translocation and subsequent inflammation that in turn pave the way for obesity and insulin resistance (Pekkala et al., 2015; Zheng et al., 2020a) (Fig. 2).

Alderete et al. (2018) reported a decrease of *Corynebacteriaceae* gut population, which has been associated with increased excretion of cholesterol in animal models (Martínez et al., 2013), suggesting that the metabolism of the host, in this case cholesterol excretion, might affect the gut microbiota.

Alderete et al. (2018) reported an increased abundance of *Collinsella* associated with exposure to TRAP. *Collinsella* is positively correlated with insulin levels in pregnant women, as well as with maternal triglycerides and very-low-density lipoprotein cholesterol levels (Gomez-Arango et al., 2016). Outside of pregnancy, higher abundance of *Collinsella* has been reported in type 2 diabetes (Lambeth et al., 2015; Zhang et al., 2013) and is positively correlated with serum cholesterol (Lahti et al., 2013) and bile acid deconjugation (Clavel et al., 2014). Weight loss has been associated with decreased levels of *Collinsella* in adults (Walker et al., 2011), and a slower increase of *Collinsella* abundance in infants was associated with lower body fat at a later age (Dogra et al., 2015). Overall, this suggest the role of *Collinsella* in fat and glucose metabolism.

Roslund et al. (2019) observed a decrease in the Peroxisome proliferator-activated receptor (PPAR) and adipocytokine signaling pathways predicted from the gut metagenome with increasing concentrations of chrysene in the air (Roslund et al., 2019). The decrease in these signaling pathways could be associated with increase circulating triglyceride and free fatty acid and increase insulin resistance (Blaschke et al., 2006).

3.2.2.1. Summary of potential mechanisms by exposure to air pollution on the gut microbiome. Overall, in a systemic and interrelated view, exposure to air pollutants have shown the capability to alter the composition and function of human gut microbiota, producing hazardous metabolites, modulating immune responses, affecting metabolic pathways leading to obesity, increased cholesterol levels and type 2 diabetes, triggering local inflammation, and finally disrupting the gut barrier (Fig. 2).

3.2.3. Skin microbiome

Increasing evidence shows that extrinsic factors, especially exposure to environmental contaminants contribute to a wide range of skin damage. Air pollutants, in particular, have attracted the greatest attention over the recent decade. A growing body of literature prove that long-

term exposure to inhalable airborne pollutants could accelerate skin aging (Krutmann et al., 2021). In addition, the premature skin aging might be induced through oxidative chemicals such as fluorinated compounds carried by aerosols (Mousavi et al., 2020). On the other hand, recent studies suggest that skin microbiome play a pivotal role in the skin health. Some cutaneous disorders are associated with dermal microbial dysbiosis, for example, reduced diversity of the skin microbiome and reduced connectivity of the microbial network may be associated with skin diseases, such as atopic dermatitis (Kong et al., 2012), psoriasis (Statnikov et al., 2013), and dandruff/seborrheic dermatitis (Park et al., 2017). That's why using microbes and pro- and prebiotics has been emerged as a promising strategies for both treating skin diseases (Byrd et al., 2018) and protecting skin from external factors such as solar ultraviolet radiation (Byrd et al., 2018; Patra et al., 2020). The skin microbiome was reported to be more diverse and with a rich connectivity among the microbial network in non-megacities compared to those measured in megacities (Kim et al., 2018), which generally have better air quality conditions than megacities (Marlier et al., 2016; Molina, 2021).

According to the findings of a study on daycare children, gaseous PAHs concentrations in ambient air and surface soil could disturb the balance in dermal microbiome. In this cross-sectional study, Roslund et al. observed a correlation between signaling pathways predicted from skin metagenome and chrysene levels in the air ($p=0.05$) and phenanthrene levels in the daycare yard soil ($p=0.01$). The composition of dermal flora was associated with PAHs levels from OTU to phylum level. The abundance of *Actinobacteria, Bacteroidetes*, and *Proteobacteria* on the children's skin was affected by increasing PAH contaminations in the living environment. A rational deduction might be that an increase in energy sources in an environment, whether biotic such as the skin, or abiotic such as the soil, may change the residential microbiomes and colonize with pollutant-degrading microbiomes, some of which are pathogenic. Therefore, exposure to environmental pollutants not only changes human microbiome communities in different sites of body, it has this capability to induce shifts in the living environment, which may be an indirect pathway for human microbiota. The discrimination reported between the skin microbial composition of rural and urban children is consistent with this interpretation that neighborhood environmental conditions play a part in skin microbiota (Lehtimäki et al., 2017). Recently, Wu et al. demonstrated that the composition and function of facial microbiome are influenced by the air quality. Therefore, it could be deduced that changing skin microbiome induced by air pollutants might be a mediatory factor contributing to skin aging.

Based on the foregoing findings depicted in Fig. 2, air pollution uptake could change the human microbiome communities. On the other hand, differences in the development of individual microbial communities likely affect the uptake and metabolism of inhaled pollutants through modulating immunological and clearance responses consistent with (Adar et al., 2016).

3.3. Potential mechanisms triggered by exposure to EDCs

3.3.1. Oral/respiratory microbiome

Pesticides are a group of EDCs that are intensively used for various purposes. The quantification of blood concentrations of the organophosphate insecticide azinphos-methyl in farmworkers revealed a significant association between exposure to this organophosphate and substantial perturbations in the composition of oral buccal microbiota (Stanaway et al., 2017). Such dysbiosis in buccal bacteria taxa could be attributed to the close interplay between the immune system and tight junction tissue sites. Additionally, systemic disruption of bacterial ecology could play a part in compositional effects in the buccal context

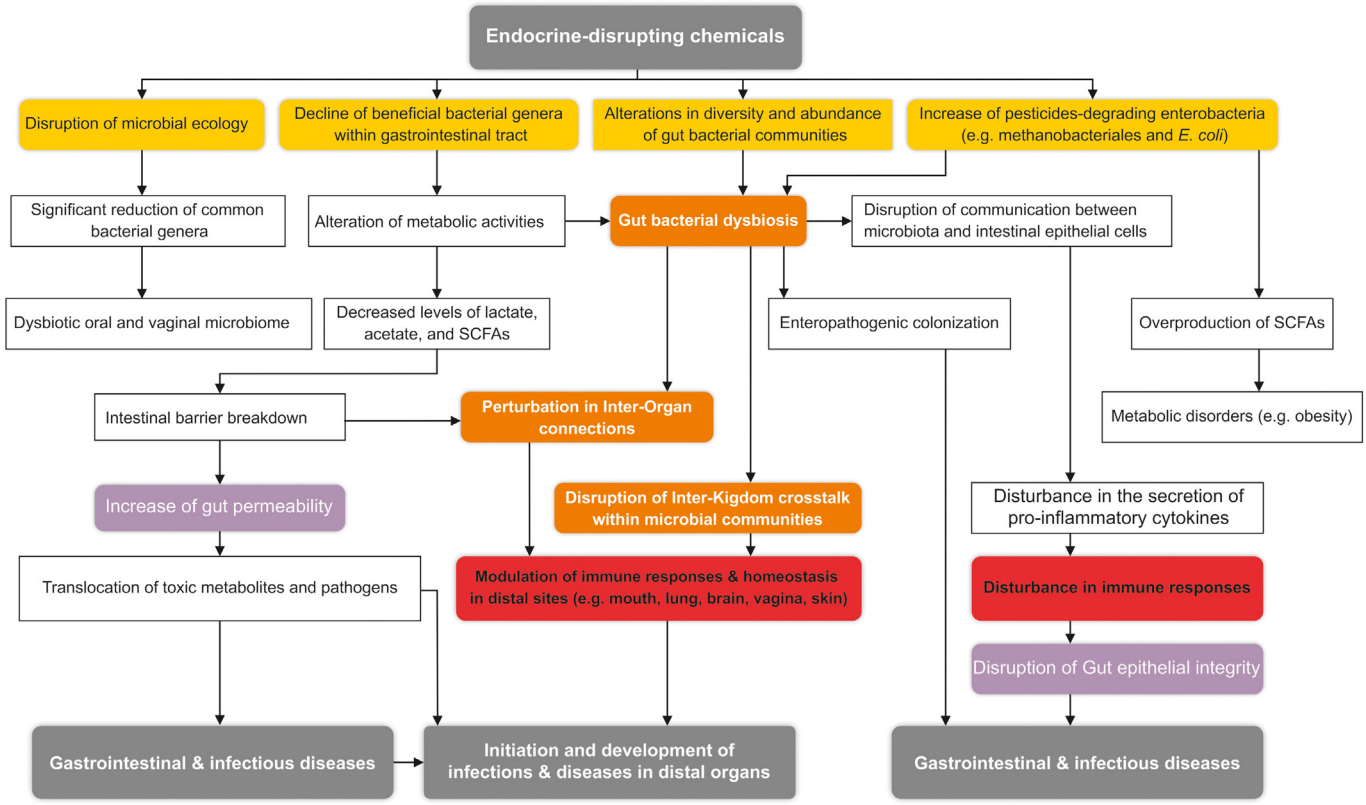

Fig. 3. The interactions between EDCs and the human microbiota.

through a significant reduction of common bacterial genera (Stanaway et al., 2017) (Fig. 3).

3.3.2. Gut microbiome

Pesticide residues in food and drinking water are considered a global public health concern. This group of environmental toxicants is involved in the significant alterations of the human gut microbiome contributing to cardiovascular (Jie et al., 2017), metabolic (Lee et al., 2011), and neurological (Roman et al., 2019) disorders.

3.3.2.1. SHIME® model. Having a healthy GIT is dependent on maintaining a well-balanced or eubiotic gut microbial ecosystem. According to studies performed on the relationship between the intestinal microbiome and organophosphates with the help of the SHIME® model, chronic low dose exposure to insecticide chlorpyrifos (CPF) results in gut bacterial dysbiosis (Joly et al., 2013; Reygner et al., 2016). An increase in total aerobic and anaerobic counts of cultured bacteria, a pattern related to bacterial dysbiosis, was reported in samples collected from an in vitro model of the human intestinal tract exposed to CPF. Joly et al. (2013) observed a decline in the number of beneficial mutualistic bacterial genera *Bifidobacterium* spp. and *Lactobacillus* spp. in samples from SHIME model affected by CPF. Moreover, they reported an incremental quantity in pathogenic strains *Enterococcus* spp. and *Bacteroides* spp. Authors suggested that decreased level of *lactobacilli* and *bifidobacteria* causes the decreased release of lactate and consequently pH increase (Joly et al., 2013) which in turn facilitates pathogenic and enteric colonization (Duncan et al., 2009).

Similar disruptive effects exerted by CPF over intestinal microbiota have been found by another study on SHIME® model by Reygner et al. Decreased count of *bifidobacteria* and increased count of *Enterococcus* spp., *Bacteroides* spp., *Clostridium* spp., and *E. coli* took place under exposure to 1 mg/day CPF (Reygner et al., 2016). Alterations in the diversity and metabolic activity of microbiota were also reported in that experimental study. Changes in the L- and D-lactate, and SCFAs would be interpreted as the influence of CPF exposure on the fermentative activity of gut flora (Reygner et al., 2016). It is demonstrated that decreased production of acetate by the *bifidobacterial* population improves defensive ability against *enteropathogenic* infections (Fukuda et al., 2011). Therefore, as shown in Fig. 3, the transient decline of this bacterial metabolite, as a consequence of CPF exposure, might partially explain the outgrowth of pathogenic genera reported by Reygner and colleagues (Reygner et al., 2016). On the other hand, some facultative areoanaerobic bacteria such as *E. coli* express methyl parathion degrading (mpd) gene encoding organophosphorus hydrolase which degrades CPF as a nutrient source (Yang et al., 2006). As a potential mechanism, the increase of chlorpyrifos-degrading *enterobacteria*, including *E.coli* (as reported by Reygner et al.) would be a result of their ability in using pesticides as a source of carbon and phosphorus for their growth and proliferation. Eventually, this family becomes dominant and alters the fermentative activity of microbiota leading to bacterial dysbiosis and consequently gastrointestinal diseases (Fig. 3). It is of note that these CPF-derived metabolic alterations were varied by different compartments of the in vitro intestinal model (Reygner et al., 2016).

3.3.2.2. Epidemiological observations. Exposure to elevated concentrations of persistent toxicants, particularly halogenated chemicals, in breastmilk could disrupt infant gut microbial composition and function. The decreased level of SCFAs in the high exposed group of infants to PBDEs is partially attributed to the declined abundance of *Veillonella*, a bacterial genus involved in the production of SCFA metabolites (Iszatt et al., 2019). As highlighted in Fig. 3, such changes in the microbial community intercept the communication between microbiota and intestinal epithelial cells via inducing disturbance in the secretion of pro-inflammatory cytokines that leads to perturbation of the development of the immune system (Kabat et al., 2014). Loss of microbial diversity (PFOS), greater relative abundance of pathogenic genera *Streptococcus* (pesticides) and *Enterococcus* (PFOA), decreased level of SCFAs (all examined toxicants except for PCB-167 and PFOA), and absence of some sub-OTUs of the beneficial and vital genus *Lactobacillus* (PFOA and dioxin-like PCBs) were reported to occur upon exposure to high concentrations of EDCs (Iszatt et al., 2019). Due to such undesirable changes in infant gut microbial composition and function derived from exposure to environmental pollutants, it is suggested that dysbiotic microbiome might be a consequence of the interaction between the early-life gut microbiome and environmental persistent contaminants.

One of the main functions of intestinal microbiota is nutrition absorption and energy regulation (Krajmalnik-Brown et al., 2012). Methanogenic microorganisms, such as *Methanobacteriales,* become abundant in oil-enriched environments to harvest energy from lipophilic petroleum derivatives. Through a cross-sectional study on Korean women, it was explored that exposure to organochlorine pesticides plays a determining role in the number of methanogens, a group of microbes that are capable of extracting energy from the degradation of petroleum-based man-made chemicals. Lee and colleagues found a strong correlation between *Methanobacteriales* in Korean women's gut and the serum concentration of organochlorines, including cis-nonchlor ($r=+0.53$, $p<0.05$), oxychlordane ($r=+0.46$, $p<0.1$), and trans-nonachlor ($r=+0.43$, $p<0.1$). Moreover, they observed a positive association between obesity and the abundance of GIT methanogens which suggests that disequilibrium in human gut flora triggered via exposure to pesticides could contribute to metabolic disorders (Lee et al., 2011). The gut microbiome of obese people has a high fermentative ability for producing SCFAs, microbiota-induced fermentation products implicating in obesity (Goffredo et al., 2016; Kim et al., 2019). Therefore, one of the most likely mechanisms linking organochlorine pesticides to obesity is that the abundance of SCFAs producers, including some methanogens might use the pesticides as a source of energy and ferment these chemicals generating SCFAs that leads to overweight and obesity (Fig. 3). The presence of methanogens in the colon that remove H_2 might be another mechanism. H_2 is a product of fermentation of polysaccharides which inhibits the yield of ATP, therefore improving the efficiency of polysaccharide fermentation by the *Bacteroidetes* and the *Firmicutes* (the primary bacterial fermenters in the gut) and hence promoting calorie harvest and adiposis (Samuel and Gordon, 2006; Lee et al., 2011). A reduction of H2 due to the presence of methanogens, associated with pesticide exposure, might lead to obesity.

Based on experimental studies, phthalates are also capable of inducing dysbiosis in the gut microbiota(Wang et al., 2020).

3.3.2.3. Summary of potential mechanisms by exposure to EDCs on the gut microbiome. Results from SHIME® and epidemiological studies suggest that the microbial disequilibrium in the GIT might be a consequence of exposure to pesticides resulting in the dominant population of some resident gut bacteria that generate metabolites involved in metabolic disorders.

Fig. 3. shows the interactions between EDCs and the human microbiota. Exposure to EDCs alters the structure and function of microbial communities resulting in microbiome dysbiosis. Such condition causes microbial-induced metabolic dysfunctions, intestinal barrier breakdown, perturbations in immune reactions and homeostasis, translocation of toxic metabolites and pathogens, and disruption of inter-organ connections, all of them contribute to the onset and development of infectious and gastrointestinal diseases.

3.3.3. Vaginal microbiome

Exposure to EDCs not only induces disruptions in oral, lung, and gut microbiota but also there is evidence that bacterial vaginosis, a microbiological syndrome characterized by a shift in the vaginal microbiome from dominant *Lactobacillus* to anaerobic flora (Onderdonk et al., 2016), could occur via exposure to phthalate-containing consumer products (Geller et al., 2018). Phthalates, a group of EDCs, are widely applied in manufacturing personal care products, including lubricant,

ultrasound gel, vaginal douches, and wipes. A cross-sectional study reported that the levels of MnBP and ΣDEHP metabolites were associated with Nugent-score bacterial vaginosis (Geller et al., 2018).

3.4. Expansion of health outcomes caused by environmentally-induced dysbiosis by the dialogues between the distant sites of the body

Microbial communities colonize different sites of the body through a symbiotic or mutualistic relationship with the host. Perturbations in the composition and function of the niche-specific microbiota would occur as a response to undesirable genetic and environmental factors, thus affecting the symbiotic and mutualistic relationships. The current review suggests that exposure to environmental pollutants could trigger microbial dysbiosis in different sites, including the oral cavity, the upper and lower airways, the intestinal tract, and the vagina. Moreover, recent observations provide compelling proof that there are cross-talks among microbiota at sites of the body that are anatomically distant from each other. In this concept, local microbiota influences the immunity of distal organs. As a result, terms such as gut-brain axis, gut-lung axis, gut-skin axis, and even gut-vagina axis have been developing in this ever-expanding field during the last years.

3.4.1. Gut-brain axis

The gut microbiome exploits a sustainable nutrient-rich microenvironment and bestow vital functions to the host, including fermentation of dietary constituents, production of beneficial nutrients and metabolites, absorption of essential ions, regulation of energy, protection against infectious agents, histological developments, and maintenance of tissue and immune homeostasis (Dang and Marsland, 2019; Hillman et al., 2017; Krajmalnik-Brown et al., 2012). In addition, the microbiota locally and systematically contributes to the education, development, and function of the immune system (Dang and Marsland, 2019).

On the other hand, according to the findings obtained from the studies included in this review, air pollution and EDCs, pesticides in particular, induce disequilibrium in the composition and metabolism of the gut microbiome. Such dysbiotic condition might affect the immune system development and dysregulate the expression and activity of immune mediators, which in turn contribute to intestinal barrier breakdown and subsequently increase the risk of related diseases (Fung, 2020; Takiishi et al., 2017).

Phylogenetically related commensal and pathogenic bacteria have an elevated degree of antigenic similarity. Therefore, natural immunity against pathogens in most adults might be the outcome of repeated colonization by commensals that share epitopes during childhood and youth (Shekhar et al., 2018). This is the case for commensal *streptococci* and *Streptococcus pneumonia* (Engen et al., 2014; Skov Sørensen et al., 2016) and for commensal *Neisseria lactamica* spp. and pathogenic *Neisseria meningitides* (Troncoso et al., 2002; Troncoso et al., 2000). Therefore, a reduction on commensal microbiota phylogenetically related to pathogens might result in reduced natural immunity against such pathogens. This is the case of exposure to smog, which reduces relative abundance of *Neisseria* in the respiratory tract (Qin et al., 2019); $PM_{2.5}$ that reduces abundance of *Corynebacterium* in the nasal cavity (Padhye et al., 2021); and exposure to incense burning smoke reduces the abundance of *Streptococcus* in the oral cavity (Vallès et al., 2019).

Further evidence is needed to underpin the proposed air pollution-derived mechanisms, as well as to uncovered other mechanisms involved in the pathogenesis of microbiota-mediated respiratory diseases.

3.4.2. Gut-lung axis

Regarding the gut-lung axis, a rich body of literature suggests a bidirectional connection between gut and lungs in which the gut microbiome affects the immune reactions in the lungs, and lung stimulation elicits gut responses. Gut and LRT play vital roles in the regulation, development, and maintenance of healthy immune responses (Barcik et al., 2020). Since the environmental exposures have shown substantial capabilities to change the constituents of the gut microbiome and probably disrupt the synthesis of essential metabolites involving in the immune responses and homeostasis, it can be hypothesized that dysregulation of the gut microbiota by exposure to chemical contaminants may impose adverse impacts on the function of the respiratory tracts and vice versa (Fig. 2). Additionally, this communication may establish a vicious cycle deteriorating detrimental effects (e.g. worsening the symptoms of CRDs) caused by microbial dysbiosis. No scientific evidence yet exists examining the effects of air pollution or EDC exposure on the lung-gut microbiome axis, or among any other distal site microbiomes in humans.

3.4.3. Role of short-chain fatty acids (SCFAs) in gut-brain and gut-lung axis

SCFAs can boost the integrity of the intestinal epithelial cells and hinder the translocation of toxic microbiota-originated metabolites and pathogenic microorganisms from the intestinal lumen to distal organs such as the lung and brain by the help of the systemic circulation. This eventually triggers tissue-specific immune reactions leading to the upregulation of inflammatory factors (Zheng et al., 2020a). Based on the aforementioned evidence, two completely different mechanisms can be proposed regarding the metabolic effects of exposure to pesticides. Firstly, exposure to both organochlorine and organophosphate pesticides may decrease the population of SCFAs producers which in turn diminishes the gut epithelial integrity participating in the onset or worsening the infectious diseases and perturbations in the immunological landscape of distant sites through the foregoing inter-organ connections, including gut-lung axis (Fig. 3).

Secondly, some resident microbiota can use these chemicals as a source of food and ferment them for overproduction of SCFAs leading to metabolic disorders such as obesity. As a result, both down-regulation and up-regulation of SCFAs synthesis caused by pesticide exposure have detrimental effects on the body via stimulating immunomodulatory and metabolic reactions. In addition to the inter-organ connections, from the perspective of the microbial ecology, the inter-kingdom cross-talk within a niche-specific microbial community plays an integral part in the maintenance of host homeostasis and disease evolution (Enaud et al., 2020) (Fig. 3). Decoding the role of viral and fungal kingdoms within the mentioned connections needs further investigation.

Besides, SCFAs, especially butyrate, acetate, and propionate generated by the gut microbiota inhibit the inflammatory responses in the pulmonary system (Barcik et al., 2020). Microbiome-originated SCFAs boost bone marrow hematopoiesis, and the primed myeloid cells subsequently translocate to the lung, shaping the lung's immunological landscape and providing protection against the airway inflammation (Trompette et al., 2018). As a result, lung immunological profile may experience undesirable changes if gut dysbiosis disrupts the production of helpful metabolites that play a mediatory part in the development of the immune system in distal sites (Zhang et al., 2020). Such a connection between gut microbiota and lung health refers to the gut-lung axis. Fig. 2 illustrates air pollution-induced microbiome imbalances in the respiratory and gastrointestinal tracts, the possible connection between these two sites, and subsequent biological mechanisms and health outcomes.

3.4.4. Gut-vagina axis

Recent research also suggests that a high-fat diet triggers gut bacterial dysbiosis and subsequently systemic inflammation in obese women. This, in turn, contributes to disorders such as infertility, lower conception rate, or early pregnancy loss all of which could also result from bacterial vaginosis (Davis, 2016; Faucher et al., 2019). The association found between obesity and vaginal dysbiosis in reproductive-aged women (Brookheart et al., 2019) can be partially explained by this pathway. Indeed, it could be hypothesized that environmentally-derived obesity mediated by gut microbial dysbiosis, like what has been

reported regarding organochlorine pesticides (Lee et al., 2011), could initiate vaginal dysbiosis through the probable communication between these two organs known as the gut-vagina axis. It is assumed that the physiological changes derived by dysregulation of the gut microbiome may interfere the maintenance of the intestinal barrier function and the regulation of immune responses as intestinal inflammation could contribute to the pathogenesis of vaginal diseases (Yeruva and Lee, 2019).

3.5. Limitations and strengths

A limitation of the evidence reviewed is the scarce number of existing studies assessing microbiomes from individual systems. Whilst more evidence exists for the effects of air pollutants and EDC on the respiratory tract and the gut microbiome, there is a paucity of studies focusing on other system microbiomes, such as reproductive or skin microbiomes. Likewise, limited number of studies have focused on assessing the effect of EDC on the microbiome. The paucity of studies limits the ability to extract robust new knowledge from the existing evidence for those specific system microbiomes, as well as for the EDC. Nonetheless, a pattern of indicative associations between exposure to air pollution and EDC and microbial dysbiosis can be observed in the studies examined. A larger body of evidence is required to extract consistent, instead of suggestive, associations. Therefore, further research would be helpful to increade the available body of evidence.

Some degree of variability in the results might be expected since the chemical composition of the atmospheric mixture might be different among the different locations were studies have been conducted, thus affecting the response elicited in the human microbiomes. In addition to differences in exposure patterns and chemical composition of airborne pollutants and pesticides, there is a wide variety of populations across the world where these results have been reported. Genetic differences across different population studied might be expected (Huang et al., 2015), which could be relevant to the interaction of exposure to air pollution and microbiome dysbiosis (Kolde et al., 2018).

This systematic literature review only includes articles in English published until March 9, 2021. Therefore, any relevant scientific article published in a different language or after the cutoff date has not been included in this review.

Nonetheless, a strength of this work is that, to the best of knowledge of the authors, this is the first systematic review assessing the effects of two groups of environmental toxicants, such as air pollutants and EDC, and focusing on different areas of the human microbiome.

4. Research gap and future research

Most of the existing research has been done focusing on a particular microbiome, such as the respiratory tract; whereas fewer studies have focused on the gut, and even less on other microbiomes. Considering that the respiratory tract could act as the port of entry of toxins in the body, which can be distributed across through the circulatory system, further research should study the effects of exposure to air pollution on other microbiomes.

Moreover, little has been done studying alterations in the body system functioning network. Since the human body system is a complex network that functions in perfect harmony, research focused only on one microbiome might not take into account the effect on other microbiomes of the body. Therefore interactions on the effects of distal sites in the body should be undertaken.

In addition, most available evidence focused on a particular toxicant, but exposures normally occur to a combination of chemical mixtures emitted from various sources. Therefore, further research should investigate the existence of synergistic effects among pollutants; or whether specific compounds or sources might be responsible of the observed effects in microbiota changes.

Likewise, research should be undertaken to understand the interaction between aerial microbiome exposures and the human microbiome.

5. Conclusion

Environmental exposures are capable of inducing perturbations in human microbial ecosystems, including but not limited to respiratory tract, the gastrointestinal tract e.g. (Iszatt et al., 2019; Lee et al., 2011), vagina (Geller et al., 2018), and mouth (Stanaway et al., 2017). Such perturbation on the human microbiome might result in modulation of immune responses and increased vulnerability against infections, the production of hazardous metabolites, effects on metabolic pathways leading to obesity, increased cholesterol levels and type 2 diabetes, and triggering local and systemic inflammation, and consequently increasing the incidence of inflammatory diseases (e.g. asthma, irritable vowel syndrome, psoriasis).

Whilst there is insufficient number of studies to observe a consistent trend for most of the microbiota, the examined studies suggest an association between an increase of abundance of *streptococcus* and *veillionellales* with exposure to air pollution.

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CRediT authorship contribution statement

Sayed Esmaeil Mousavi (SEM) and **Lode Godderis (LG):** study conceptualization and design. **SEM:** investigation, writing – original draft (abstract, methodology, discussion), writing – reviewing and editing, visualization (Graphical Abstract, Figs. 1 (PRISMA), 2 & 3), project administration. **Juana Maria Delgado-Saborit (JMDS):** investigation, writing – original draft (results, discussion and conclusion), writing – reviewing and editing, visualization (Tables 1 and S1, Fig. S1), Supervision. **Anna Adivi (AA):** writing - original draft (introduction and results), visualization (Table 1). **Sara Pauwels (SP)**: writing - original draft (introduction and results). **LG**: validation, writing – reviewing and editing, Supervision. **All authors** contributed to the methodology section. **SEM** and **LG** draw the outline of the methodology. **LG** developed the search strings, searched the databases, and uploaded the results on Rayyan Systematic Review Web Application. **SEM** and **AA** screened the articles. **SEM** and **JMDS** did the quality assessment. **SEM**, **AA** and **SP** did the NTP OHAT bias assessment, and **JMDS** reviewed the assessment. **AA**, **SP**, and **JMDS** extracted data from the included papers. **All authors** have approved the final draft of the manuscript.

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Declaration of competing interest

The authors declare they have no actual or potential competing financial interests.

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