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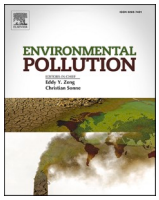

Probiotics, prebiotics, and synbiotics to prevent or combat air pollution consequences: The gut-lung axis☆

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ABSTRACT

Air pollution exposure is a public health emergency, which attributes globally to an estimated seven million deaths on a yearly basis We are all exposed to air pollutants, varying from ambient air pollution hanging over cities to dust inside the home. It is a mixture of airborne particulate matter and gases that can be subdivided into three categories based on particle diameter. The smallest category called $PM_{0.1}$ is the most abundant. A fraction of the particles included in this category might enter the blood stream spreading to other parts of the body. As air pollutants can enter the body via the lungs and gut, growing evidence links its exposure to gastrointestinal and respiratory impairments and diseases, like asthma, rhinitis, respiratory tract infections, Crohn's disease, ulcerative colitis, and abdominal pain. It has become evident that there exists a crosstalk between the respiratory and gastrointestinal tracts, commonly referred to as the gut-lung axis. Via microbial secretions, metabolites, immune mediators and lipid profiles, these two separate organ systems can influence each other. Well-known immunomodulators and gut health stimulators are probiotics, prebiotics, together called synbiotics. They might combat air pollution-induced systemic inflammation and oxidative stress by optimizing the microbiota composition and microbial metabolites, thereby stimulating anti-inflammatory pathways and strengthening mucosal and epithelial barriers. Although clinical studies investigating the role of probiotics, prebiotics, and synbiotics in an air pollution setting are lacking, these interventions show promising health promoting effects by affecting the gastrointestinal- and respiratory tract. This review summarizes the current data on how air pollution can affect the gut-lung axis and might impact gut and lung health. It will further elaborate on the potential role of probiotics, prebiotics and synbiotics on the gut-lung axis, and gut and lung health.

1. Introduction

Exposure to air pollution is a major environmental risk recognized by the World Health Organisation (WHO) as a global public health emergency (WHO, 2016; ir Pollution and Ch, 2018; Harrison, 2020). Air pollution can be subdivided in two categories: ambient air pollution (AAP), faced in the external environment, and household air pollution (HAP) encountered when inside buildings. All living beings are constantly exposed to various doses of AAP and HAP. Among the world-wide population 9 out of 10 people are exposed to levels of air pollution particles exceeding the WHO guideline (WHO, 2016). AAP is already linked to 4.2 million premature deaths in 2016; of these, almost 300.000 were children under the age of five (ir Pollution and Ch, 2018). Nevertheless, the risks associated with HAP exposure can be just as high. About three billion people worldwide still depend on polluting fuels and devices for indoor cooking and heating. Moreover a large number of

Abbreviations: WHO, World Health Organization; GI, Gastrointestinal; AAP, Ambient air pollution; HAP, Household air pollution; PM, Particulate matter; AMPs, Anti-microbial peptides; SCFAs, Short chain fatty acids; MAMPs, Microbe-associated molecular patterns; ROS, Reactive oxygen species; ox-LDL, Oxidized LDL; GOS, Galacto-oligosaccharides; FOS, Fructo-oligosaccharides.

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people still smoke indoors with cigarette smoke being a large contributor to HAP (ir Pollution and Ch, 2018; Exposure to household air, 2018). Consequently, HAP is connected with 3.8 million premature deaths in 2016, including over 400.000 deaths of children under the age of five (ir Pollution and Ch, 2018; Burden of disease from ho, 2018).

There is growing evidence that exposure to air pollution has a negative effect on gut and lung health and functioning (Fig. 1). Most well-documented adverse effects related to air pollution exposure are an impaired respiratory functioning and elevated infection rates (ir Pollution and Ch, 2018; Zielinska and Hamulka, 2019). Not only the lung development of a child can be impaired (Korten et al., 2017; Gauderman et al., 2015; Veras et al., 2017), substantial evidence also shows an increased risk of allergic rhinitis (Deng et al., 2016; Chen et al., 2018; Norback et al., 2018) or asthma development (Chen et al., 2018; Norback et al., 2018; Dong et al., 2011) later in life. Next to the increased susceptibility to pneumonia (Kim et al., 2018a; Fuertes et al., 2014; MacIntyre et al., 2014), AAP also increases the risk of developing otitis media episodes (Kennedy et al., 2018; Bowatte et al., 2018). Relatively new hypothesized health outcomes associated with air pollution exposure are gastrointestinal (GI) disorders like inflammatory bowel disease (IBD) (Kaplan et al., 2010; Ananthakrishnan et al., 2011), appendicitis (Kaplan et al., 2013), and irritable bowel syndrome (IBS) (Kaplan et al., 2012).

Over the years, it has become evident that there exists a crosstalk between the respiratory tract and the GI tract, commonly referred to as the gut-lung axis. Via this pathway, the two separate organ systems can communicate and influence each other (Dang and Marsland, 2019; Enaud et al., 2020). To prevent or combat the negative health consequences of air pollution exposure in one of the two organ systems, it is therefore key to also examine the involvement of the gut-lung axis.

Well-known immunomodulators and gut health stimulators are probiotics, prebiotics and when used together synbiotics. Besides their established effect on supporting a healthy microbiota composition and gut health, evidence on how these engines could promote lung health is emerging. In this review current pre-clinical and clinical data will be summarized on how air pollution impacts gut and lung health and what this means for the gut-lung axis. Furthermore, this review will elaborate on the potential role of probiotics, prebiotics and synbiotics, together addressed as biotics, in mitigating the negative health consequences of pollution exposure via protective and supporting functions on gut health and therefore via the gut-lung axis affect lung health. Over the last decade, a broader definition of air pollution has been established and now includes AAP and HAP cigarette smoke, but also considers other pollutants like traffic related air pollution (TRAP), Ozone (O_3), nitrogen dioxide (NO_2) and sulphur dioxide (SO_2) (WHO, 2016). In this review we use the term air pollution, capturing its broadest definition unless specifically indicated.

2. Air pollution: route of exposure

Air pollution is a mixture of airborne particulate matter (PM) and gases. It contains a mixture of organic materials (e.g. pollen, spores and microbial particles) and inorganic materials (e.g. polycyclic aromatic hydrocarbons, sulphates, nitrates, metals, mineral dust and ions) (Adams et al., 2015). Their sources range from traffic and industrial emission to windblown soil and road dust. PM is a major contributor to the adverse health effects of pollutants and mainly used as a proxy indicator for the level of air pollution exposure.

PM can be subdivided into three categories based on particle diameter; coarse particles (PM_{10}, diameter <10 μm), fine particles ($PM_{2.5}$, diameter <2.5 μm) and ultrafine particles ($PM_{0.1}$, diameter <0.1 μm) (Adams et al., 2015). Depending on their size, PM particles might penetrate deep into the lungs reaching the lower airways. There is increasing evidence that the smallest PMs ($PM_{0.1}$) are the most abundant particles and pose the highest risk due to their increased inflammatory potential and capacity to access the blood circulation (Terzano et al., 2010). A secondary route how air pollution can reach different body parts is via the intake of urban or industrial-contaminated water and foods. On average, an individual consuming a typical western diet ingests 10^{12}–10^{14} p.m. per day. From this it is estimated that approximately 1% (10^{9}-10^{12} particles per person per day) of the PM are entering the systemic circulation via mucosal-associated uptake mechanisms (Salim et al., 2014). Finally, the GI tract is also exposed to pollutants through the mucociliary clearance of inhaled pollutants that are removed and transported by the lungs to the gut. In that way a large proportion of particles, which do not enter the blood stream via the lungs, might still enter the blood via the GI tract (Kreyling et al., 2006; Moller et al., 2004).

3. Air pollution: impact on gut and lung health during all stages of life

3.1. Gut health implications

A few clinical studies link air pollution exposure to intestinal health impairment, especially IBD. Cigarette smoke as HAP received a lot of attention in the early 2000s, as both passive and active smoking was associated with the development of IBD. A meta-analysis (Mahid et al., 2006) evaluating 11.741 patients with ulcerative colitis (UC) and 10.610 Crohn's disease (CD) patients, concluded that active smoking is an important factor in the development of IBD, but exhibits different effects on CD and UC. Where current active smoking showed a low risk for UC, it did demonstrate a significant higher risk for CD (Mahid et al., 2006). This association was also found in early life, where active and passive maternal smoke exposure was associated with an independent increase in the risk of CD-related hospitalizations during childhood (Lindoso et al., 2018). However this association for passive smoking is weaker, as a meta-analysis on childhood passive smoke exposure and CD did not show a strong association and highlighted a small number of studies with a high degree of heterogenicity, precluding strong conclusions (Jones et al., 2008).

Although the relation between air pollution exposure and GI disease is well researched for exposure to cigarette smoke (Mahid et al., 2006; Jones et al., 2008; Li et al., 2019a; Kurata and Nogawa, 1997), limited clinical evidence starts to hypothesize a similar effect on GI health for other air pollutants. A recent review (Vignal et al., 2021) concluded that air pollution exposure, when also including SO_2, CO, NO_2 and PM to the definition, could cause GI defects as well. Elevated SO_2 atmospheric concentrations were associated with increased emergency visits or hospital visits related to IBD (Kaplan et al., 2010; Ananthakrishnan et al., 2011), enteritis (Xu et al., 2016), appendicitis (Kaplan et al., 2009), abdominal pain (Kaplan et al., 2012) and peptic ulcers (Tsai et al., 2019). Likewise, the effects of NO_2 exposure have been hypothesized to be positively associated with IBS (Elten et al., 2020), appendicitis (Kaplan et al., 2009; Chen and Yang, 2018), non-specific abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), and peptic ulcers (Kaplan et al., 2010). Finally, a potential contribution of CO to emergency visits or development of IBS (Tan et al., 2019), IBD (Ananthakrishnan et al., 2011), non-specific abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), appendicitis (Kaplan et al., 2009; Chen and Yang, 2018), and peptic ulcers (Tsai et al., 2019) have been reported. Data regarding PM exposure and its impact on GI health is less predictable. For instance, high atmospheric levels of $PM_{2.5}$ are associated with an increased risk of hospitalizations for IBD (Ananthakrishnan et al., 2011), non-specific abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), peptic ulcers (Tsai et al., 2019), under-5 mortality from diarrhoea (He et al., 2022), while PM_{10} exposure is reported to decrease the risk of IBD (Kaplan et al., 2010; Opstelten et al., 2016). These studies show that the association between air pollution and GI diseases is complex as results differ depending on the type of air pollutants, age of the subject, the origin of the pollutants (traffic vs. industry) and type of GI diseases.

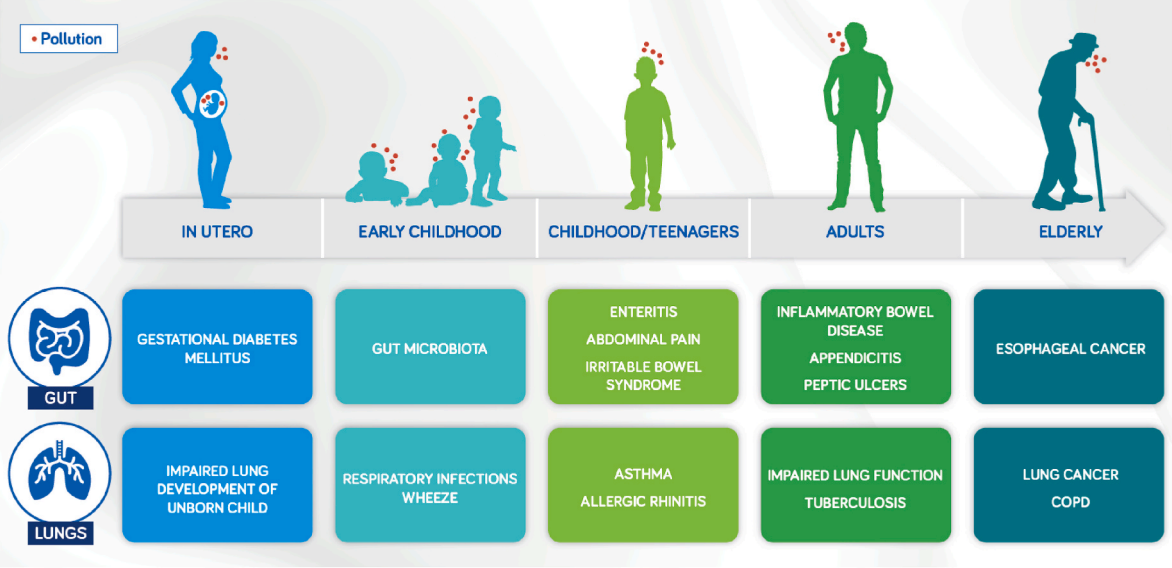

Fig. 1. The association between air pollution exposure and effects in the gut and lungs during all stages of life. Exposure to air pollution is associated with negative effects on gut and lung health and functioning. Exposure can be linked to acute and later life negative health outcomes. Boxes represent documented possible health consequences on gut and lungs such as irritable bowel syndrome, inflammatory bowel disease, asthma, impaired lung function and COPD, for which the body of evidence behind the associations vary from immature for GI diseases to more robust for respiratory health consequences.

3.2. Lung health implications

Exposure to air pollution can impair lung development, reduce lung function and increase the risk of chronic lung diseases (ir Pollution and Ch, 2018). Several meta-analysis and epidemiological studies related to AAP have reported that PM exposure is associated with an increased development of wheeze (Gasana et al., 2012; Luong et al., 2019; Yan et al., 2020) or asthma (Yan et al., 2020; Khreis et al., 2017), decreased forced expiratory volume 1 (FeV1) (Edginton et al., 2019), more asthma attacks (Slaughter et al., 2003) and more frequent asthma medication intake (Slaughter et al., 2003). Additionally, NO_x, SO_2, CO and/or black carbon (BC) exposure increases the risk of developing wheeze (Gasana et al., 2012), asthma (Gasana et al., 2012; Luong et al., 2019; Khreis et al., 2017) and chronic obstructive pulmonary disease (COPD) (Huangfu and Atkinson, 2020). Additionally, evidence supports the association between AAP exposure and the increased risk of lung infections. Especially an increased exposure to $PM_{2.5}$ (Li et al., 2021) is associated with risk of acute respiratory infections (ARI). Furthermore, number of hospitalizations or emergency room visits due to ARIs and pneumonia were linked with higher levels of $PM_{2.5}$ (Nhung et al., 2017; Yee et al., 2021), PM_{10}, NO_2, SO_2 and O_3 (Yee et al., 2021). Increased SO_2 and NO_2 exposure were significantly associated with the number of clinical visits for upper respiratory tract infections (URTI) among college students in Wuhan, China (Zhang et al., 2021). Increased exposure to air pollution was also hypothesized to form a risk factor for an enhanced COVID distribution (Katoto et al., 2021; Maleki et al., 2021; Rahimi et al., 2021). Higher air pollution concentrations favour the COVID transmission (Rosário Filho et al., 2021; Liu et al., 2020) and enhance the presentence of the virus in the atmosphere (Rosário Filho et al., 2021; Setti et al., 2020). There is an increased mortality risk of COVID in regions with higher $PM_{2.5}$ concentrations (Setti et al., 2020; Wu et al., 2020; Conticini et al., 2020).

Studies investigating the potential effects of HAP on lung development and function are emerging. Several meta-analysis reported that exposure to HAP, like domestic cooking and heating, is associated with a higher risk of developing COPD (Lee et al., 2020; Saleh et al., 2020; Sana et al., 2018), lung cancer (Lee et al., 2020; Josyula et al., 2015; Bruce et al., 2015; Hosgood et al., 2011) and respiratory related mortality (Lee et al., 2020). An incremental increase in NO_2 and $PM_{2.5}$ was associated with more cough and dyspnoea symptoms, while gas cooking was linked with a higher risk for asthma (Lee et al., 2020). Additionally, HAP exposure is related to an increased risk of developing lung infections such as ARIs (Lee et al., 2020; Fakunle et al., 2020; Enyew et al., 2021; Thakur et al., 2018; Jary et al., 2016), tuberculosis (Lee et al., 2020), pneumonia (Thakur et al., 2018) and chronic bronchitis (Sana et al., 2018).

4. Gut-lung axis: the cross-talk between gut and lungs

Accumulating evidence indicates a connection between events in the respiratory tract and effects on gut health and vice versa with a central role for the immune system, the microbiota and microbial metabolites, commonly referred to as the gut-lung axis (Dang and Marsland, 2019; Enaud et al., 2020). Both organs play a crucial role in immunity, controlling local and systemic inflammation by regulating the secretion of chemokines, cytokines, and anti-microbial compounds. The close interaction between the two organs can partly be explained by their shared origin from the same embryonic organ, the foregut (Girosi et al., 2006; Espírito Santo et al., 2021). Both are exposed to the outside environment via the mouth and pharynx and share aspects of physiology and structure. One of these structures is the physical barrier with projections of microvilli in the gut and cilia in the respiratory tract. Besides, both organs contain anti-microbial peptides (AMP) and mucus-producing goblet cells offering a protective layer against the external environment (Budden et al., 2017). Additionally, they both contain a diverse microbial community, where the bacterial phyla level in the lung and gut are identical, but at the species level differences were observed between these organs (Dumas et al., 2018; McAleer and Kolls, 2018; Stavropoulou et al., 2021). Finally, both the gut and the lungs are connected to the blood circulation and lymphatic system, which enables the cross-talk between the two systems by bi-directionally transferring immune cells, cytokines, chemokines, and microbial metabolites from the one organ to the other (Espírito Santo et al., 2021).

4.1. Gut to lung communication in homeostasis

Although the mechanism behind the gut-lung axis is not yet fully understood, multiple studies demonstrate the important role of the gut

microbiota and its metabolites as a defence mechanism. In homeostasis (Fig. 2, left), the commensal gut microbiota produces short chain fatty acids (SCFA) as a result of fermentation of undigested soluble dietary fibres. These metabolites together with microbe-associated molecular patterns (MAMPs) derived from the gut microbiota, activate and control cellular responses necessary to maintain an inflammatory tone, which drives a state of equilibrium between microbiota and the host, referred to as a steady state immune homeostasis (Garrett et al., 2010). This homeostasis is crucial for the maintenance of tolerance, while making sure offenders (i.e. air pollutants, pathogens, toxic substances) are adequately dealt with (Chistiakov et al., 2015). Mechanistically, toll-like receptor recognition of MAMPs in concert with SCFA-receptor activation, drives antigen presenting cells to release anti-inflammatory mediators. Additionally, they promote the generation and maintenance of tolerogenic innate and adaptive cells, such as regulatory T-cells and immunoglobin A (IgA) producing B-cells. These cells control local inflammatory responses, but are also able to travel systemically and perform their function at remote sites such as the lung.

The epithelial barrier consists of an outer layer of mucus, a layer of epithelial cells and finally the lamina propria, which houses the various immune cells. The epithelial barrier forms the first line of defence against harmful substances, including air pollutants, and microorganisms but also assures the absorption of nutrients, lipids, vitamins, minerals, ions and water. The function of the epithelial barrier depends on a variety of proteins that together form a tight junction network creating a selective barrier. Recognition of MAMPs by toll-like receptors expressed by epithelial cells and SCFAs together orchestrate the production of tight-junction proteins necessary to generate and maintain a strong epithelial barrier (Semin et al., 2021). This protects the body against the penetration of air pollutants, ROS and air pollution induced oxidized products to enter the circulation. Furthermore, the generation and maintenance of IgA producing B-cells promote mucus production and activates cell survival and repair-mechanisms to thicken the mucosal layer, preventing pathogens and harmful substances, including air pollutants, from invading the body. Additionally, host-produced factors in response to microbial triggering of MAMPS and SCFA are molecules such as AMPs and secretory IgA (sIgA) which, together, function to control microbial overgrowth and contribute to the formation and maintenance of a balanced microbiota composition (Muniz et al., 2012; Nakajima et al., 2018).

4.2. *Lung to gut communication in homeostasis*

Similar to the gut, a steady state immune homeostasis is maintained by the constant interactions between the resident microbiota, microbial metabolites and the network of tissue-resident immune cells in the lung. In health these complex mechanisms ensure tolerance towards harmless inhaled particles, while at the same time elicit adequate responses towards invading pathogens, air pollutants or noxious substances. Compared to the current knowledge on the role of microbiota and microbial metabolites in orchestrating intestinal homeostasis, its exact mechanism of action when it comes to lung immunity is still unclear. Nevertheless, there are associations between lower airway microbial compositions and the appearance of regulatory T-cells (Gollwitzer et al., 2014) macrophage phenotypes (Bernasconi et al., 2016) and cytokine profiles (Wang et al., 2019). IgA producing B-cells also occur in the lung governed by the microbial recognition of lung dendritic cells, instructing B-cells to differentiate into a IgA producing B-cell. Lung epithelial

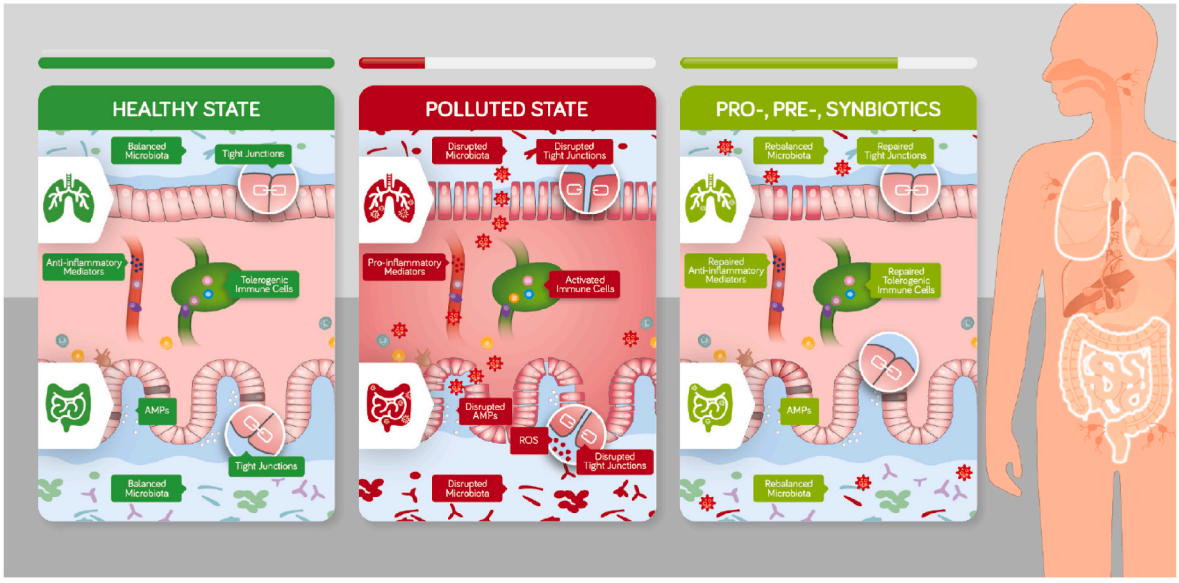

Fig. 2. The gut-lung axis in a healthy state, impacted by air pollution exposure, and influenced by biotic supplementation - In a healthy state (left), short chain fatty acids (SCFA) together with microbe associated molecular patterns (MAMPs) derived from the gut microbiota, maintain and promote a steady state immune homeostasis by stimulating the anti-inflammatory mediator production and ensuring the presence of tolerogenic immune cells, including regulatory T-cells and IgA producing B-cells. Furthermore, MAMPs and SCFA drive epithelial integrity and the production of mucus and AMPs, maintaining a strong barrier function. In homeostasis, these defense mechanisms protect against environmental exposures such as air pollutants, blocking their penetration into the body. In the case of prolonged or excessive air pollution exposure (middle), air pollution-induced changes in microbiota composition (incl. MAMPs) and microbial metabolites (i.e. SCFA) combined with the direct effects of PM and noxious gasses drive an pro-inflammatory response at the loss of steady state immune homeostasis. Over-abundance of reactive oxygen species (ROS) damages epithelial cells, leading to a loss of barrier function and, as a consequence, host tissues become exposed to luminal content (pathogens, microbes, noxious materials) adding to the pro-inflammatory pressure. Additionally, dietary lipids become increasingly oxidized and lipid mediator profiles are changed even further adding its own pro-inflammatory effects. Biotic supplementation (right), rebalance the air pollution-induced microbiota changes and normalizes microbial metabolite patterns driving anti-inflammatory responses to reduce the pro-inflammatory pressure. They promote tight junction and mucus production, repairing the barrier functions enabling scavenging/inactivating of PMs and ROS. The bars indicate the ability of the body to protect against air pollution induced health consequences (Left: maximum protection in case of a steady state homeostasis, Middle: minimum protection as the excessive or prolonged air pollution exposure damaged the defense mechanisms, Right: immune defense mechanisms which for the majority are restored towards a healthy steady state homeostasis due to the biotic support, functioning as an additional boost to keep the defense mechanisms alive in times of excessive or prolonged air pollution exposure.

integrity maintenance seems to be in a large part similarly regulated as in the gut with preclinical evidence showing a clear role for SCFAs and MAMPs-TLR interactions to support barrier function (Shaykhiev et al., 2008; Lewandowska-Polak et al., 2018; Richards et al., 2020). In-line with gut-to-lung communication, immune cells and mediators generated in the lung become systemically available and contribute to the maintenance of a steady state immune homeostasis in remote tissues such as the gut. Different from the intestines, there seems to be no substantial production of SCFAs in the lungs, suggesting that the effects of SCFA on lung immunity are one-directional from the gut to the lungs (Yue et al., 2020).

5. The impact of air pollutants on the gut-lung axis

As discussed in the previous paragraph on route of air pollution exposure, both the gut and lung are a target of air pollution constituents. Interactions of the epithelial barriers with air pollution cause a disbalance in the gut-lung axis moving from a state of homeostasis towards inflammation. In the below paragraphs we will discuss how air pollution effects different compartments and systems (Fig. 2, middle).

5.1. Microbiota composition and functionality

Excessive or prolonged air pollution exposure may alter the gut microbiota and gut health. Although a number of preclinical studies have examined the effects of air pollution and the microbiota (Bailey et al., 2020), human data are still scarce. Here we will focus on human studies designed to find correlations between air pollution exposure and microbiota shifts.

The composition and function of the gut and lung microbiota is sensitive to changes in environmental stressors, including air pollutants (Karl et al., 2018). Whole-genome sequencing in young adults living in Southern California indicated a lower gut bacterial diversity and changes in multiple bacterial gene pathways, suggestive of a change in gut microbial functionality and possibly production of gut microbial metabolites, as a consequence of air pollution exposure (Fouladi et al., 2020). A study involving adults from a community in Guandong, reported an association of $PM_{2.5}$ and PM_1 with a reduction in gut microbiota diversity. They showed a negative association of the relative abundance of Firmicutes, Proteobacteria and Verrucomicrobia bacteria in the GI tract, with $PM_{2.5}$ and PM_1 concentrations (Liu et al., 2019). In another study, the intestinal microbiome of asthmatic and healthy children aged 5–12 years old from the Beijing area changed between clean and smog days. Especially the relative abundance of bacteria belonging to the Firmicutes phylum were negatively associated with concentrations of $PM_{2.5}$, PM_{10}, NO_2, and SO_2, indicating that short bouts of air pollution exposure might already be effective in changing the intestinal microbiota (Zheng et al., 2020).

Another aspect that gains increasing interest is that air pollution comes with its own specific microbiome. Air pollution microbiome analyses of samples from different geographical locations, seasons and PMs revealed that there is a large variety between samples but all contain airborne bacteria, viruses and fungi (Moelling and Broecker, 2020). Inhalation of air pollutants might therefore induce environmental microorganisms into the respiratory tract. Although the evidence is very limited and requires validation, a study in Beijing (Mao et al., 2019) collecting air samples reported that air pollution-associated microbiome contains *Pseudomonas, Moraxella, Micrococcus, Streptomyces*, and *Bacillus* bacterial genera. The majority of these inhaled microbes are cleared from the respiratory tract following coughing or mucociliary clearance. Prolonged air pollution exposure in high concentrations might impair the ability of the body to clear these microbes, resulting in elevated presence of these air pollution associated microbes in the lung and GI tract. Furthermore, increased susceptibility to pollutants in patients with a reduced lung microbiota diversity suggests a potential role of the host microbiome in its ability to protect or respond against air pollution exposure (Hamidou Soumana and Carlsten, 2021). Nevertheless, their potential risk to human health remains a field of active research (Tang and Li, 2019).

5.2. Oxidative stress

Reactive oxygen species (ROS) are continuously produced by cells under homeostatic conditions and contribute to the regulation of cellular proliferation and apoptosis. It is only when the host anti-oxidative defences are overwhelmed that ROS starts to play a role in disease pathogenesis and progression (Ray et al., 2012). Oxidative stress appears to be a common factor driving the harmful effects induced by excessive or prolonged air pollution exposure. PM itself contains organic and inorganic ROS and redox-active components, which can cause oxidative stress resulting in the destruction of cells and tissues including the epithelial and endothelial cell layers in the gut and lungs respectively (Leni et al., 2020; Mazuryk et al., 2020; Fang et al., 2019).

Oxidative stress responses are a common threat in the lung and accumulating evidence suggest they are also of import in the activation of systemic inflammatory processes and generation of ROS (Rao et al., 2018). These two processes together further lead to an additional overabundance of ROS or redox-active components, worsening the oxidative stress response, ultimately disrupting the tight junction and ultimately to an increase in permeability of the epithelial barrier of the intestines (Mutlu et al., 2011a; Kish et al., 2013), the nose and lungs (Hong et al., 2016; Caraballo et al., 2011) and the blood vessels (Wang et al., 2012).

5.3. Disrupted lipid homeostasis

Bioactive lipids play a major role in regulating inflammatory processes with both anti- and pro-inflammatory lipid mediators regulating initiation and resolution of inflammation. Preclinical data clearly shows a relation between air pollution and changes in profiles of lipid-mediators potentially accelerating or augmenting systemic inflammatory reactions (Beck-Speier et al., 2012; Wang et al., 2021a). Next to a change in the balance of lipid mediators, air pollution also induces the occurrence of oxidized lipids. A clinical study with healthy adults in China, demonstrated that a two-fold increase in $PM_{2.5}$, was followed by a median increase of oxidized LDL (ox-LDL) levels by 6.43% (Qin et al., 2021). Furthermore, a randomized controlled trial in Beijing showed significant associations between indoor airborne phthalic acid esters and ox-LDL (Wang et al., 2021b). A meta-analysis (Moller et al., 2004) showed that oxidative damage to the epithelial barrier as a consequence of air pollution is associated with elevated blood level biomarkers of lipid peroxidation. Excess availability of oxidized lipids activates innate immune cells to drive systemic pro-inflammatory responses (Zhivaki and Kagan, 2021). Moreover, given the close relationship between microbiota and lipid metabolism, air pollution-induced changes in microbiota composition could also contribute to elevated levels of circulating oxidized lipids potentially driving systemic pathologies (Feng et al., 2020).

5.4. Barrier dysfunction

Tight junctions in the epithelial barrier of the intestine and the lungs form an important barrier to the entry of air pollutants, toxins, pathogens and allergens. It manifest a selective prevention of transport for these components into the paracellular space and selectively allows permeability to cations (Rao, 2008). The epithelial barriers consist of three distinct components: adherence junctions and tight junctions, which together form the apical junctional complex; and desmosomes that form bonds between cells and induce the mechanical strength to tissues (Crawford et al., 2021).

Air pollutants are thought to perturb the barrier integrity by increasing the availability of inflammatory mediators and ROS, and by

affecting gene transcription and expression of tight junction proteins, disrupting the epithelial and endothelial barrier by destabilizing the tight junctions in the GI and lungs (Wang et al., 2012; Woodby et al., 2020; Mutlu et al., 2011b; Nur Husna et al., 2021). The increased permeability to injurious factors including air pollutants further enhances inflammation and mucosal injury. The increased permeability play a crucial role in the pathogenesis of multiple GI disorders, such as IBD and enterocolitis. However, this proposed mechanisms awaits further validation (Rao, 2008).

An in vivo study in mice suggested that ozone exposure of lung epithelium resulted in a reduction of the transepithelial electrical resistance (TEER) and increased the tight junction gene expression of claudin-3 (Kim et al., 2018b). Claudin-3 expression has been linked to a reduced barrier function in the alveolar epithelial cells of rats. Similar findings were reported for PM exposure, resulting in an reduced TEER of the same rat alveolar epithelial cells (Mitchell et al., 2011; Wang et al., 2003). Furthermore, chronic PM exposure for 12 months results in epithelial lesions and confluence of inflammatory cells in murine colons (Li et al., 2019b). More recently, $PM_{2.5}$ exposure increased the intestinal permeability in a human intestinal model by decreasing tight junction proteins, claudin-1 and desmosome proteins (Woodby et al., 2020).

Excessive or prolonged exposure to air pollution can also directly have an impact on mucus production and gene expression linked to mucociliary assembly and movement (Smyth and Georas, 2021). $PM_{2.5}$ exposure was shown to cause a reduction in the gene expression securing mucociliary clearance in primary human airway epithelial cells (Montgomery et al., 2020). PM exposure has been linked to alterations in the mucus production and secretion, suggesting an enhanced secretion of inflammatory rather than homeostatic mucus (Okuda et al., 2019). Exposure to $PM_{2.5}$ exhibited increased expression of genes association with O-linked glycosylation of mucins (Montgomery et al., 2020). Nevertheless these effects are air pollution source dependent (Gillois et al., 2018; He et al., 2017).

5.5. Systemic inflammation

The combined effects of air pollution-induced loss of epithelial integrity, increased epithelial permeability, and changes in the mucosal barrier allows pathogens to enter the lamina propria and circulation (Espírito Santo et al., 2021; Jin et al., 2019). This increases immune cell activity evidenced by proinflammatory responses both locally and systemically. Pollution-induced damage to the endothelial and epithelial cells themselves also lead to the production and systemic release of proinflammatory mediators, such as tumor necrosis factor-α, Interleukin (IL) 6 and IL-1β. These factors contribute to the further loss of barrier function locally, but also induce a systemic inflammation affecting distant organs (Calderon-Garciduenas et al., 2007; McKay and Baird, 1999).

6. Biotics as dietary interventions to prevent or combat air pollution-induced health consequences

A wealth of data demonstrates the benefits of a healthy diet in reducing the risk of chronic diseases and in promoting human health, while intake of a less nutritious diet is associated with a higher risk of developing chronic diseases (Diet and nutrition and the p, 2003). Interestingly, there is a potential benefit of using biotics as dietary interventions in preventing or combating air pollution-related health outcomes. Although promising, biotic interventions have not made it yet to a therapeutic or preventive use in a pollution clinical setting. Therefore, our hypothesis is based on data from pre-clinical models, testing these engines in an pollution setting, or clinical studies investigating their role on clinical outcomes often impacted by air pollution.

6.1. Probiotics

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014). Already in 2012, the International Scientific Association for Probiotics and Prebiotics (ISAPP) recognized the role of probiotics in supporting a healthy GI tract and immune system (Hill et al., 2014). A meta-analysis (Ritchie and Romanuk, 2012) showed a significant benefit for probiotics in the prevention and treatment of GI diseases, including pouchitis, infectious diarrhoea, and IBS, which have been hypothesized to be associated with air pollution exposure. Although the evidence behind air pollution and UC is yet fully understood, a Cochrane review of 2020 (Kaur et al., 2020) concluded that probiotics may induce clinical remission in active UC when compared to placebo. In addition to the standard care treatment, probiotics may slightly improve the induction of clinical remission, though the evidence is very limited. The intestinal microbiota composition of IBD patients showed an increased number of aerobic bacteria, e.g., *Escherichia coli*, and anaerobic bacteria of the genus Bacteroides, and a decreased number of Lactobacilli and Bifidobacteria, suggesting a potential benefit of probiotic use in IBD therapy (Wasilewski et al., 2015).

Probiotics also show promise as dietary interventions to prevent and treat lung infections, including URTIs and ARIs (Hill et al., 2014), which might be triggered by air pollution as well. A 2015 Cochrane review (Hao et al., 2015) evaluating 12 randomized controlled trials in both paediatric and adult populations concluded that probiotics were better than placebo in preventing ARIs; the number of subject experiencing episodes of ARIs was about 47% lower in the probiotic group. Also in relation to the treatment of ARIs, probiotics provide a benefit compared to placebo treatment, with a shortened episode duration by about 1.89 days. These benefits in the prevention and treatment were reconfirmed in a more recent meta-analysis demonstrating a significantly reduced incidence and mean duration of URTI episodes (Li et al., 2020).

Nevertheless, the ISAPP underlines the important influence of factors like type of disease and probiotic species, when choosing to use probiotics in the prevention or treatment of GI and respiratory diseases (Ritchie and Romanuk, 2012). Although the available evidence is very limited, clinical evidence start to indicate a potential strain-specific effect on GI outcomes which are suggested to be impacted by air pollution exposure as well, including IBS and diarrhoea. A meta-analysis evaluating the effectiveness of *Lactobacillus rhamnosus GG* on childhood diarrhoea, demonstrated that high-dose supplementation reduces the duration of diarrhoea and the stool number per day (Li et al., 2019c). Another meta-analysis in children with acute gastroenteritis reconfirmed the impact of *Lactobacillus rhamnosus GG* supplementation on lowering the duration of diarrhoea (Szajewska et al., 2019). Nevertheless, these findings in the latter meta-analysis were recommended to be interpretated in the context of methodological limitations and high heterogenicity. More limited evidence, shows that supplementation of IBS patients with *Bifidobacterium breve* M-16 V in combination with *Bifidobacterium infantis* M-63 and *Bifidobacterium longum* BB536 decreased the prevalence and severity of abdominal pain and improved patient's quality of life (Giannetti et al., 2017).

Clinical and preclinical evidence also has been published around the role of specific probiotic strains in the support of respiratory health, leading to the hypothesis that this might also apply in an air pollution setting. Maternal intake of *Bifidobacterium breve* M-16 V might prevent and/or alleviate allergic reactions predisposed by prenatal exposure to air pollution in neonates. Its supplementation resulted in fewer eosinophils in the bronchoalveolar lavage fluid and a reduction of allergic lung inflammation in the offspring compared to the control group (Terada-Ikeda et al., 2020). The potential of influencing the gut-lung axis is also demonstrated in pre-clinical and clinical studies, not directly related to air pollution. In combination with *Bifidobacterium infantis M-63 and Bifidobacterium longum BB536*, *Bifidobacterium breve* M-16 V supplementation for 4 weeks significantly improved allergic rhinitis

symptoms and the quality of life in children with pollen-induced allergic rhinitis and intermittent asthma (Miraglia Del Giudice et al., 2017). Compared to *Bifidobacterium infantis* NumRes251, *Bifidobacterium animalis* NumRes252, *Bifidobacterium animalis* NumRes253, *Lactobacillus plantarum* NumRes8 and *Lactobacillus rhamnosus* NumRes6, *Bifidobacterium breve* M-16 V induced the strongest attenuating effect on lung inflammation in ovalbumin-sensitized mice (Hougee et al., 2010). Additionally, *Bifidobacterium breve* M-16 V supplementation, resulted in a reduced allergic lung inflammation and improved lung function in mice (Hougee et al., 2010; Sagar et al., 2014a), while protecting against the allergy-induced lung damage (Sagar et al., 2014a).

6.2. Prebiotics

Prebiotics are defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit to the host (Gibson et al., 2017). There are many types of prebiotics, of which the majority belongs to a subset of oligosaccharides. They are naturally abundant in food products including asparagus, sugar beet, chicory, onion, wheat, barley, human milk, and cow's milk. As the prebiotic concentrations in the majority of the foods are low, they are manufactured on an industrial scale. The most investigated industrial produced prebiotics can be classified as galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) (Davani-Davari et al., 2019). For more than three decades they are recognized for their role in the development of the immune system, and improving GI and respiratory health.

The GI health-promoting role of GOS and FOS was reported. The consumption of infant formula supplemented with GOS and FOS by preterm infants for approximately 28 days, resulted in higher stool frequency (Boehm et al., 2003; Westerbeek et al., 2011), significantly softer stools which were closer to the breastfed reference (Boehm et al., 2003), and lower stool viscosity (Westerbeek et al., 2011). Lower stool viscosity in these preterm infants can lead to shorter duration for luminal nutrients to remain in the intestine, preventing the inflammation and ultimately reducing the risk of developing Necrotising enterocolitis (Westerbeek et al., 2011). Similar GI health-promoting effects were also found in term-born infants reporting higher stool frequency (Fanaro et al., 2005), lower stool consistency (Fanaro et al., 2005; Moro et al., 2003; Piemontese et al., 2011), and softer stools that where closer to breastfed infants compared to controls (Fanaro et al., 2005; Moro et al., 2003; Piemontese et al., 2011). The GOS/FOS supplementation did not induce GI symptoms such as regurgitation, posseting, vomiting, colic, flatulence, and cramps as the incidence rate of these reports were equal between the test and control group (Piemontese et al., 2011).

Clinical evidence also reports lung health promoting effects of GOS and FOS, including its impact on lung infections, asthma, and lung inflammation, reported to be impacted by air pollution as well. In healthy term-born infants with a parental history of atopy (Arslanoglu et al., 2008), consumption of a formula based on partially hydrolysed proteins supplemented with GOS and FOS resulted in lower cumulative incidence of recurrent wheezing compared to the control group. The same test population reported significantly fewer respiratory tract infections and antibiotic use in the first 2 years of life compared to the control group. However, this effect might be population-dependent as in preterm infants, enteral supplementation with GOS and FOS resulted in an equal incidence of physician-diagnosed bronchial hyperreactivity and respiratory tract infections compared to the control group who received the same enteral formula supplemented with maltodextrin (Niele et al., 2013). Supplementation of GOS, FOS and pAOS reduced lung inflammatory markers and improved lung function in an allergic asthma mice model (Vos et al., 2007). Furthermore, lung inflammation and airway hyperresponsiveness were reduced after supplementation with GOS in a house dust mite-allergic mice model (Verheijden et al., 2015a).

6.3. Synbiotics

In 2019, the definition of synbiotics was updated by the ISAPP to "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host". These synbiotics were sub-divided into two categories; complementary and synergistic synbiotics. The first category includes probiotic (s) combined with prebiotic(s), which targets autochthonous microorganisms, while synergistic synbiotics composes a substrate that selectivity utilizes the co-administered microorganism(s) (Swanson et al., 2020). So far systematic reviews on the benefits of synbiotics do not differentiate the potential effect of these two categories separately (Chan et al., 2020).

Like probiotics and prebiotics applied separately, the potential role of synbiotics on GI and respiratory health have also been investigated. Only a few clinical studies investigated the synbiotic effects on GI diseases, like IBD and IBS (Ishikawa et al., 2011; Chermesh et al., 2007; Steed et al., 2010; Furrie et al., 2005; Fujimori et al., 2009), reported to be potentially impacted by air pollution exposure. The majority of them (Ishikawa et al., 2011; Steed et al., 2010; Furrie et al., 2005) hypothesized a benefit of synbiotic consumption in patients with IBD. However, as the measured outcome parameters and synbiotic blends varied among the studies, more evidence is needed to draw a conclusion. Only 2 studies (Tsuchiya et al., 2004; Min et al., 2012) investigated the potential effect on IBS. The meta-analysis on these two studies (Ford et al., 2018) showed overall that synbiotics seem not to reduce symptoms. The finding might be caused by the heterogenicity of the studies as the individual studies were both positive.

A meta-analysis (Chan et al., 2020) including 10.443 individuals revealed a preventive effect of synbiotics on respiratory tract infections by demonstrating reduced incidence rates and lower proportions experiencing respiratory tract infection, both by 16%. As respiratory infections are associated with air pollution exposure, this evidence suggests that this might also work in a polluted setting as well. The clinical evidence related to other respiratory health outcomes, like asthma and rhinitis, is less abundant. Nevertheless, as with probiotics, the potential effect might be mixture dependent.

Potential effects of a mixture of *Bifidobacterium breve* M-16 V, GOS and FOS on GI health were reported in infants with atopic dermatitis. Supplementation of this synbiotic blend softened the stool and resulted in fewer children with episodes of dry stools, diaper dermatitis or parent-reported constipation (van der Aa et al., 2010).

Some clinical studies also reported on the potential benefit of a synbiotic mixture containing oligosaccharides and *Bifidobacterium breve* M-16 V on respiratory outcomes. A clinical trial in infants with atopic dermatitis consuming a synbiotic blend of GOS, FOS and *Bifidobacterium breve* M-16 V, resulted in less children who started asthma medication during the intervention with the synbiotic mix (van der Aa et al., 2011). Another randomized controlled trial in adults with asthma and house dust mite allergy reported an improved peak expiratory flow after 4 weeks supplementation with *Bifidobacterium breve* M-16 V, GOS and FOS (van de Pol et al., 2011). Furthermore, *Bifidobacterium breve* M16V and FOS together reduced allergic lung inflammation when tested in a murine model (Verheijden et al., 2016).

7. Biotics target the gut-lung axis

During the last decades, both preclinical and clinical studies illustrated the role of pro-, pre-, and synbiotics in targeting the microbiota composition and their metabolites, epithelial and mucosal function, and immune system (Fig. 2, right). Although so far only pre-clinical evidence tested the impact of biotics on the gut-lung axis and steady state immune homeostasis in an air pollution setting, the multiplicity of data suggests that this mechanism could also apply in clinical setting investigating air pollution-impacted infants, children or adults.

7.1. Microbiota and metabolite shift

The gut microbiota composition is not only sensitive to harmful environmental exposures like pollutants but can be modulated by dietary interventions like biotics. It is key that the health promoting microbial organisms like the ingested probiotics are provided with enough energy to keep them alive, as multiple microbial organisms are competing for nutrition and an adhesion site to the GI tract with the host resident microbiota that could have been impacted by air pollution exposure (Markowiak and Śliżewska, 2017). Prebiotics function as the energy source for the ingested probiotics and the beneficial gut microbes already present. Furthermore, fermentation of prebiotics alters the pH of the gut, ultimately supporting the elimination of harmful acid-sensitive species, promoting the survival of butyrate producing microbes, like Bifidobacteria and Firmicutes (Davani-Davari et al., 2019; Markowiak and Śliżewska, 2017; Walker et al., 2005).

Multiple clinical studies (Moro et al., 2003; Arslanoglu et al., 2008; van der Aa et al., 2010; Moro et al., 2006; Boehm and Moro, 2008; Arslanoglu et al., 2007; Salvini et al., 2011; Scholtens et al., 2006; Moro et al., 2005; Boehm et al., 2002; Westerbeek et al., 2013; Scholtens et al., 2008; Fox et al., 2019) have reported that dietary supplementation with the probiotic *Bifidobacterium breve* M-16 V, prebiotic mixtures GOS and FOS, or a synbiotic mixture of these ingredients together, promotes the growth and survival of Bifidobacteria over time in a dose-dependent manner. Supplementation of these specific pro-, pre-, and synbiotic ingredients therefore have shown to bring the gut microbiota composition of formula-fed infants closer to the breastfed references (van der Aa et al., 2010; Fox et al., 2019; Chua et al., 2017). Subsequently to the bifidogenic effect, supplementation of these specific ingredients are also reported to induce a butyrogenic effect, revitalizing a healthy microbiota composition by reducing the pH and pathogenic bacteria like Enterobacteriaceae and *Clostridium difficile* (van der Aa et al., 2010; Boehm and Moro, 2008; Fox et al., 2019; Abrahamse-Berkeveld et al., 2016). The impact of GOS and FOS was less consistent for Lactobacilli, showing higher or equal counts compared to the controls (Boehm et al., 2003; Moro et al., 2003; Moro et al., 2006; Salvini et al., 2011; Moro et al., 2002).

7.2. Oxidative stress

Oxidative stress occurs when there is an imbalance between the generation and elimination of ROS. Air pollution constituent contain ROS and elicit ROS production by the host, prolonged exposure leads to disproportional generation of ROS which overwhelm existing anti-oxidant defenses (Leni et al., 2020). Measures of oxidative stress are nitric oxide (NO), superoxide dismutase (SOD), glutathione (GSH), serum GSH reductase (GSHR) and total anti-oxidant capacity (TAC) (Gregorczyk-Maga et al., 2019; Roshan et al., 2019; Okesene-Gafa et al., 2020).

Biotics may support the host natural anti-oxidant defence systems. Nevertheless, clinical studies testing the potential role of probiotics and synbiotics on oxidative stress were controversial due to the large variations in study populations and type of pro- or synbiotics used. Furthermore, these engines are often investigated together with other anti-oxidant molecules (Pourrajab et al., 2022). A Cochrane review of 2020 (Okesene-Gafa et al., 2020) on maternal health with gestational diabetes concluded that there is evidence showing the role of probiotics on increasing GHS and GSHR. Little to no evidence was found for their role on TAC and NO. Furthermore a meta-analysis (Pourrajab et al., 2022) investing the role of probiotics and synbiotics in the adults did show a significant increase of serum level TAC, GHS, NO when consuming these engines. Especially in adults aged $\leq$50 years a significant increase in TAC and NO was seen after synbiotic and probiotic supplementation compared to adults >50 years. Additionally, TAC, NO and GSH levels significantly increased in participants with a BMI 25–28.9 kg/m^2 versus subjects with other BMI values. When it comes to strain specific effects, *Bifidobacterium, Lactobacillus fermentum, Lactobacillus reuteri* and *Lactococcus* strains showed to increase of GSH release (Roshan et al., 2019; Asemi et al., 2012).

7.3. Lipid homeostasis

Emerging evidence suggests a significant role for the microbiota in human lipid homeostasis with microbial species not only transforming lipid structures but also producing various lipids. Disruptions in the microbiota composition may affect microbiota-dependent lipid transformations, ultimately contributing to disease pathogenesis (Lamichhane et al., 2021). Biotics may therefore support host resilience through supporting or restoring a healthy microbiome, positively contributing to the microbe-host-lipid-co-metabolism. In addition, biotics may support a healthy lipid metabolism by scavenging or preventing the generation of oxidized lipid mediators.

Although data on the potential effect of biotics on lipid mediators impacted by air pollution exposure is lacking, preclinical and clinical research is emerging suggesting an impact of these engines on ox-LDL, reported to be increased by $PM_{2.5}$ exposure. A 6-week supplementation of a probiotic blend consisting of *Bifidobacterium longum* CECT 7347, *Lactobacillus casei* CECT 9104, and *Lactobacillus rhamnosus* CECT 8361 tested with an oxidative stress model of physical exercise, resulted in a significant decrease of ox-LDL (Sánchez Macarro et al., 2021). A significant serum reduction in ox-LDL was also demonstrated after a 10 week consumption of a probiotic yogurt enriched with *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 in patients with a chronic heart failure (Pourrajab et al., 2020). However, another study (Rezazadeh et al., 2021) with the probiotic enriched yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 in metabolic syndrome patients for 8 weeks, did not show the significant reduction in ox-LDL. Though they confirmed a non-significant decrease of this oxidized lipoprotein. Two pre-clinical models suggested the potential effect of *Lactobacillus plantarum* on ox-LDL. Supplementation of *Lactobacillus plantarum* ATCC 14917 in ApoE−/− mice significantly reduced ox-LDL (Hassan et al., 2020). Additionally a significant reduction on ox-LDL was also reported in a rat model when consuming a high fat diet in combination with the probiotic *Lactobacillus plantarum* LS/07 or in combination with the prebiotic inulin (Hijova et al., 2020). Nevertheless, more research is needed to test these hypotheses.

7.4. Barrier function

Biotics are well recognized to support intestinal barrier functions. The air pollution-induced damage to the epithelial barriers and mucosal defence mechanisms, expressed in reduced tight junctions, decreased TEER, increased claudin-3, lowered sIgA, thin mucosal layer, might potentially be restored by biotic modulation (Alizadeh et al., 2016a; Alizadeh et al., 2016b; Akbari et al., 2017; Azagra-Boronat et al., 2018; Akbari et al., 2015; Rigo-Adrover et al., 2017). Dietary GOS supplementation upregulated mRNA expression of various tight junctions in the intestine and increased villi thickness and length in the duodenum and jejunum, representing an improvement in the epithelial barrier function when investigated in a piglet model (Alizadeh et al., 2016a). Additionally, incubation of GOS and FOS in deoxynivalenol model, illustrates the ability of these engines to increase TEER (Akbari et al., 2017). GOS supplementation prevented the deoxynivalenol-induced mRNA overexpression of claudin-3 in mice (Akbari et al., 2015). Furthermore, supplementation of healthy term infants with GOS and FOS for 26 weeks increases the sIgA production compared to the control group, representing an improved mucosal defence mechanism (Scholtens et al., 2008). This prebiotic and synbiotic induced increase in sIgA production is also supported by preclinical evidence (Alizadeh et al., 2016a; Azagra-Boronat et al., 2018; Rigo-Adrover et al., 2017).

Mechanistically, the improved epithelial barrier function and mucosal defence mechanism could be a consequence of the improved

gut microbiota composition and associated MAMPS pattern. Moreover, biotics affect the SCFA production, associated with air pollution exposure which changes the SCFA produced. Supplementation of healthy infants (van der Aa et al., 2010), infants with atopic dermatitis (van der Aa et al., 2010), c-section born infants (Chua et al., 2017), and preterm infants (Westerbeek et al., 2013) with GOS/FOS, sometimes combined with *Bifidobacterium breve* M-16 V, increases butyrate, acetate and propionate production. Butyrate is the primary substrate for colonocytes supporting epithelial barrier function by increasing the barrier integrity. As butyrate can travel through the enterocytes to the blood circulation, it could also stimulate a healthy epithelial barrier function in distant organs, like the lungs. Furthermore, acetate contributes via cross-feeding to the production of butyrate, elevating the butyrate-induced benefits (Canani et al., 2011).

7.5. Systemic inflammation

Whether microbiota imbalances precede an increased host inflammatory response or vice vera is still a matter of debate. Regardless, long-term imbalances in either are strongly associated with a state of chronic inflammation. Clinical as well as preclinical evidences suggest that biotic intervention are able to drive anti-inflammatory processes by influencing immune cell functions.

Both local as well as systemic air pollution-induced inflammation potentially can be restored into a steady state homeostasis by biotics due to their anti-inflammatory capacity. Therefore, these dietary interventions do not only affect gut health, but most likely also impact distant organs, like the lungs.

Multiple pre-clinical models showed that biotics could impact the T-cell differentiation, rebalancing Th1/Th2 responses (Sagar et al., 2014a; de Kivit et al., 2013; van Hoffen et al., 2010; Schouten et al., 2009; Kostadinova et al., 2016; van Esch et al., 2016; de Kivit et al., 2017; Kostadinova et al., 2017) and inducing functional regulatory T-cell production (Sagar et al., 2014a; de Kivit et al., 2013; de Kivit et al., 2017; Kostadinova et al., 2017; Schouten et al., 2010; Vonk et al., 2017; Vonk et al., 2019; Kerperien et al., 2018; Zheng et al., 2014). A cow's milk allergic mice model confirmed that supplementation with FOS enhanced the regulatory T-cell functionality (Vonk et al., 2019). Furthermore, the attenuated T-cell production and its presence were confirmed in the lungs, intestine and lymph nodes. As an example, the therapeutic administration of *Bifidobacterium breve* M16V showed to induce regulatory T-cell responses in the lungs as well as in the blood (Sagar et al., 2014a). Moreover, supplementation of GOS, FOS and pectin-derived acidic oligosaccharides (pAOS) in a cow's milk allergic mice model resulted in an increase frequency of regulatory T-cells in the mesenteric lymph nodes (Kerperien et al., 2018). In addition, regulatory T-cell development and reduction of Th2 cells in the gut were reported after supplementation of GOS, FOS and *Bifidobacterium breve* M16V in food-allergic mice (de Kivit et al., 2017; Kostadinova et al., 2017). Finally, using an *in vitro* model with human peripheral blood mononuclear cells, substantiated the systemic impact of probiotics on T-cell differentiation. Both *Lactobacillus rhamnosus* and *Bifidobacterium breve* M16V incubations reduced Th17 and increased Th2 cells. In addition, *Bifidobacterium breve* M16V reduced Th1 and increased regulatory T-cell subsets in contrast to *Lactobacillus rhamnosus* (Zheng et al., 2014).

Next to the effects of biotics on T-cell differentiation, they have the capacity to reduce inflammatory markers in the gut and lungs. Supplementation reduces pro-inflammatory cytokines (van de Pol et al., 2011; Akbari et al., 2015; van Hoffen et al., 2010; Verheijden et al., 2015b) and cell activation (Schouten et al., 2009; Kerperien et al., 2018; Plantinga et al., 2012; Zheng et al., 2016; Sagar et al., 2014b), while increasing anti-inflammatory cytokines (Kerperien et al., 2018). A meta-analysis investigating the role of *Lactobacillus acidophilus* supplementation on immune regulation suggested that this probiotic strain might have an immune regulatory role by increasing the levels of IgA and T-cell differentiation, while decreasing the concentrations of pro-inflammatory cytokines as TNF-α and IL-6 (Zhao et al., 2020). The same immunomodulating effect was suggested for *Lactobacillus Plantarum* by increasing anti-inflammatory cytokine concentrations of IL-10, while significantly reducing pro-inflammatory markers as IL-4, IFN-y, and TNF-α (Zhao et al., 2021).

8. Conclusion and future perspectives

In the context of air pollution which negatively affects health in all stages of life, this review hypothesizes a promising role for biotics in preventing and combating gut and lung diseases related to its exposure. Evidences show an association between air pollution exposure and impaired lung function, lung development, and pneumonia, and relatively new associations are hypothesized for gut health implications. There is however, a clear need to additionally clinically validate the link between air pollution exposure and the occurrence of GI diseases. Furthermore, it is clear that the impact of air pollution exposure varies among type of air pollutants, age of the subjects, the origin of the pollutants (traffic vs. industry), and type of GI and respiratory diseases, and the general health of the subject. An important complicating factor is that there exist a great heterogeneity in sources and components of air pollution which vary considerably between cities, countries and other environments.

There is a great need for studies using validated exposure protocols and standardized mixtures of pollutants to investigate where pathways overlap and where they differ in their effects on the microbiota, tissue barrier functions and immunity.

All these uncertainties could be a reason why there is only very limited information available reporting on the effects of biotic interventions. However, based on preclinical biotic interventions and generic evidence of the health promoting effects of biotics, clinical biotic intervention studies are warranted. However, the potential effectiveness of biotics to prevent or combat air pollution-induced GI and respiratory health effects are most likely strain and blend specific and depend on the general health of the host, the host microbiome composition, duration of consumption, and the age of the subject. This review suggests a role of the probiotics *Bifidobacteria* and *Lactobacilli,* and oligosaccharides as the prebiotic part, followed by the synbiotic mixture of the two together. While the number of clinical studies is limited, these specific biotic mixtures demonstrated beneficial effects on GI and respiratory clinical symptoms and gut-lung axis parameters, that could be affected by air pollution exposure. Nevertheless, as mentioned before, clinical studies designed in an air pollution setting for testing these engines are not available yet.

As air pollution levels are projected to rise globally and are an immense threat to global health, demands for health professionals to respond with urgent action is needed. While continued research on the rigorous impact of air pollution exposure on gut and lung health remains valuable, a swift of action to find interventions that prevent or combat air pollution-induced negative health consequences is required. Biotic interventions could play a role here based on their positive contributions to the gut-lung axis. Future clinical studies investigating their role on gut and lung health in an air pollution designed setting will form a next step in unravelling the impact of biotics in this public health emergency.

Author statement

Loret Keulers: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Ali Dehghani**: Conceptualization, Writing – review & editing. **Leon Knippels**: Conceptualization, Writing – review & editing, Supervision. **Johan Garssen**: Writing – review & editing, Supervision. **Nikolaos Papadopoulos**: Writing – review & editing, Supervision. **Gert Folkerts**: Conceptualization, Writing – review & editing. **Saskia Braber**: Conceptualization, Writing – review & editing. **Jeroen van Bergenhenegouwen**: Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision

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References

van der Aa, L.B., Heymans, H.S., van Aalderen, W.M., Sillevis Smitt, J.H., Knol, J., Ben Amor, K., et al., 2010. Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. Clin. Exp. Allergy : journal of the British Society for Allergy and Clinical Immunology 40 (5), 795–804.

van der Aa, L.B., van Aalderen, W.M., Heymans, H.S., Henk Sillevis Smitt, J., Nauta, A.J., Knippels, L.M., et al., 2011. Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. Allergy 66 (2), 170–177.

Abrahamse-Berkeveld, M., Alles, M., Franke-Beckmann, E., Helm, K., Knecht, R., Köllges, R., et al., 2016. Infant formula containing galacto-and fructo-oligosaccharides and Bifidobacterium breve M-16V supports adequate growth and tolerance in healthy infants in a randomised, controlled, double-blind, prospective, multicentre study. Journal of nutritional science 5, e42.

Adams, K., Greenbaum, D.S., Shaikh, R., van Erp, A.M., Russell, A.G., 2015. Particulate matter components, sources, and health: systematic approaches to testing effects. J. Air Waste Manag. Assoc. 65 (5), 544–558.

Akbari, P., Braber, S., Alizadeh, A., Verheijden, K.A., Schoterman, M.H., Kraneveld, A.D., et al., 2015. Galacto-oligosaccharides protect the intestinal barrier by maintaining the tight junction network and modulating the inflammatory responses after a challenge with the mycotoxin deoxynivalenol in human caco-2 cell monolayers and B6C3F1 mice. J. Nutr. 145 (7), 1604–1613.

Akbari, P., Fink-Gremmels, J., Willems, R., Difilippo, E., Schols, H.A., Schoterman, M.H. C., et al., 2017. Characterizing microbiota-independent effects of oligosaccharides on intestinal epithelial cells: insight into the role of structure and size : structure-activity relationships of non-digestible oligosaccharides. Eur. J. Nutr. 56 (5), 1919–1930.

Alizadeh, A., Akbari, P., Difilippo, E., Schols, H.A., Ulfman, L.H., Schoterman, M.H., et al., 2016a. The piglet as a model for studying dietary components in infant diets: effects of galacto-oligosaccharides on intestinal functions. Br. J. Nutr. 115 (4), 605–618.

Alizadeh, A., Braber, S., Akbari, P., Kraneveld, A., Garssen, J., Fink-Gremmels, J., 2016b. Deoxynivalenol and its modified forms: are there major differences? Toxins 8 (11).

Ananthakrishnan, A.N., McGinley, E.L., Binion, D.G., Saeian, K., 2011. Ambient air pollution correlates with hospitalizations for inflammatory bowel disease: an ecologic analysis. Inflamm. Bowel Dis. 17 (5), 1138–1145.

Arslanoglu, S., Moro, G.E., Boehm, G., 2007. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. J. Nutr. 137 (11), 2420–2424.

Arslanoglu, S., Moro, G.E., Schmitt, J., Tandoi, L., Rizzardi, S., Boehm, G., 2008. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J. Nutr. 138 (6), 1091–1095.

Asemi, Z., Jazayeri, S., Najafi, M., Samimi, M., Mofid, V., Shidfar, F., et al., 2012. Effect of daily consumption of probiotic yogurt on oxidative stress in pregnant women: a randomized controlled clinical trial. Ann. Nutr. Metabol. 60 (1), 62–68.

Azagra-Boronat, I., Massot-Cladera, M., Knipping, K., van't Land, B., Stahl, B., Garssen, J., et al., 2018. Supplementation with 2′-FL and scGOS/lcFOS Ameliorates Rotavirus-Induced Diarrhea in Suckling Rats, vol. 8, 372.

Bailey, M.J., Naik, N.N., Wild, L.E., Patterson, W.B., Alderete, T.L., 2020. Exposure to air pollutants and the gut microbiota: a potential link between exposure, obesity, and type 2 diabetes. Gut Microb. 11 (5), 1188–1202.

Beck-Speier, I., Karg, E., Behrendt, H., Stoeger, T., Alessandrini, F., 2012. Ultrafine particles affect the balance of endogenous pro- and anti-inflammatory lipid mediators in the lung: in-vitro and in-vivo studies. Part. Fibre Toxicol. 9 (1), 27.

Bernasconi, E., Pattaroni, C., Koutsokera, A., Pison, C., Kessler, R., Benden, C., et al., 2016. Airway microbiota determines innate cell inflammatory or tissue remodeling profiles in lung transplantation. Am. J. Respir. Crit. Care Med. 194 (10), 1252–1263.

Boehm, G., Moro, G., 2008. Structural and functional aspects of prebiotics used in infant nutrition. J. Nutr. 138 (9), 1818S-28S.

Boehm, G., Lidestri, M., Casetta, P., Jelinek, J., Negretti, F., Stahl, B., et al., 2002. Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. Arch. Dis. Child. Fetal Neonatal Ed. 86 (3), F178–F181.

Boehm, G., Fanaro, S., Jelinek, J., Stahl, B., Marini, A., 2003. Prebiotic concept for infant nutrition. Acta Paediatr. Suppl. 91 (441), 64–67.

Bowatte, G., Tham, R., Perret, J.L., Bloom, M.S., Dong, G., Waidyatillake, N., et al., 2018. Air pollution and otitis media in children: a systematic review of literature. Int. J. Environ. Res. Publ. Health 15 (2).

Bruce, N., Dherani, M., Liu, R., Hosgood 3rd, H.D., Sapkota, A., Smith, K.R., et al., 2015. Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax 70 (5), 433–441.

Budden, K.F., Gellatly, S.L., Wood, D.L.A., Cooper, M.A., Morrison, M., Hugenholtz, P., et al., 2017. Emerging pathogenic links between microbiota and the gut–lung axis. Nat. Rev. Microbiol. 15 (1), 55–63.

Burden of disease from household air pollution for 2016, 2018. Version 3 April 2018 Summary of Results. World Health Organization, Geneva. http://www.who.int/airpollution/data/en/. August 2018.

Calderon-Garciduenas, L., Franco-Lira, M., Torres-Jardon, R., Henriquez-Roldan, C., Barragan-Mejia, G., Valencia-Salazar, G., et al., 2007. Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. Toxicol. Pathol. 35 (1), 154–162.

Canani, R.B., Costanzo, M.D., Leone, L., Pedata, M., Meli, R., Calignano, A., 2011. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J. Gastroenterol. 17 (12), 1519–1528.

Caraballo, J.C., Yshii, C., Westphal, W., Moninger, T., Comellas, A.P., 2011. Ambient particulate matter affects occludin distribution and increases alveolar transepithelial electrical conductance. Respirology 16 (2), 340–349.

Chan, C.K.Y., Tao, J., Chan, O.S., Li, H.B., Pang, H., 2020. Preventing respiratory tract infections by synbiotic interventions: a systematic review and meta-analysis of randomized controlled trials. Advances in nutrition (Bethesda, Md) 11 (4), 979–988.

Chen, C.-C., Yang, C.-Y., 2018. Effects of ambient air pollution exposure on frequency of hospital admissions for appendicitis in Taipei, Taiwan. J. Toxicol. Environ. Health, Part A. 81 (17), 854–860.

Chen, F., Lin, Z., Chen, R., Norback, D., Liu, C., Kan, H., et al., 2018. The effects of PM2.5 on asthmatic and allergic diseases or symptoms in preschool children of six Chinese cities, based on China, Children, Homes and Health (CCHH) project. Environ. Pollut. 232, 329–337.

Chermesh, I., Tamir, A., Reshef, R., Chowers, Y., Suissa, A., Katz, D., et al., 2007. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. Dig. Dis. Sci. 52 (2), 385–389.

Chistiakov, D.A., Bobryshev, Y.V., Kozarov, E., Sobenin, I.A., Orekhov, A.N., 2015. Intestinal mucosal tolerance and impact of gut microbiota to mucosal tolerance 5 (781).

Chua, M.C., Ben-Amor, K., Lay, C., Goh, A.E.N., Chiang, W.C., Rao, R., et al., 2017. Effect of synbiotic on the gut microbiota of cesarean delivered infants: a randomized, double-blind. Multicenter Study 65 (1), 102–106.

Conticini, E., Frediani, B., Caro, D., 2020. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy? Environ. Pollut. 261, 114465.

Crawford, MsS., Nordgren, T.M., McCole, D.F., 2021. Every breath you take: impacts of environmental dust exposure on intestinal barrier function-from the gut-lung axis to COVID-19. Am. J. Physiol. Gastrointest. Liver Physiol. 320 (4), G586–G600.

Dang, A.T., Marsland, B.J., 2019. Microbes, metabolites, and the gut-lung axis. Mucosal Immunol. 12 (4), 843–850.

Davani-Davari, D., Negahdaripour, M., Karimzadeh, I., Seifan, M., Mohkam, M., Masoumi, S.J., et al., 2019. Prebiotics: definition, types, sources, mechanisms, and clinical applications. Foods 8 (3).

Deng, Q., Lu, C., Yu, Y., Li, Y., Sundell, J., Norback, D., 2016. Early life exposure to traffic-related air pollution and allergic rhinitis in preschool children. Respir. Med. 121, 67–73.

Diet, nutrition and the prevention of chronic diseases. World Health Organ Tech Rep Ser 916 (i-viii), 2003, 1–149 (backcover).

Dong, G.H., Chen, T., Liu, M.M., Wang, D., Ma, Y.N., Ren, W.H., et al., 2011. Gender differences and effect of air pollution on asthma in children with and without allergic predisposition: northeast Chinese children health study. PLoS One 6 (7), e22470.

Dumas, A., Bernard, L., Poquet, Y., Lugo-Villarino, G., Neyrolles, O., 2018. The Role of the Lung Microbiota and the Gut–Lung axis in Respiratory Infectious Diseases, vol. 20, e12966, 12.

Edginton, S., O'Sullivan, D.E., King, W., Lougheed, M.D., 2019. Effect of outdoor particulate air pollution on FEV1 in healthy adults: a systematic review and meta-analysis. Occup. Environ. Med. 76 (8), 583–591.

Elten, M., Benchimol, E.I., Fell, D.B., Kuenzig, M.E., Smith, G., Chen, H., et al., 2020. Ambient air pollution and the risk of pediatric-onset inflammatory bowel disease: a population-based cohort study. Environ. Int. 138, 105676.

Enaud, R., Prevel, R., Ciarlo, E., Beaufils, F., Wieers, G., Guery, B., et al., 2020. The gut-lung Axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Front Cell Infect Microbiol 10, 9.

Enyew, H.D., Mereta, S.T., Hailu, A.B., 2021. Biomass fuel use and acute respiratory infection among children younger than 5 years in Ethiopia: a systematic review and meta-analysis. Publ. Health 193, 29–40.

van Esch, B.C., Abbring, S., Diks, M.A., Dingjan, G.M., Harthoorn, L.F., Vos, A.P., et al., 2016. Post-sensitization administration of non-digestible oligosaccharides and Bifidobacterium breve M-16V reduces allergic symptoms in mice. Immunity, inflammation and disease 4 (2), 155–165.

Espírito Santo, C., Caseiro, C., Martins, M.J., Monteiro, R., Brandão, I., 2021. Gut microbiota, in the halfway between nutrition and lung function. Nutrients 13 (5).

Exposure to household air pollution for 2016, 2018. Version 5 April 2018. Summary of Results. World Health Organization, Geneva. http://www.who.int/airpollution/data/cities/en/. August 2018.

Fakunle, A.G., Jafta, N., Okekunle, A.P., Naidoo, R.N., 2020. Indoor microbiome and risk of lower respiratory tract infections among children under-five years: a meta-analysis. Indoor Air 30 (5), 795–804.

Fanaro, S., Jelinek, J., Stahl, B., Boehm, G., Kock, R., Vigi, V., 2005. Acidic oligosaccharides from pectin hydrolysate as new component for infant formulae: effect on intestinal flora, stool characteristics, and pH. J. Pediatr. Gastroenterol. Nutr. 41 (2), 186–190.
Fang, T., Lakey, P.S.J., Weber, R.J., Shiraiwa, M., 2019. Oxidative potential of particulate matter and generation of reactive oxygen species in epithelial lining fluid. Environ. Sci. Technol. 53 (21), 12784–12792.
Feng, J., Cavallero, S., Hsiai, T., Li, R., 2020. Impact of air pollution on intestinal redox lipidome and microbiome. Free Radic. Biol. Med. 1, 99–110. https://doi.org/10.1016/j.freeradbiomed.2019.12.044.
Ford, A.C., Harris, L.A., Lacy, B.E., Quigley, E.M.M., Moayyedi, P., 2018. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment. Pharmacol. Ther. 48 (10), 1044–1060.
Fouladi, F., Bailey, M.J., Patterson, W.B., Sioda, M., Blakley, I.C., Fodor, A.A., et al., 2020. Air pollution exposure is associated with the gut microbiome as revealed by shotgun metagenomic sequencing. Environ. Int. 138, 105604.
Fox, A.T., Wopereis, H., Van Ampting, M.T.J., Oude Nijhuis, M.M., Butt, A.M., Peroni, D. G., et al., 2019. A specific synbiotic-containing amino acid-based formula in dietary management of cow's milk allergy: a randomized controlled trial. Clin. Transl. Allergy 9 (1), 5.
Fuertes, E., MacIntyre, E., Agius, R., Beelen, R., Brunekreef, B., Bucci, S., et al., 2014. Associations between particulate matter elements and early-life pneumonia in seven birth cohorts: results from the ESCAPE and TRANSPHORM projects. Int. J. Hyg Environ. Health 217 (8), 819–829.
Fujimori, S., Gudis, K., Mitsui, K., Seo, T., Yonezawa, M., Tanaka, S., et al., 2009. A randomized controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis. Nutrition 25 (5), 520–525.
Furrie, E., Macfarlane, S., Kennedy, A., Cummings, J.H., Walsh, S.V., O'Neil, D.A., et al., 2005. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. Gut 54 (2), 242–249.
Garrett, W.S., Gordon, J.I., Glimcher, L.H., 2010. Homeostasis and inflammation in the intestine. Cell 140 (6), 859–870.
Gasana, J., Dillikar, D., Mendy, A., Forno, E., Ramos Vieira, E., 2012. Motor vehicle air pollution and asthma in children: a meta-analysis. Environ. Res. 117, 36–45.
Gauderman, W.J., Urman, R., Avol, E., Berhane, K., McConnell, R., Rappaport, E., et al., 2015. Association of improved air quality with lung development in children. N. Engl. J. Med. 372 (10), 905–913.
Giannetti, E., Maglione, M., Alessandrella, A., Strisciuglio, C., De Giovanni, D., Campanozzi, A., et al., 2017. A mixture of 3 bifidobacteria decreases abdominal pain and improves the quality of life in children with irritable bowel syndrome: a multicenter, randomized, double-blind, placebo-controlled, crossover trial. J. Clin. Gastroenterol. 51 (1), e5–e10.
Gibson, G.R., Hutkins, R., Sanders, M.E., Prescott, S.L., Reimer, R.A., Salminen, S.J., et al., 2017. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat. Rev. Gastroenterol. Hepatol. 14 (8), 491–502.
Gillois, K., Lévêque, M., Théodorou, V., Robert, H., Mercier-Bonin, M., 2018. Mucus: an underestimated gut target for environmental pollutants and food additives. Microorganisms 6 (2).
Girosi, D., Bellodi, S., Sabatini, F., Rossi, G.A., 2006. The lung and the gut: common origins, close links. Paediatr. Respir. Rev. 7 (Suppl. 1), S235–S239.
Gollwitzer, E.S., Saglani, S., Trompette, A., Yadava, K., Sherburn, R., McCoy, K.D., et al., 2014. Lung microbiota promotes tolerance to allergens in neonates via PD-L1. Nat. Med. 20 (6), 642–647.
Gregorczyk-Maga, I., Celejewska-Wojcik, N., Gosiewska-Pawlica, D., Darczuk, D., Kesek, B., Maga, M., et al., 2019. Exposure to air pollution and oxidative stress markers in patients with potentially malignant oral disorders. J. Physiol. Pharmacol. : an official journal of the Polish Physiological Society 70 (1).
Hamidou Soumana, I., Carlsten, C., 2021. Air pollution and the respiratory microbiome. J. Allergy Clin. Immunol. 148 (1), 67–69.
Hao, Q., Dong, B.R., Wu, T., 2015. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst. Rev. (2), CD006895
Harrison, R.M., 2020. Airborne particulate matter. Philos Trans A Math Phys Eng Sci 378 (2183), 20190319.
Hassan, A., Din, A.U., Zhu, Y., Zhang, K., Li, T., Wang, Y., et al., 2020. Anti-atherosclerotic effects of Lactobacillus plantarum ATCC 14917 in ApoE(-/-) mice through modulation of proinflammatory cytokines and oxidative stress. Appl. Microbiol. Biotechnol. 104 (14), 6337–6350.
He, F., Liao, B., Pu, J., Li, C., Zheng, M., Huang, L., et al., 2017. Exposure to ambient particulate matter induced COPD in a rat model and a description of the underlying mechanism. Sci. Rep. 7, 45666.
He, C., Liu, C., Chen, R., Meng, X., Wang, W., Ji, J., et al., 2022. Fine particulate matter air pollution and under-5 children mortality in China: a national time-stratified case-crossover study. Environ. Int. 159, 107022.
Hijova, E., Strojný, L., Bertková, I., Bomba, A., Štofilová, J., 2020. Dietary Lactobacillus plantarum LS/07 and inulin in the management of chronic disease risk factors. Acta Biochim. Pol. 67 (4), 447–451.
Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., et al., 2014. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat. Rev. Gastroenterol. Hepatol. 11 (8), 506–514.
van Hoffen, E., Korthagen, N.M., de Kivit, S., Schouten, B., Bardoel, B., Duivelshof, A., et al., 2010. Exposure of intestinal epithelial cells to UV-killed Lactobacillus GG but not Bifidobacterium breve enhances the effector immune response in vitro. Int. Arch. Allergy Immunol. 152 (2), 159–168.
Hong, Z., Guo, Z., Zhang, R., Xu, J., Dong, W., Zhuang, G., et al., 2016. Airborne fine particulate matter induces oxidative stress and inflammation in human nasal epithelial cells. Tohoku J. Exp. Med. 239 (2), 117–125.
Hosgood 3rd, H.D., Wei, H., Sapkota, A., Choudhury, I., Bruce, N., Smith, K.R., et al., 2011. Household coal use and lung cancer: systematic review and meta-analysis of case-control studies, with an emphasis on geographic variation. Int. J. Epidemiol. 40 (3), 719–728.
Hougee, S., Vriesema, A.J.M., Wijering, S.C., Knippels, L.M.J., Folkerts, G., Nijkamp, F. P., et al., 2010. Oral treatment with probiotics reduces allergic symptoms in ovalbumin-sensitized mice: a bacterial strain comparative study. Int. Arch. Allergy Immunol. 151 (2), 107–117.
Huangfu, P., Atkinson, R., 2020. Long-term exposure to NO(2) and O(3) and all-cause and respiratory mortality: a systematic review and meta-analysis. Environ. Int. 144, 105998.
WHO, 2018. Air Pollution and Child Health: Prescribing Clean Air.
Ishikawa, H., Matsumoto, S., Ohashi, Y., Imaoka, A., Setoyama, H., Umesaki, Y., et al., 2011. Beneficial effects of probiotic bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: a randomized controlled study. Digestion 84 (2), 128–133.
Jary, H., Simpson, H., Havens, D., Manda, G., Pope, D., Bruce, N., et al., 2016. Household air pollution and acute lower respiratory infections in adults: a systematic review. PLoS One 11 (12), e0167656.
Jin, Y., Lu, L., Tu, W., Luo, T., Fu, Z., 2019. Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. Sci. Total Environ. 649, 308–317.
Jones, D.T., Osterman, M.T., Bewtra, M., Lewis, J.D., 2008. Passive smoking and inflammatory bowel disease: a meta-analysis. Am. J. Gastroenterol. 103 (9), 2382–2393.
Josyula, S., Lin, J., Xue, X., Rothman, N., Lan, Q., Rohan, T.E., et al., 2015. Household air pollution and cancers other than lung: a meta-analysis. Environ. Health 14, 24.
Kaplan, G.G., Dixon, E., Panaccione, R., Fong, A., Chen, L., Szyszkowicz, M., et al., 2009. Effect of ambient air pollution on the incidence of appendicitis. Can. Med. Assoc. J. 181 (9), 591.
Kaplan, G.G., Hubbard, J., Korzenik, J., Sands, B.E., Panaccione, R., Ghosh, S., et al., 2010. The inflammatory bowel diseases and ambient air pollution: a novel association. Am. J. Gastroenterol. 105 (11), 2412–2419.
Kaplan, G.G., Szyszkowicz, M., Fichna, J., Rowe, B.H., Porada, E., Vincent, R., et al., 2012. Non-specific abdominal pain and air pollution: a novel association. PLoS One 7 (10), e47669.
Kaplan, G.G., Tanyingoh, D., Dixon, E., Johnson, M., Wheeler, A.J., Myers, R.P., et al., 2013. Ambient ozone concentrations and the risk of perforated and nonperforated appendicitis: a multicity case-crossover study. Environ. Health Perspect. 121 (8), 939–943.
Karl, J.P., Hatch, A.M., Arcidiacono, S.M., Pearce, S.C., Pantoja-Feliciano, I.G., Doherty, L.A., et al., 2018. Effects of psychological, environmental and physical stressors on the gut microbiota. Front. Microbiol. 9, 2013.
Katoto, P., Brand, A.S., Bakan, B., Obadia, P.M., Kuhangana, C., Kayembe-Kitenge, T., et al., 2021. Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity and mortality of COVID-19: a rapid systematic review. Environ. Health 20 (1), 41.
Kaur, L., Gordon, M., Baines, P.A., Iheozor-Ejiofor, Z., Sinopoulou, V., Akobeng, A.K., 2020. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst. Rev. 3 (3), Cd005573.
Kennedy, C.M., Pennington, A.F., Darrow, L.A., Klein, M., Zhai, X., Bates, J.T., et al., 2018. Associations of mobile source air pollution during the first year of life with childhood pneumonia, bronchiolitis, and otitis media. Environ Epidemiol 2 (1).
Kerperien, J., Veening-Griffioen, D., Wehkamp, T., van Esch, B., Hofman, G.A., Cornelissen, P., et al., 2018. IL-10 receptor or TGF-beta neutralization abrogates the protective effect of a specific nondigestible oligosaccharide mixture in cow-milk-allergic mice. J. Nutr. 148 (8), 1372–1379.
Khreis, H., Kelly, C., Tate, J., Parslow, R., Lucas, K., Nieuwenhuijsen, M., 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ. Int. 100, 1–31.
Kim, D., Chen, Z., Zhou, L.F., Huang, S.X., 2018a. Air pollutants and early origins of respiratory diseases. Chronic Dis Transl Med 4 (2), 75–94.
Kim, B.G., Lee, P.H., Lee, S.H., Park, C.S., Jang, A.S., 2018b. Impact of ozone on claudins and tight junctions in the lungs. Environ. Toxicol. 33 (7), 798–806.
Kish, L., Hotte, N., Kaplan, G.G., Vincent, R., Tso, R., Ganzle, M., et al., 2013. Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome. PLoS One 8 (4), e62220.
de Kivit, S., Kraneveld, A.D., Knippels, L.M., van Kooyk, Y., Garssen, J., Willemsen, L.E., 2013. Intestinal epithelium-derived galectin-9 is involved in the immunomodulating effects of nondigestible oligosaccharides. Journal of innate immunity 5 (6), 625–638.
de Kivit, S., Kostadinova, A.I., Kerperien, J., Morgan, M.E., Muruzabal, V.A., Hofman, G. A., et al., 2017. Dietary, nondigestible oligosaccharides and Bifidobacterium breve M-16V suppress allergic inflammation in intestine via targeting dendritic cell maturation. J. Leukoc. Biol. 102 (1), 105–115.
Korten, I., Ramsey, K., Latzin, P., 2017. Air pollution during pregnancy and lung development in the child. Paediatr. Respir. Rev. 21, 38–46.
Kostadinova, A.I., Meulenbroek, L.A., van Esch, B.C., Hofman, G.A., Garssen, J., Willemsen, L.E., et al., 2016. A specific mixture of fructo-oligosaccharides and bifidobacterium breve M-16V facilitates partial non-responsiveness to whey protein in mice orally exposed to β-lactoglobulin-derived peptides. Front. Immunol. 7, 673.
Kostadinova, A.I., Pablos-Tanarro, A., Diks, M.A.P., van Esch, B., Garssen, J., Knippels, L. M.J., et al., 2017. Dietary intervention with β-lactoglobulin-derived peptides and a

specific mixture of fructo-oligosaccharides and bifidobacterium breve M-16V facilitates the prevention of whey-induced allergy in mice by supporting a tolerance-prone immune environment. Front. Immunol. 8, 1303.
Kreyling, W.G., Semmler-Behnke, M., Moller, W., 2006. Ultrafine particle-lung interactions: does size matter? J. Aerosol Med. 19 (1), 74–83.
Kurata, J.H., Nogawa, A.N., 1997. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, Helicobacter pylori, and smoking. J. Clin. Gastroenterol. 24 (1), 2–17.
Lamichhane, S., Sen, P., Alves, M.A., Ribeiro, H.C., Raunioniemi, P., Hyötyläinen, T., et al., 2021. Linking gut microbiome and lipid metabolism: moving beyond associations. Metabolites 11 (1), 55.
Lee, K.K., Bing, R., Kiang, J., Bashir, S., Spath, N., Stelzle, D., et al., 2020. Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study. Lancet Global Health 8 (11), e1427–e1434.
Leni, Z., Künzi, L., Geiser, M., 2020. Air pollution causing oxidative stress. Current Opinion in Toxicology 20–21, 1–8.
Lewandowska-Polak, A., Brauncajs, M., Jarzębska, M., Pawełczyk, M., Kurowski, M., Chałubiński, M., et al., 2018. Toll-like receptor agonists modulate wound regeneration in airway epithelial cells. Int. J. Mol. Sci. 19 (8).
Li, W.Y., Han, Y., Xu, H.M., Wang, Z.N., Xu, Y.Y., Song, Y.X., et al., 2019a. Smoking status and subsequent gastric cancer risk in men compared with women: a meta-analysis of prospective observational studies. BMC Cancer 19 (1), 377.
Li, X., Cui, J., Yang, H., Sun, H., Lu, R., Gao, N., et al., 2019b. Colonic injuries induced by inhalational exposure to particulate-matter air pollution. Adv. Sci. 6 (11), 1900180.
Li, Y.-T., Xu, H., Ye, J.-Z., Wu, W.-R., Shi, D., Fang, D.-Q., et al., 2019c. Efficacy of Lactobacillus rhamnosus GG in treatment of acute pediatric diarrhea: a systematic review with meta-analysis. World J. Gastroenterol. 25 (33), 4999–5016.
Li, L., Hong, K., Sun, Q., Xiao, H., Lai, L., Ming, M., et al., 2020. Probiotics for preventing upper respiratory tract infections in adults: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2020, 8734140.
Li, Y., Li, C., Liu, J., Meng, C., Xu, C., Liu, Z., et al., 2021. An association between PM (2.5) and pediatric respiratory outpatient visits in four Chinese cities. Chemosphere 280, 130843.
Lindoso, L., Mondal, K., Venkateswaran, S., Somineni, H.K., Ballengee, C., Walters, T.D., et al., 2018. The effect of early-life environmental exposures on disease phenotype and clinical course of crohn's disease in children. Am. J. Gastroenterol. 113 (10), 1524–1529.
Liu, T., Chen, X., Xu, Y., Wu, W., Tang, W., Chen, Z., et al., 2019. Gut microbiota partially mediates the effects of fine particulate matter on type 2 diabetes: evidence from a population-based epidemiological study. Environ. Int. 130, 104882.
Liu, J., Zhou, J., Yao, J., Zhang, X., Li, L., Xu, X., et al., 2020. Impact of meteorological factors on the COVID-19 transmission: a multi-city study in China. Sci. Total Environ. 726, 138513.
Luong, L.M.T., Sly, P.D., Thai, P.K., Phung, D., 2019. Impact of ambient air pollution and wheeze-associated disorders in children in Southeast Asia: a systematic review and meta-analysis. Rev. Environ. Health 34 (2), 125–139.
MacIntyre, E.A., Gehring, U., Molter, A., Fuertes, E., Klumper, C., Kramer, U., et al., 2014. Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE Project. Environ. Health Perspect. 122 (1), 107–113.
Mahid, S.S., Minor, K.S., Soto, R.E., Hornung, C.A., Galandiuk, S., 2006. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin. Proc. 81 (11), 1462–1471.
Maleki, M., Anvari, E., Hopke, P.K., Noorimotlagh, Z., Mirzaee, S.A., 2021. An updated systematic review on the association between atmospheric particulate matter pollution and prevalence of SARS-CoV-2. Environ. Res. 195, 110898.
Mao, Y., Ding, P., Wang, Y., Ding, C., Wu, L., Zheng, P., et al., 2019. Comparison of culturable antibiotic-resistant bacteria in polluted and non-polluted air in Beijing, China. Environ. Int. 131, 104936.
Markowiak, P., Śliżewska, K., 2017. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients 9 (9).
Mazuryk, O., Stochel, G., Brindell, M., 2020. Variations in Reactive Oxygen Species Generation by Urban Airborne Particulate Matter in Lung Epithelial Cells—Impact of Inorganic Fraction, vol. 8, 1132.
WHO, 2016. Ambient (Outdoor) Air Pollution. Available from: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health.
McAleer, J.P., Kolls, J.K., 2018. Contributions of the Intestinal Microbiome in Lung Immunity, vol. 48, pp. 39–49, 1.
McKay, D.M., Baird, A.W., 1999. Cytokine regulation of epithelial permeability and ion transport. Gut 44 (2), 283–289.
Min, Y.W., Park, S.U., Jang, Y.S., Kim, Y.H., Rhee, P.L., Ko, S.H., et al., 2012. Effect of composite yogurt enriched with acacia fiber and Bifidobacterium lactis. World J. Gastroenterol. 18 (33), 4563–4569.
Miraglia Del Giudice, M., Indolfi, C., Capasso, M., Maiello, N., Decimo, F., Ciprandi, G., 2017. Bifidobacterium mixture (B longum BB536, B infantis M-63, B breve M-16V) treatment in children with seasonal allergic rhinitis and intermittent asthma. Ital. J. Pediatr. 43 (1), 25.
Mitchell, L.A., Overgaard, C.E., Ward, C., Margulies, S.S., Koval, M., 2011. Differential effects of claudin-3 and claudin-4 on alveolar epithelial barrier function. Am. J. Physiol. Lung Cell Mol. Physiol. 301 (1), L40–L49.
Moelling, K., Broecker, F., 2020. Air microbiome and pollution: composition and potential effects on human health, including SARS coronavirus infection. Journal of Environmental and Public Health 2020, 1646943.
Moller, W., Haussinger, K., Winkler-Heil, R., Stahlhofen, W., Meyer, T., Hofmann, W., et al., 2004. Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. J. Appl. Physiol. 97 (6), 2200–2206.
Montgomery, M.T., Sajuthi, S.P., Cho, S.H., Everman, J.L., Rios, C.L., Goldfarbmuren, K. C., et al., 2020. Genome-wide analysis reveals mucociliary remodeling of the nasal airway epithelium induced by urban PM(2.5). Am. J. Respir. Cell Mol. Biol. 63 (2), 172–184.
Moro, G., Minoli, I., Mosca, M., Fanaro, S., Jelinek, J., Stahl, B., et al., 2002. Dosage-related bifidogenic effects of galacto- and fructooligosaccharides in formula-fed term infants. J. Pediatr. Gastroenterol. Nutr. 34 (3), 291–295.
Moro, G.E., Mosca, F., Miniello, V., Fanaro, S., Jelinek, J., Stahl, B., et al., 2003. Effects of a new mixture of prebiotics on faecal flora and stools in term infants. Acta Paediatr. Suppl. 91 (441), 77–79.
Moro, G.E., Stahl, B., Fanaro, S., Jelinek, J., Boehm, G., Coppa, G.V., 2005. Dietary prebiotic oligosaccharides are detectable in the faeces of formula-fed infants. Acta Paediatr. Suppl. 94 (449), 27–30.
Moro, G., Arslanoglu, S., Stahl, B., Jelinek, J., Wahn, U., Boehm, G., 2006. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch. Dis. Child. 91 (10), 814–819.
Muniz, L.R., Knosp, C., Yeretssian, G., 2012. Intestinal antimicrobial peptides during homeostasis, infection, and disease. Front. Immunol. 3, 310.
Mutlu, E.A., Engen, P.A., Soberanes, S., Urich, D., Forsyth, C.B., Nigdelioglu, R., et al., 2011a. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. Part. Fibre Toxicol. 8, 19.
Mutlu, E.A., Engen, P.A., Soberanes, S., Urich, D., Forsyth, C.B., Nigdelioglu, R., et al., 2011b. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. Part. Fibre Toxicol. 8 (1), 19.
Nakajima, A., Vogelzang, A., Maruya, M., Miyajima, M., Murata, M., Son, A., et al., 2018. IgA regulates the composition and metabolic function of gut microbiota by promoting symbiosis between bacteria. J. Exp. Med. 215 (8), 2019–2034.
Nhung, N.T.T., Amini, H., Schindler, C., Kutlar Joss, M., Dien, T.M., Probst-Hensch, N., et al., 2017. Short-term association between ambient air pollution and pneumonia in children: a systematic review and meta-analysis of time-series and case-crossover studies. Environ. Pollut. 230, 1000–1008.
Niele, N., van Zwol, A., Westerbeek, E.A., Lafeber, H.N., van Elburg, R.M., 2013. Effect of non-human neutral and acidic oligosaccharides on allergic and infectious diseases in preterm infants. Eur. J. Pediatr. 172 (3), 317–323.
Norback, D., Lu, C., Wang, J., Zhang, Y., Li, B., Zhao, Z., et al., 2018. Asthma and rhinitis among Chinese children - indoor and outdoor air pollution and indicators of socioeconomic status (SES). Environ. Int. 115, 1–8.
Nur Husna, S.M., Siti Sarah, C.O., Tan, H.T., Md Shukri, N., Mohd Ashari, N.S., Wong, K. K., 2021. Reduced occludin and claudin-7 expression is associated with urban locations and exposure to second-hand smoke in allergic rhinitis patients. Sci. Rep. 11 (1), 1245.
Okesene-Gafa, K.A., Moore, A.E., Jordan, V., McCowan, L., Crowther, C.A., 2020. Probiotic treatment for women with gestational diabetes to improve maternal and infant health and well-being. Cochrane Database Syst. Rev. 6 (6), Cd012970.
Okuda, K., Chen, G., Subramani, D.B., Wolf, M., Gilmore, R.C., Kato, T., et al., 2019. Localization of secretory mucins MUC5AC and MUC5B in normal/healthy human airways. Am. J. Respir. Crit. Care Med. 199 (6), 715–727.
Opstelten, J.L., Beelen, R.M.J., Leenders, M., Hoek, G., Brunekreef, B., van Schaik, F.D. M., et al., 2016. Exposure to ambient air pollution and the risk of inflammatory bowel disease: a European nested case-control study. Dig. Dis. Sci. 61 (10), 2963–2971.
Piemontese, P., Gianni, M.L., Braegger, C.P., Chirico, G., Gruber, C., Riedler, J., et al., 2011. Tolerance and safety evaluation in a large cohort of healthy infants fed an innovative prebiotic formula: a randomized controlled trial. PLoS One 6 (11), e28010.
Plantinga, T.S., van Bergenhenegouwen, J., Jacobs, C., Joosten, L.A., van't Land, B., Garssen, J., et al., 2012. Modulation of Toll-like receptor ligands and Candida albicans-induced cytokine responses by specific probiotics. Cytokine 59 (1), 159–165.
van de Pol, M.A., Lutter, R., Smids, B.S., Weersink, E.J., van der Zee, J.S., 2011. Synbiotics reduce allergen-induced T-helper 2 response and improve peak expiratory flow in allergic asthmatics. Allergy 66 (1), 39–47.
Pourrajab, B., Naderi, N., Janani, L., Mofid, V., Hajahmadi, M., Dehnad, A., et al., 2020. Comparison of probiotic yogurt and ordinary yogurt consumption on serum Pentraxin 3, NT-proBNP, oxLDL, and ApoB100 in patients with chronic heart failure: a randomized, triple-blind, controlled trial. Food Funct. 11 (11), 10000–10010.
Pourrajab, B., Fatahi, S., Sohouli, M.H., Găman, M.-A., Shidfar, F., 2022. The effects of probiotic/synbiotic supplementation compared to placebo on biomarkers of oxidative stress in adults: a systematic review and meta-analysis of randomized controlled trials. Crit. Rev. Food Sci. Nutr. 62 (2), 490–507.
Qin, J., Xia, W., Liang, G., Xu, S., Zhao, X., Wang, D., et al., 2021. Association of fine particulate matter with glucose and lipid metabolism: a longitudinal study in young adults. Occup. Environ. Med. 78, 448–453. https://doi.org/10.1136/oemed-2020-107039.
Rahimi, N.R., Fouladi-Fard, R., Aali, R., Shahryari, A., Rezaali, M., Ghafouri, Y., et al., 2021. Bidirectional association between COVID-19 and the environment: a systematic review. Environ. Res. 194, 110692.
Rao, R., 2008. Oxidative stress-induced disruption of epithelial and endothelial tight junctions. Front. Biosci. 13, 7210–7226.
Rao, X., Zhong, J., Brook, R.D., Rajagopalan, S., 2018. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. Antioxidants Redox Signal. 28 (9), 797–818.
Ray, P.D., Huang, B.-W., Tsuji, Y., 2012. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell. Signal. 24 (5), 981–990.
Rezazadeh, L., Alipour, B., Jafarabadi, M.A., Behrooz, M., Gargari, B.P., 2021. Daily consumption effects of probiotic yogurt containing Lactobacillus acidophilus La5

and Bifidobacterium lactis Bb12 on oxidative stress in metabolic syndrome patients. Clinical nutrition ESPEN 41, 136–142.
Richards, L.B., Li, M., Folkerts, G., Henricks, P.A.J., Garssen, J., van Esch, B., 2020. Butyrate and propionate restore the cytokine and house dust mite compromised barrier function of human bronchial airway epithelial cells. Int. J. Mol. Sci. 22 (1).
Rigo-Adrover, M., Pérez-Berezo, T., Ramos-Romero, S., van Limpt, K., Knipping, K., Garssen, J., et al., 2017. A fermented milk concentrate and a combination of short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides/pectin-derived acidic oligosaccharides protect suckling rats from rotavirus gastroenteritis. Br. J. Nutr. 117 (2), 209–217.
Ritchie, M.L., Romanuk, T.N., 2012. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 7 (4), e34938.
Rosário Filho, N.A., Urrutia-Pereira, M., D'Amato, G., Cecchi, L., Ansotegui, I.J., Galán, C., et al., 2021. Air pollution and indoor settings. World Allergy Organization Journal 14 (1), 100499.
Roshan, H., Ghaedi, E., Rahmani, J., Barati, M., Najafi, M., Karimzedeh, M., et al., 2019. Effects of probiotics and synbiotic supplementation on antioxidant status: a meta-analysis of randomized clinical trials. Clinical nutrition ESPEN 30, 81–88.
Sagar, S., Morgan, M.E., Chen, S., Vos, A.P., Garssen, J., van Bergenhenegouwen, J., et al., 2014a. Bifidobacterium breve and Lactobacillus rhamnosus treatment is as effective as budesonide at reducing inflammation in a murine model for chronic asthma. Respir. Res. 15 (1), 46.
Sagar, S., Vos, A.P., Morgan, M.E., Garssen, J., Georgiou, N.A., Boon, L., et al., 2014b. The combination of Bifidobacterium breve with non-digestible oligosaccharides suppresses airway inflammation in a murine model for chronic asthma. Biochim. Biophys. Acta 1842 (4), 573–583.
Saleh, S., Shepherd, W., Jewell, C., Lam, N.L., Balmes, J., Bates, M.N., et al., 2020. Air pollution interventions and respiratory health: a systematic review. Int. J. Tubercul. Lung Dis. : the official journal of the International Union against Tuberculosis and Lung Disease 24 (2), 150–164.
Salim, S.Y., Kaplan, G.G., Madsen, K.L., 2014. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. Gut Microb. 5 (2), 215–219.
Salvini, F., Riva, E., Salvatici, E., Boehm, G., Jelinek, J., Banderali, G., et al., 2011. A specific prebiotic mixture added to starting infant formula has long-lasting bifidogenic effects. J. Nutr. 141 (7), 1335–1339.
Sana, A., Somda, S.M.A., Meda, N., Bouland, C., 2018. Chronic obstructive pulmonary disease associated with biomass fuel use in women: a systematic review and meta-analysis. BMJ open respiratory research 5 (1), e000246.
Sánchez Macarro, M., Ávila-Gandía, V., Pérez-Piñero, S., Cánovas, F., García-Muñoz, A. M., Abellán-Ruiz, M.S., et al., 2021. Antioxidant effect of a probiotic product on a model of oxidative stress induced by high-intensity and duration physical exercise. Antioxidants 10 (2).
Scholtens, P.A., Alles, M.S., Bindels, J.G., van der Linde, E.G., Tolboom, J.J., Knol, J., 2006. Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. J. Pediatr. Gastroenterol. Nutr. 42 (5), 553–559.
Scholtens, P.A., Alliet, P., Raes, M., Alles, M.S., Kroes, H., Boehm, G., et al., 2008. Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. J. Nutr. 138 (6), 1141–1147.
Schouten, B., van Esch, B.C., Hofman, G.A., van Doorn, S.A., Knol, J., Nauta, A.J., et al., 2009. Cow milk allergy symptoms are reduced in mice fed dietary synbiotics during oral sensitization with whey. J. Nutr. 139 (7), 1398–1403.
Schouten, B., van Esch, B.C.A.M., Hofman, G.A., Boon, L., Knippels, LoMJ., Willemsen, L. E.M., et al., 2010. Oligosaccharide-induced whey-specific CD25+ regulatory T-cells are involved in the suppression of cow milk allergy in mice. J. Nutr. 140 (4), 835–841.
Semin, I., Ninnemann, J., Bondareva, M., Gimaev, I., Kruglov, A.A., 2021. Interplay between microbiota. Toll-Like Receptors and Cytokines for the Maintenance of Epithelial Barrier Integrity 8 (787).
Setti, L., Passarini, F., De Gennaro, G., Barbieri, P., Perrone, M.G., Borelli, M., et al., 2020. SARS-Cov-2RNA found on particulate matter of Bergamo in Northern Italy: first evidence. Environ. Res. 188, 109754.
Shaykhiev, R., Behr, J., Bals, R., 2008. Microbial patterns signaling via Toll-like receptors 2 and 5 contribute to epithelial repair, growth and survival. PLoS One 3 (1), e1393.
Slaughter, J.C., Lumley, T., Sheppard, L., Koenig, J.Q., Shapiro, G.G., 2003. Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann. Allergy Asthma Immunol. : official publication of the American College of Allergy, Asthma, & Immunology 91 (4), 346–353.
Smyth, T., Georas, S.N., 2021. Effects of ozone and particulate matter on airway epithelial barrier structure and function: a review of in vitro and in vivo studies. Inhal. Toxicol. 33 (5), 177–192.
Stavropoulou, E., Kantartzi, K., Tsigalou, C., Konstantinidis, T., Voidarou, C., Konstantinidis, T., et al., 2021. Unraveling the interconnection patterns across lung microbiome, respiratory diseases. and COVID-19 10 (892).
Steed, H., Macfarlane, G.T., Blackett, K.L., Bahrami, B., Reynolds, N., Walsh, S.V., et al., 2010. Clinical trial: the microbiological and immunological effects of synbiotic consumption - a randomized double-blind placebo-controlled study in active Crohn's disease. Aliment. Pharmacol. Ther. 32 (7), 872–883.
Swanson, K.S., Gibson, G.R., Hutkins, R., Reimer, R.A., Reid, G., Verbeke, K., et al., 2020. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nat. Rev. Gastroenterol. Hepatol. 17 (11), 687–701.
Szajewska, H., Kołodziej, M., Gieruszczak-Białek, D., Skórka, A., Ruszczyński, M., Shamir, R., 2019. Systematic review with meta-analysis: Lactobacillus rhamnosus GG for treating acute gastroenteritis in children - a 2019 update. Aliment. Pharmacol. Ther. 49 (11), 1376–1384.
Tan, T.K., Saps, M., Lin, C.L., Wei, C.C., 2019. Is long-term ambient air pollutant exposure a risk factor for irritable bowel syndrome in children? A 12-year longitudinal cohort study. J Neurogastroenterol Motil 25 (2), 241–249.
Tang, J.W., Li, Y., 2019. Editorial: the airborne microbiome - implications for aerosol transmission and infection control – special issue. BMC Infect. Dis. 19 (1), 755.
Terada-Ikeda, C., Kitabatake, M., Hiraku, A., Kato, K., Yasui, S., Imakita, N., et al., 2020. Maternal supplementation with Bifidobacterium breve M-16V prevents their offspring from allergic airway inflammation accelerated by the prenatal exposure to an air pollutant aerosol. PLoS One 15 (9), e0238923.
Terzano, C., Di Stefano, F., Conti, V., Graziani, E., Petroianni, A., 2010. Air pollution ultrafine particles: toxicity beyond the lung. Eur. Rev. Med. Pharmacol. Sci. 14 (10), 809–821.
Thakur, M., Nuyts, P.A.W., Boudewijns, E.A., Flores Kim, J., Faber, T., Babu, G.R., et al., 2018. Impact of improved cookstoves on women's and child health in low and middle income countries: a systematic review and meta-analysis. Thorax 73 (11), 1026–1040.
Tsai, S.-S., Chiu, H.-F., Yang, C.-Y., 2019. Ambient air pollution and hospital admissions for peptic ulcers in taipei: a time-stratified case-crossover study. Int. J. Environ. Res. Publ. Health 16 (11).
Tsuchiya, J., Barreto, R., Okura, R., Kawakita, S., Fesce, E., Marotta, F., 2004. Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome. Chin. J. Dig. Dis. 5 (4), 169–174.
Veras, M.M., de Oliveira Alves, N., Fajersztajn, L., Saldiva, P., 2017. Before the first breath: prenatal exposures to air pollution and lung development. Cell Tissue Res. 367 (3), 445–455.
Verheijden, K.A., Willemsen, L.E., Braber, S., Leusink-Muis, T., Delsing, D.J., Garssen, J., et al., 2015a. Dietary galacto-oligosaccharides prevent airway eosinophilia and hyperresponsiveness in a murine house dust mite-induced asthma model. Respir. Res. 16 (1), 17.
Verheijden, K.A.T., Akbari, P., Willemsen, L.E.M., Kraneveld, A.D., Folkerts, G., Garssen, J., et al., 2015b. Inflammation-induced expression of the alarmin Interleukin 33 can Be suppressed by galacto-oligosaccharides. Int. Arch. Allergy Immunol. 167 (2), 127–136.
Verheijden, K.A., Willemsen, L.E., Braber, S., Leusink-Muis, T., Jeurink, P.V., Garssen, J., et al., 2016. The development of allergic inflammation in a murine house dust mite asthma model is suppressed by synbiotic mixtures of non-digestible oligosaccharides and Bifidobacterium breve M-16V. Eur. J. Nutr. 55 (3), 1141–1151.
Vignal, C., Guilloteau, E., Gower-Rousseau, C., Body-Malapel, M., 2021. Review article: epidemiological and animal evidence for the role of air pollution in intestinal diseases. Sci. Total Environ. 757, 143718.
Vonk, M.M., Diks, M.A.P., Wagenaar, L., Smit, J.J., Pieters, R.H.H., Garssen, J., et al., 2017. Improved Efficacy of Oral Immunotherapy Using Non-digestible Oligosaccharides in a Murine Cow's Milk Allergy Model: A Potential Role for Foxp3+ Regulatory T Cells, vol. 8, 1230.
Vonk, M.M., Blokhuis, B.R.J., Diks, M.A.P., Wagenaar, L., Smit, J.J., Pieters, R.H.H., et al., 2019. Butyrate enhances desensitization induced by oral immunotherapy in cow's milk allergic mice. Mediat. Inflamm. 2019, 9062537.
Vos, A.P., van Esch, B.C., Stahl, B., M'Rabet, L., Folkerts, G., Nijkamp, F.P., et al., 2007. Dietary supplementation with specific oligosaccharide mixtures decreases parameters of allergic asthma in mice. Int. Immunopharm. 7 (12), 1582–1587.
Walker, A.W., Duncan, S.H., McWilliam Leitch, E.C., Child, M.W., Flint, H.J., 2005. pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. Appl. Environ. Microbiol. 71 (7), 3692–3700.
Wang, F., Daugherty, B., Keise, L.L., Wei, Z., Foley, J.P., Savani, R.C., et al., 2003. Heterogeneity of claudin expression by alveolar epithelial cells. Am. J. Respir. Cell Mol. Biol. 29 (1), 62–70.
Wang, T., Wang, L., Moreno-Vinasco, L., Lang, G.D., Siegler, J.H., Mathew, B., et al., 2012. Particulate matter air pollution disrupts endothelial cell barrier via calpain-mediated tight junction protein degradation. Part. Fibre Toxicol. 9, 35.
Wang, H., Zhou, Q., Dai, W., Feng, X., Lu, Z., Yang, Z., et al., 2019. Lung microbiota and pulmonary inflammatory cytokines expression vary in children with tracheomalacia and adenoviral or mycoplasma pneumoniae pneumonia. Frontiers in pediatrics 7, 265.
Wang, T., Han, Y., Li, H., Wang, Y., Xue, T., Chen, X., et al., 2021a. Changes in bioactive lipid mediators in response to short-term exposure to ambient air particulate matter: a targeted lipidomic analysis of oxylipin signaling pathways. Environ. Int. 147, 106314.
Wang, J., Shi, J., Zhao, Y., Xue, L., Li, G., Wang, B., et al., 2021b. Cardiorespiratory responses in healthy young adults with exposure to indoor airborne PAEs: a randomized, crossover trial of air purification. Environ. Int. 156, 106761.
Wasilewski, A., Zielińska, M., Storr, M., Fichna, J., 2015. Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. Inflamm. Bowel Dis. 21 (7), 1674–1682.
Westerbeek, E.A., Hensgens, R.L., Mihatsch, W.A., Boehm, G., Lafeber, H.N., van Elburg, R.M., 2011. The effect of neutral and acidic oligosaccharides on stool viscosity, stool frequency and stool pH in preterm infants. Acta Paediatr. 100 (11), 1426–1431.
Westerbeek, E.A., Slump, R.A., Lafeber, H.N., Knol, J., Georgi, G., Fetter, W.P., et al., 2013. The effect of enteral supplementation of specific neutral and acidic oligosaccharides on the faecal microbiota and intestinal microenvironment in preterm infants. Eur. J. Clin. Microbiol. Infect. Dis. 32 (2), 269–276.

Woodby, B., Schiavone, M.L., Pambianchi, E., Mastaloudis, A., S, N.H., S, M.W., et al., 2020. Particulate matter decreases intestinal barrier-associated proteins levels in 3D human intestinal model. Int. J. Environ. Res. Publ. Health 17 (9).
Wu, X., Nethery, R.C., Sabath, B.M., Braun, D., Dominici, F., 2020. Exposure to Air Pollution and COVID-19 Mortality in the United States: A Nationwide Cross-Sectional Study. medRxiv.
Xu, C., Kan, H.-D., Fan, Y.-N., Chen, R.-J., Liu, J.-H., Li, Y.-F., et al., 2016. Acute effects of air pollution on enteritis admissions in Xi'an, China. J. Toxicol. Environ. Health, Part A. 79 (24), 1183–1189.
Yan, W., Wang, X., Dong, T., Sun, M., Zhang, M., Fang, K., et al., 2020. The impact of prenatal exposure to PM2.5 on childhood asthma and wheezing: a meta-analysis of observational studies. Environ. Sci. Pollut. Res. Int. 27 (23), 29280–29290.
Yee, J., Cho, Y.A., Yoo, H.J., Yun, H., Gwak, H.S., 2021. Short-term exposure to air pollution and hospital admission for pneumonia: a systematic review and meta-analysis. Environ. Health 20 (1), 6.
Yue, M., Kim, J.H., Evans, C.R., Kachman, M., Erb-Downward, J.R., D'Souza, J., et al., 2020. Measurement of short-chain fatty acids in respiratory samples: keep your assay above the water line. Am. J. Respir. Crit. Care Med. 202 (4), 610–612.
Zhang, F., Zhang, H., Wu, C., Zhang, M., Feng, H., Li, D., et al., 2021. Acute effects of ambient air pollution on clinic visits of college students for upper respiratory tract infection in Wuhan, China. Environ. Sci. Pollut. Res. Int. 28 (23), 29820–29830.
Zhao, W., Liu, Y., Kwok, L.-Y., Cai, T., Zhang, W., 2020. The immune regulatory role of Lactobacillus acidophilus: an updated meta-analysis of randomized controlled trials. Food Biosci. 36, 100656.
Zhao, W., Peng, C., Sakandar, H.A., Kwok, L.-Y., Zhang, W., 2021. Meta-Analysis: Randomized Trials of Lactobacillus Plantarum on Immune Regulation over the Last Decades, vol. 12.
Zheng, B., van Bergenhenegouwen, J., Overbeek, S., van de Kant, H.J.G., Garssen, J., Folkerts, G., et al., 2014. Bifidobacterium breve attenuates murine dextran sodium sulfate-induced colitis and increases regulatory T cell responses. PLoS One 9 (5), e95441.
Zheng, B., van Bergenhenegouwen, J., van de Kant, H.J., Folkerts, G., Garssen, J., Vos, A. P., et al., 2016. Specific probiotic dietary supplementation leads to different effects during remission and relapse in murine chronic colitis. Benef. Microbes 7 (2), 205–213.
Zheng, P., Zhang, B., Zhang, K., Lv, X., Wang, Q., Bai, X., 2020. The impact of air pollution on intestinal microbiome of asthmatic children: a panel study. BioMed Res. Int. 2020, 5753427.
Zhivaki, D., Kagan, J.C., 2021. Innate immune detection of lipid oxidation as a threat assessment strategy. Nat. Rev. Immunol. 21, 1–9.
Zielinska, M.A., Hamulka, J., 2019. Protective effect of breastfeeding on the adverse health effects induced by air pollution: current evidence and possible mechanisms. Int. J. Environ. Res. Publ. Health 16 (21).