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Review

Air Pollution and the Airways: Lessons from a Century of Human Urbanization

Janne Goossens [1,†], Anne-Charlotte Jonckheere [1,†], Lieven J. Dupont [2,3] and Dominique M. A. Bullens [1,4,*]

1 KU Leuven, Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, 3000 Leuven, Belgium; janne.goossens@kuleuven.be (J.G.); annecharlotte.jonckheere@kuleuven.be (A.-C.J.)
2 KU Leuven, Department of Chronic Diseases, Metabolism and Ageing, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), 3000 Leuven, Belgium; lieven.dupont@uzleuven.be
3 UZ Leuven, Clinical Division of Respiratory Medicine, 3000 Leuven, Belgium
4 UZ Leuven, Clinical Division of Paediatrics, 3000 Leuven, Belgium
* Correspondence: dominique.bullens@kuleuven.be
† Contributed equally to the manuscript.

Abstract: Since the industrial revolution, air pollution has become a major problem causing several health problems involving the airways as well as the cardiovascular, reproductive, or neurological system. According to the WHO, about 3.6 million deaths every year are related to inhalation of polluted air, specifically due to pulmonary diseases. Polluted air first encounters the airways, which are a major human defense mechanism to reduce the risk of this aggressor. Air pollution consists of a mixture of potentially harmful compounds such as particulate matter, ozone, carbon monoxide, volatile organic compounds, and heavy metals, each having its own effects on the human body. In the last decades, a lot of research investigating the underlying risks and effects of air pollution and/or its specific compounds on the airways, has been performed, involving both *in vivo* and *in vitro* experiments. The goal of this review is to give an overview of the recent data on the effects of air pollution on healthy and diseased airways or models of airway disease, such as asthma or chronic obstructive pulmonary disease. Therefore, we focused on studies involving pollution and airway symptoms and/or damage both in mice and humans.

Keywords: air pollution; respiratory system; mouse studies; human models

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1. Introduction

Air pollution has become a hot topic in the last couple of years as more and more negative effects on the respiratory, cardiovascular, neurological, and reproductive systems were discovered. According to the World Health Organization (WHO), about 4.2 million people died in relation to ambient air pollution suggesting a high impact of air pollution on our quality of life and on our health system [1,2]. Looking closer to deaths caused by pulmonary diseases, around 3.6 million deaths occur worldwide [3,4]. One of the major sources of air pollution, next to natural sources such as volcanos or wildfires, is industrialization. Developed countries are constantly trying to reduce air pollution, but developing countries that still need industrialization to grow, observe increased levels of air pollution [5]. This leads to the fact that 80% of people who live in urban regions are exposed to air pollution levels exceeding the WHO guidelines [5,6]. Over the last five years, a lot of research has been published about the effects of air pollution or specific pollutants on the respiratory system. In this review, we aimed to give an overview of recent literature with an immunological focus on the effects on healthy and diseased airways such as asthma or chronic obstructive pulmonary disease (COPD) both in human studies as well as in murine studies. Therefore, we divided this review into two parts after the definition of air pollution and the respiratory system. First, we describe lessons learned from murine

and *in vitro* studies highlighting the immunological response, and secondly, we assess the impact of air pollution on human health focusing on respiratory diseases.

2. Definition of Air Pollution

The definition of air pollution according to the Engineers Joint Council, is "the presence in the outdoor atmosphere of one or more contaminants, such as characteristics and levels of dust, fumes, gas, mist, odor, smoke, or vapor, to be injurious to human, plant, animal life or property. Their presence might also unreasonably interfere with the comfortable enjoyment of life and property." [7,8]. Based on the physical state and particle size, several distinctions can be made. Firstly, two main types of pollutants based on the composition can be distinguished: gaseous compounds and particulate matter (PM) [5,9]. Gaseous compounds contributing to air pollution are ozone, nitrogen oxides (NOx, as reviewed by [10–12]), carbon monoxide (CO), carbon dioxide (CO_2) and volatile organic compounds ((VOCs); polyaromatic hydrocarbons (PAH), and heavy metals) [9]. Secondly, PM (consisting of solid and liquid particles) can be subdivided based on particle size into PM_{10} (<10 μm), $PM_{2.5}$ (<2.5 μm), and ultrafine particles (<0.1 μm) [5,9]. Although gaseous compounds can have a negative effect on the airways, particulate matter is supposed to have the greatest impact on our respiratory system [5]. Another important subdivision is by primary and secondary pollutants. Primary pollutants are those directly emitted by the sources like CO or SO_2, while secondary pollutants are those formed in the atmosphere as a consequence of chemical and physical reactions. Examples of secondary pollutants are ozone, NO_2, sulfates, and ultra-fine particles (UFP) [13].

3. The Respiratory System and Air Pollution

The respiratory system is composed of two main zones: the conducting zone and the respiratory zone each with their specific function, respectively transportation of gases and gas exchange [14]. The conducting zone consists of the trachea, bronchi up to the terminal bronchioles, whereas the respiratory zone consists of the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli [14]. Chronic lung diseases, such as asthma and COPD, result from inflamed or obstructive lungs [15] and are one of the two world's biggest burdens on the health system [16].

Air pollution and, more specifically, particle matter can deposit in several regions of the lung depending on the size of the particle, shape, density, and breathing pattern (Figure 1) [17]. Particles with a size > 10 μm usually do not penetrate the lower airways as they will be filtered by the nose and upper airways [18,19]. On the other hand PM_{10}, $PM_{2.5,}$ and ultrafine particles (UFP) will penetrate the lower airways and deposit deeper into the lungs with the smallest particles ($PM_{2.5}$ and UFP) accumulating in the terminal bronchioles and alveoli and the PM_{10} more in the conducting airways [18,19]. Furthermore, UFP can even diffuse into the systemic circulation via the blood-air barrier reaching even the heart, liver, spleen, or brain [19]. Particles will be eliminated through distinct pathways depending on the site of deposition. Mucociliary transport and clearance by airway macrophages are the two major pathways [20,21].

Looking closer into the airways, inhaled pollutants will first come into contact with the bronchial epithelium which is the protective barrier against all environmental compounds, regulating both innate and adaptive immune responses [18,22]. Secondly, innate immune players such as the alveolar macrophages can also contribute to the clearance of particles via phagocytosis [18]. Both pathways eventually lead to the induction of oxidative stress and inflammatory responses in the airways causing damage to the lungs [18,22].

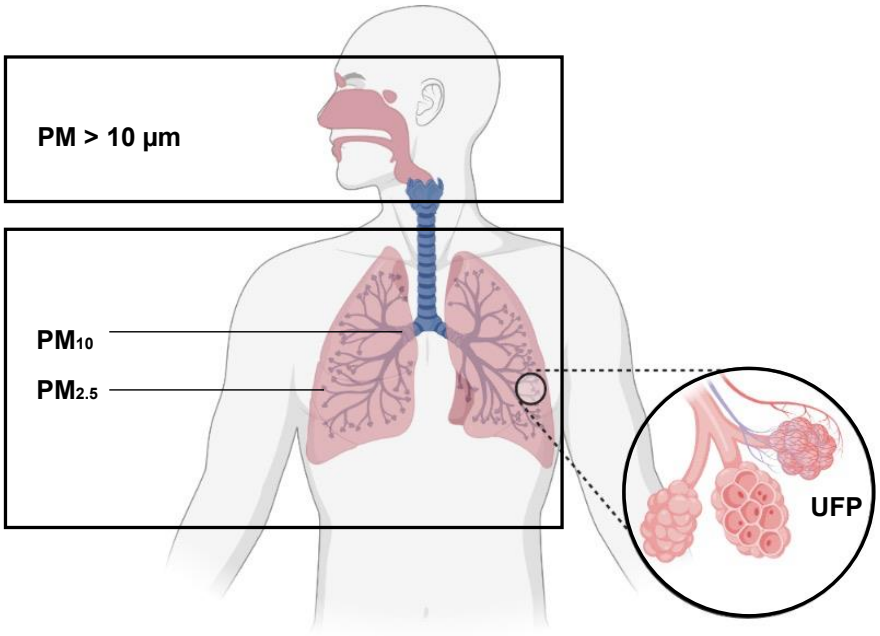

Figure 1. Deposition of particulate matter in the airways. Particulate matter (PM) consists of several particle sizes which deposit in the airways at different levels. PM > 10 µm will accumulate in the upper airways and filtered by the nose. PM < 10 µm (PM_{10}) will penetrate in the lower airways up to the level of the conducting airways. PM < 2.5 µm ($PM_{2.5}$) will also deposit in the lower airways but will accumulate deeper in the terminal bronchioles and alveoli. Ultrafine particles (UFP < 0.1 µm) will reside at the level of the alveoli in the lower airways and can even diffuse into the systemic circulation. Created with BioRender.com.

4. Lessons Learned from Exposure Models: Murine and Human Data

A lot of research about the effects of air pollution on the airways has been done in both *in vivo* and *in vitro* models. In this part, the different types of pollutants will be discussed in relation to the airways in murine and *in vitro* models and humans with a focus on the immunological response.

4.1. Ozone

Depending on the dose and the frequency, ozone can induce different injuries and inflammation in the lungs [23,24]. It is already known that being exposed to even a small amount of ozone, can cause an asthma exacerbation and further worsening of the symptoms of respiratory diseases, with even an increase in mortality [25]. Therefore, a lot of murine models and studies have been performed to investigate the underlying mechanisms and possible risk factors that enhance ozone-induced lung inflammation and injury.

Acute exposure to ozone (single exposure with low or high amounts) leads to acute disruption of the airway epithelium with desquamation of epithelial cells and leakage due to disrupted tight junctions [23,24]. Especially, a recent study has shown that ozone changes the claudin 3 and 4 expressions in mouse bronchial epithelium leading to a leaky barrier probably via reactive oxygen species (ROS) secreted by alveolar macrophages [26,27]. The ozone-induced epithelial disruption is related to the release of interleukin (IL)-1α and IL-33 by epithelial cells together with chemokines CXCL1 and CCL2, macrophage inflammatory protein-2 (MIP-2), and IL-6 resulting in macrophage and neutrophil recruitment to the airways, inducing neutrophilic inflammation [23,24,28,29].

Also, oxidative stress (via mitochondrial ROS) and activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome are induced after acute exposure to ozone and are playing a crucial role in the pathogenesis of the induced airway inflammation [30,31]. As a result of NLRP3 inflammation activation, ozone induces IL-17A produced by innate

immune cells such as innate lymphoid cells or $\gamma\delta$ T cells which also contributes to activation and attraction of neutrophils to the airways leading to airway hyperreactivity [32].

Chronic ozone exposure (multiple exposures with small or high amounts of ozone) induces similar problems as acute exposure but is amplified. Indeed, studies in mice have shown that repeated exposure to ozone leads to lung inflammation, oxidative stress, mitochondrial dysfunction, activation of the NLRP3 inflammasome, and eventually emphysema with fibrosis in the lungs [23,33]. Secondly, recently it has also been shown that chronic ozone exposure leads to activation of the aryl hydrocarbon receptor (AhR), which is broadly expressed on immune cells and epithelial cells, and which plays a protective role via IL-22 production in the lungs [34]. AhR can have several effects depending on the nature of the ligand and the environment [34]. Ozone induced the production of tryptophan and lipoxin A4 (LXA_4), both ligands for AhR. After activation of this receptor, IL-22 levels together with ILC3 and $\gamma\delta$ T cells are repressed leading to lesser inflammation and induction of tissue remodeling [34].

Several studies have shown that obesity and being overweight lead to limitations in pulmonary function leading to the hypothesis that air pollution can have a bigger effect on the lungs [35]. Also, other effects of air pollution have been described between gender [36]. Therefore, obesity and sex differences have been described as risk factors to augment the response towards ozone [37]. In obese mice, it has been shown that acute ozone exposure leads to a further increase of IL-17A in the lungs leading to more neutrophil recruitment and airway hyperresponsiveness [38]. Secondly, different responses to ozone in the different sexes have already been investigated. Androgens, for example, are known to further increase ozone-induced airway hyperreactivity in C57BL/6 mice [39]. On the other hand, the estrous cycle and 17β-estradiol, also play an important role in reducing lung inflammation and hyperresponsiveness after ozone exposure [40,41]. This is also confirmed in a study exposing both male and female mice to ozone, where different responses in cellular inflammation and airway hyperreactivity were noted, which might be induced by a different microbiome [42,43].

Lastly, several studies described the effect of ozone exposures in allergic murine models. Last et al. (2004) showed that ozone-induced exacerbation of allergic inflammation is dependent on the sequence of exposure and on the concentration of ozone [44]. Most studies have been done in an ovalbumin (OVA) allergic murine model and most of them indicated that ozone aggravates airway inflammation, airway hyperresponsiveness, airway remodeling, and mucus secretion in OVA-allergic mice [45–47]. However, a study by Hansen et al. (2016) observed no aggravation of ozone in OVA-allergic mice, it even showed that allergic mice were protected from the effect of ozone irritation in the airways [48]. These contradictory results show that exposure time and concentration of ozone can lead to different responses in the airways making it difficult to summarize the different pathways.

Controlled human exposure to ozone causes increased inflammation as evidenced by neutrophil influx into the lung and increased levels of proinflammatory cytokines [49]. Also, plasma clara cell protein (CC16) levels, which is a common biomarker used for epithelial cell damage, were observed to be significantly increased after low-level ozone exposure in an ozone concentration-dependent manner. Metabolomics analysis of bronchoalveolar lavage (BAL) samples from volunteers exposed to ozone demonstrated oxidative stress responses and subsequent cellular repair, with metabolomic signals of increased energy usage [50]. Focusing on airway inflammation, sputum neutrophils obtained after exposure showed a small significant increase but in contrast, proinflammatory cytokines (IL-6, IL-8, and tumor necrosis factor-α (TNF- α)) were not significantly affected [51]. *in vitro*, ozone stimulated bronchial epithelial cells induced IL-6 and IL-8 expression [52]. Furthermore, ozone induced intercellular adhesion molecule 1 (ICAM-1) expression and neutrophil adhesion to human airway epithelial cells [53]. As in murine models, the effect of obesity in the response to ozone was studied. Obese females had a larger reduction in forced vital capacity (FVC) associated with the acute ozone exposure compared to normal-weight

females [54]. However, no obesity-related difference was observed in airway reactivity and inflammation [54].

4.2. Carbon Monoxide

CO is a color-free and odorless gas originating from any incomplete combustion of hydrocarbons or cigarette smoke and can lead to toxicity in the lungs [55]. Breathing high concentrations of CO leads to the forming of carboxyhemoglobin, resulting in functional anemia [56]. In this part, the focus will lie on the effects of CO as a toxic part of cigarette smoke and in short, the unexpected protective effects CO can have in other diseases.

It is well-known that cigarette smoke has several negative effects on the airways, such as induction of oxidative stress, neutrophilic airway inflammation, and emphysema leading to COPD (see 5.2) [57]. Cigarette smoke will first induce epithelial cell damage releasing alarmins and damage-associated molecular patterns (DAMPs) into the airways, further stimulating the innate and adaptive immune system resulting in neutrophilic inflammation and the symptoms of COPD [58]. It is important to take into account that several methods can be used to deliver CO in the form of cigarette smoke to the mice, namely nose-only exposure or whole-body exposure [59]. Serré et al. (2021) compared both methods and stated that after 14 weeks of cigarette smoke exposure, the mice receiving it via whole-body exposure had more inflammation in BAL fluid while nose-only exposure led to more bronchial epithelial damage, mucus production, and airspace enlargement [60]. In contrast, Kogel et al. (2021), showed also differences between nose-only exposure and whole-body exposure in $ApoE^{-/-}$ mice (murine model for atherosclerosis) which might be specific for this mouse strain, where the nose-only mice had more lung inflammation and molecular dysregulation of the respiratory system [61]. Other studies have found similar effects on the airways when exposed to cigarette smoke via a nose-only or via a whole-body system making it important to take into account when comparing studies [62,63]. Milad et al. (2021), recently showed that the recruited neutrophils together with IL-1α produced by epithelial cells can regulate the surfactant homeostasis present after exposure to cigarette smoke [64]. However, more research is needed to clearly investigate if neutrophilic inflammation is a cause for COPD or if neutrophils are just reacting to what happens in the airway environment. Next to the neutrophilic inflammation, airway remodeling is a feature of cigarette smoke-induced COPD [57]. As the complete underlying mechanisms of airway remodeling are not fully understood, murine COPD models are unraveling this. Recent evidence demonstrated that the IL-33/ST2 axis [65] and/or the AhR [66] are important for airway remodeling.

Next to its negative effects, several studies have observed that carbon monoxide can have a protective role in several lung diseases, such as acute lung injury [67,68], pulmonary interstitial inflammation [69], bronchopulmonary dysplasia [70], and bacterial infections [71,72]. In general, all these murine studies showed that carbon monoxide can alter the fibrotic processes and inflammatory processes leading to a better outcome and less fibrosis or inflammation [67–73].

For human exposure models, we also focused on studies of CO in the context of cigarette smoke and not on CO poisoning. Inhalation of cigarette smoke induces airway barrier dysfunction. Pretreatment of Calu-3 cells, an epithelial cell line, with cigarette smoke induced airway barrier dysfunction, measured by decreased transepithelial electrical resistance (TEER). In addition, cigarette smoke pretreatment induced suppressed expression of multiple tight and adherens junctions [74,75]. Besides epithelial barrier dysfunction, cigarette smoke exposure also induces oxidative stress, increased inflammatory mediators, and NLRP3 protein expression in bronchial and alveolar epithelial cell lines. Transient receptor potential protein (TRP) ion channels TRPA1 and TRPV1 are both suggested to mediate cigarette smoke-induced damage of epithelial cells via modulation of oxidative stress and inflammation [76].

4.3. Carbon Dioxide

Not much is written concerning carbon dioxide related to air pollution. Carbon dioxide is produced by the combustion of fossil fuels or forest fires [5,18]. One recent study explored the effect of carbon dioxide alone in mice and established that it leads to a range of respiratory impairments such as higher elastance in the lung and lower lung compliance [77]. This study also showed that during early life when the lungs are still growing and under development, they are most sensitive to carbon dioxide which might lead to alveolar destruction and other lung structures [77]. Combined with exposure to organic dust, low levels of carbon dioxide can alter immune responses leading to more airway inflammation and induction of pro-inflammatory cytokines [78,79]. Next to this, some studies have shown that hypercapnia (elevated levels of carbon dioxide in lung tissue and bloodstream) can have a negative effect on airway smooth muscle contraction [80,81]. Lastly, one study showed a protective effect of carbon dioxide during wound closure. Hypercapnia prevents wound closure at the site of both the large airways and the alveolar epithelium [82].

To our knowledge, there is limited recent literature on human exposure studies available on CO_2 in the context of air pollution.

4.4. Volatile Organic Compounds and Polycyclic Aromatic Hydrocarbons

Volatile organic compounds (VOCs) are gaseous compounds originating from the evaporation of carbon-containing sources such as building materials, cleaning agents, adhesives, combustion materials, et cetera [83,84]. A lot of different types/sources of VOCs exist [83]. The main sources of VOCs are natural sources (forest fires, vegetation, animal) as well as industrial and agricultural sources (road dust, soil) [83]. Several different compounds (such as wood VOCs, fuel-derived VOCs, meta-xylene, terpene, . . .) have been studied in murine models leading to contrasting results. Junge et al. (2021) studied VOCs originating from wood (in relation to asthma development) and observed that the VOCs had no effects, even in high concentrations and after long exposure, on inflammatory and asthma-promoting processes in mice [85]. In contrast, a recent study with a goal to investigate the effects of terpene on an allergic asthma model (OVA-induced asthma model), stated that VOCs reduced the production of IL-4 and IL-13 and allergic inflammation together with a reduction in the thickening of the bronchial wall suggesting that terpene has a protective effect in this murine model for allergic asthma [86]. On the other hand, negative effects of VOCs on the airways have also been reported. VOCs coming from electronic cigarettes, synthetic material, and household materials, induced lung oxidative stress, changes in the lung miRNA expression, neutrophilic infiltration, and airway hyperreactivity in the mice [87–91].

The understanding of the effects of VOCs on human airways is limited because of analytical difficulties in measuring real ambient air concentrations and in the evaluation of personal exposure. Therefore, reliable air dispersions models over a wide area, such as Europe or the United States, are needed, as used in this study by Im et al. (2018) [92]. Furthermore, there is a lack of knowledge on the mechanism of the different compounds in VOCs action. An exposure platform with cultured bronchial epithelial cells was developed to study exposure of VOCs for longer periods. Using genome-wide transcriptional analysis, Gostner et al. (2016) demonstrated that lipid biosynthesis and lung-associated functions were affected by lower exposure levels, while apoptosis was dominating in the higher exposure levels [93]. A recent meta-analysis demonstrated a medium-sized association between VOCs and pulmonary disease, including symptoms like wheezing and throat irritation [94]. Apparently, exposure to higher VOCs levels in human subjects in daily life is suggested to induce changes in airway inflammation, possibly increased T-helper (Th)2 inflammation [95]. However, VOCs are especially known as biomarkers that can guide precision medicine in respiratory diseases like asthma and COPD in humans. Exhaled breathing condensates also contain thousands of VOCs, which can reflect different disease

stages, suggesting a role as non-invasive as a biomarker for diagnosis, treatment monitoring, and exacerbation prediction [96,97].

Polycyclic aromatic hydrocarbons (PAH) are organic compounds with two or more fused aromatic benzene rings [98]. Several subtypes of PAH exist depending on the molecular weight. Low-molecular-weight PAH (two and three rings) are gaseous pollutants based in the atmosphere, high-molecular-weight PAH (five rings or more) such as benzo(α)pyrene, on the other hand, are mostly particle-bound and are harmful to human health [98]. Benzo(α)pyrene activates human epithelial cells via the AhR leading to mucus expression and oxidative stress (ROS production) in the airways [99]. Moreover, benzo(α)pyrene aggravates allergic inflammation in C57BL/6 mice leading to believe that PAH exposure has only negative effects on the airways [100–103]. Lastly, benzo(α)pyrene also alters the lipid metabolism in mice and more specifically the glycerophospholipid metabolism which is important in the progression of lung cancer and chronic airway inflammation [104,105].

4.5. Particulate Matter

Particulate matter (PM) can be subdivided into PM_{10}, $PM_{2.5}$, and UFP based on particle size [18]. Due to its known negative effects on the respiratory system, a lot of research articles have been published in the last years. PM will have its first interaction with the respiratory epithelial cells via toll-like receptor (TLR) 4 and/or TLR2 activating the NF-κB signaling pathway and NLRP3 inflammasome resulting in the induction of pro-inflammatory cytokines IL-1α, IL-1β, IL-6, CXCL8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) by innate immune cells such as macrophages, innate lymphoid cells and dendritic cells [18,106–109]. In this process, tight junctions are also essential due to their importance in maintaining an intact epithelial barrier. $PM_{2.5}$ and PM_{10} reduced occludin and zonula occludens 1 (ZO-1) expression in the nasal mucosa of mice leading to oxidative stress in the airways [110,111]. Claudins, another type of tight junctions, are also altered by PM (all particle sizes) exposure in mice. Claudin 7 expression was increased in asthmatic mice exposed to PM involving them in the maintenance of epithelial barrier integrity [112]. Secondly, $PM_{2.5}$ and PM_{10} will induce the production of ROS (oxidative stress) by leading to activation of the NLRP3 inflammasome [18,113]. Together these processes will activate the innate immune system with activation of alveolar macrophages (phagocytosis of particles), neutrophils, and dendritic cells [18,114–116]. The latter will then be the link with the adaptive immune system. Dendritic cells will then present processed antigens to T lymphocytes, activating these cells and turning them into Th1 or Th2 cells depending on the co-stimulatory molecules presented by dendritic cells [18]. Also, the newly described innate lymphoid cells (ILC) contribute to the inflammatory response induced by PM as reviewed by Estrella et al. (2019) [117]. While ILC2 will further increase the type 2 cytokine production leading to airway hyperreactivity, ILC1 together with the induction of IFN-γ will be inhibited making the mice more susceptible to infections and allergens [117]. Taken it all into account PM will lead to airway inflammation, epithelial damage, DNA damage, oxidative stress, mitochondrial damage, and lung fibrosis [18,106,115,118–120].

Murine models for allergic asthma models combined with exposure to particulate matter showed that $PM_{2.5}$ and PM_{10} exacerbated the allergic airway response by further inducing a disbalance between the Th1 and the Th2 response with increased inflammatory cell infiltration, airway hyperreactivity, allergen-induced IgE, an increase in IL-4, IL-5 and IL-13 and decrease in IFN-γ and T-bet [121–124].

Last but not least, the microbiome present in the lungs should also be mentioned. PM exposure, even subchronic, in mice leads to alterations both in the lung microbiome as well as in the gut microbiome (decreased microbiome richness) leading to lung and intestinal damage and systemic inflammation [125,126]. Secondly, microbiota dysbiosis leads to enhanced susceptibility to other bacterial infections in the lung, such as a pneumococcal infection [126]. Bacteria can also be used as a therapeutic tool, and this applies also to

PM-induced lung allergic inflammation. Lin et al. (2020), showed that *Lactobacillus paracasei* decreased the type 2 allergic response induced by OVA and PM, by decreasing the IgE levels, cytokines IL-4, IL-5, IL-13, and histamine [127]. This was confirmed by Nam et al. (2020), who also showed that probiotics can protect against PM-induced airway inflammation [128]. In contrast, Yang et al. (2021) demonstrated that the commensal microbiome can have a negative effect on the airways by promoting PM-induced acute neutrophilia in the lung via the IL-17 producing γδ T cells [114]. These T cells can be activated by TLR ligands from the microbiome leading to IL-17 production and an augmentation of the neutrophilic inflammation induced by PM [114].

Controlled PM exposure in human volunteers indeed degraded intracellular barrier proteins such as tight and adherens junctions, increasing the epithelial barrier permeability [129]. In human nasal epithelium, the exposure of $PM_{2.5}$ causes loss of barrier function through decreased expression of tight junction proteins such as claudin-1, occludin, and ZO-1 and increased release of proinflammatory cytokines like IL-8, tissue inhibitor of metallopeptidase 1 (TIMP), and thymic stromal lymphopoietin (TSLP) [130,131]. Serum CC16 levels are a common biomarker used for epithelial cell damage in humans. Acute exposure to $PM_{2.5}$ was significantly associated with serum CC16 levels [132]. PM exposure to human bronchial epithelial cells resulted in ROS-mediated activation of mitogen-activated protein kinase (MAPK) and downstream nuclear factor kappa light chain enhancer of activated B cells (NF-kB) signaling pathways [133]. In addition, inflammatory mediators like IL-1β, IL-6 and IL-8, matrix metallopeptidase 9 (MMP9), and cyclo-oxygenase 2 (COX-2) were increased in a dose-dependent manner. IL-8 expression in a human bronchial epithelial cell line was prevented by pretreatment with an endocytosis inhibitor, suggesting that exposure to $PM_{2.5}$ induced IL-8 expression through oxidative stress induction and endocytosis in airway cells [134]. Besides ROS generation also other mechanisms underlying PM-induced cell death has been investigated. The epidermal growth factor receptor (EGFR) is also found to mediate $PM_{2.5}$ mediated secretion of pro-inflammatory cytokines (IL-1β, IL-6, IL-8) in human bronchial epithelial cell lines [135]. $PM_{2.5}$ exposure was demonstrated to induce NOS2 expression and NO generation, leading to excessive autophagy [136]. So $PM_{2.5}$ is able to induce rapid autophagosome formation and subsequent cell death in human epithelial cells.

4.6. Diesel Exhaust Particles

As diesel exhaust particles (DEP) can be seen as part of particulate matter, a lot of mechanistic pathways after exposure to PM can be applied to DEP. DEP are composed of a central core of carbon and adsorbed inorganic compounds such as sulfate, nitrate, and metals [137]. It consists of fine particles (like $PM_{2.5}$) and ultrafine particles [137]. DEP exposure leads to a loss of epithelial barrier integrity, especially via a decrease in tricellulin, a tight junction both on mRNA and protein level, and specific compounds of DEP can lead to epithelial cell apoptosis [138,139]. The IL-33/ST2 axis has also been implicated in contributing to DEP-enhanced allergic airway responses. More specifically, combining DEP and allergens, IL-33 is increased in lung tissue leading to Th2 inflammation and airway hyperreactivity which is completely reversed in ST2-deficient mice [140–142]. DEP can activate the respiratory epithelium via TLR2 and TLR4 leading to increased levels of TNF-α, NF-κB signaling pathway and NLRP3 inflammasome resulting in macrophage and neutrophil infiltration in the airways [143,144]. Furthermore, TNF-α has been shown to have a regulatory role in the induction of DEP pulmonary inflammation with the help of the TNFR2 receptor [145]. Looking further downstream of the epithelium, the innate immune system gets activated by DEP exposure. Dendritic cells (DC), more specifically CD11b+ Ly6C- DC, are increased after DEP exposure in the airways further sustaining the inflammatory environment [146,147].

Secondly, DEP is also known for its induction of oxidative stress and DNA damage in the airways via ROS [147–152]. H_2O_2, a marker for oxidative stress, is increased in BAL fluid of mice exposed to DEP together with serum ceramide levels clearly indicating

that oxidative stress is induced after DEP exposure [147,149]. Furthermore, an important protective role for nuclear factor erythroid 2–related factor 2 (Nrf2), which regulates the expression of antioxidant proteins, is described [148,150]. Nrf2 can reduce the risk of oxidative stress via modulating the airway innate immune responses [150].

Thirdly, neurons and the neurogenic pathway are also involved in the induction of several effects of DEP. Transient receptor potential ankyrin 1 (TRPA1) on airway C fiber afferents is activated after DEP exposure in mice leading to neurogenic inflammation [153, 154]. This has also been studied with human lung tissue, where DEP is able to activate AhR, resulting in ROS production. These ROS activate TRPA1 on nociceptive airway c-fiber afferents, leading to respiratory symptoms like cough and bronchospasm [154]. Also, transient receptor potential vanilloid subtype 1 (TRPV1) has been indicated in playing a role in the induction of DEP-induced apoptosis of respiratory epithelial cells [155,156].

The controlled human exposure study of Wooding et al. (2019) described the respiratory effect from particle-filtered and whole diesel exhaust. They demonstrated that DEP and allergen co-exposure decreased forced expiratory volume (FEV_1) and increased peripheral white blood cell (WBC) counts, even after particle depletion [157,158]. In addition, different *in vitro* studies investigated the impact of DEP on bronchial human epithelial cells. Exposure to DEP significantly increases the secretion of inflammatory markers (CXCL8, TNFα) and oxidative stress markers (NFKB, HMOX1, GPx) [159]. Primary nasal epithelial cells from atopic subjects even produced significantly higher amounts of IL-8 and RANTES compared to control cells, indicating that allergic subjects will respond differently to DEP exposure [160]. In contrast, chronic exposure to low DEP concentrations did not induce increased levels of reactive oxygen species nor the expression of IL-6 and IL-8 [161]. Subsequently, also macrophages and their interaction with epithelial cells play an important role. DEP exposure increased the mRNA expression of typical M2 macrophages markers like IL-4, IL-10, IL-13, mannose receptor C (MRC) 1, and MRC2, promoting phenotypic alteration towards M2 subtypes [158].

4.7. Take Home Message from In Vivo Disease Models, Human and In Vitro Studies

To summarize this part, air pollution studies with all its underlying compounds demonstrated several negative effects on the airways. The airway epithelium is a key player in the response to air pollution. Epithelial cell damage, loss of epithelial integrity, induction of oxidative stress, DNA damage, NLRP3 inflammasome activation, neutrophilic inflammation, and the production of pro-inflammatory cytokines (such as IL-6, IL-1β, IL-1α, CXCL8) are the main processes that occur after exposure to air pollutants resulting in airway hyperresponsiveness (Figure 2). As already mentioned, a lot of research has been done in murine models and *in vitro* studies on air pollution and the airways. Therefore, it is important to take into account that a clear distinction between exposure time, the concentration of pollutant, and/or combination with allergens can induce different effects or no effect at all. This by itself can be seen as a limitation. Furthermore, many of these studies relied on the use of airway epithelial cell lines, or primary cultures of airway epithelial cells, which do not exactly represent the cellular diversity of the *in vivo* epithelium. There is thus considerable room to better understand the response of the airway epithelium to air pollution exposure and how this response may promote the poor respiratory outcomes associated with exposure. To translate these results to the real-world human condition we need to consider the combined effect of all different types of pollutants.

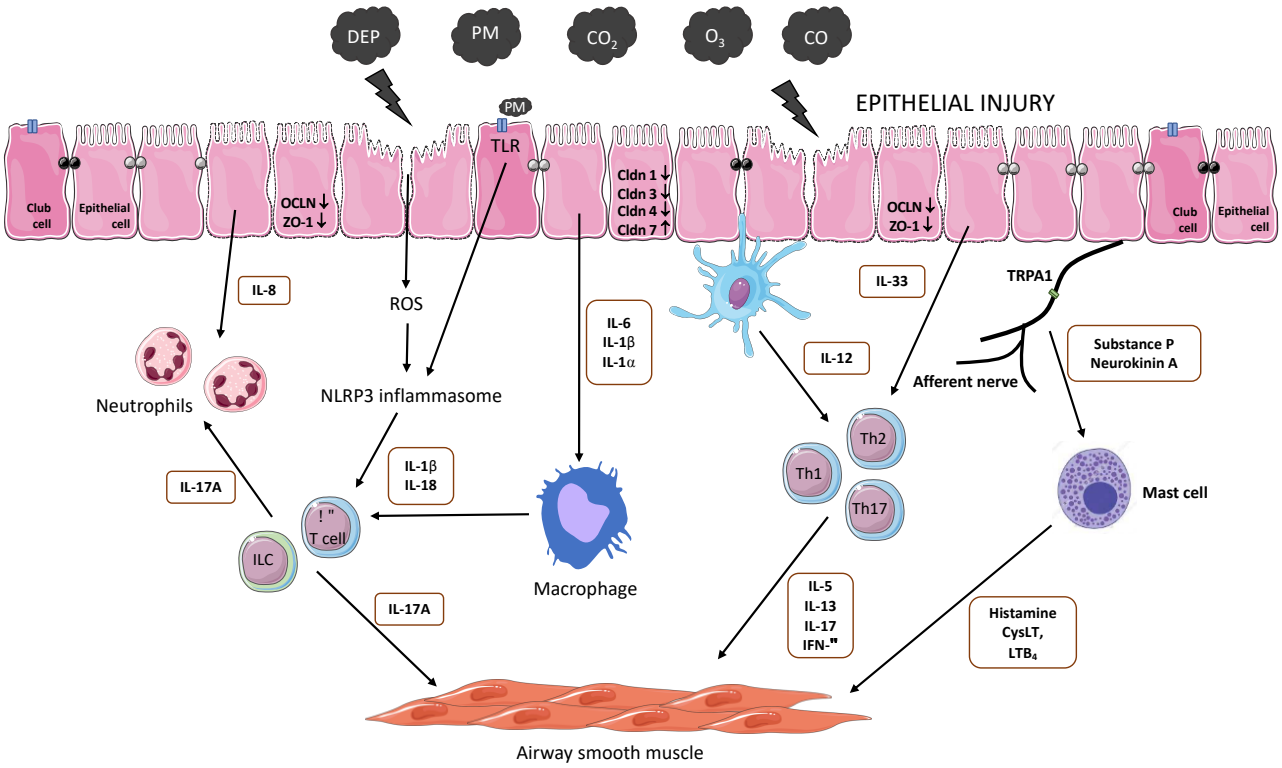

Figure 2. Overview of the inflammatory processes induced by air pollutants in the airways. Air pollutants such as diesel exhaust particles (DEP), particulate matter (PM), carbon dioxide (CO_2), ozone (O_3) and carbon monoxide (CO), will induce epithelial injury leading to a decrease in tight junctions occludin (OCLN), zonula occludens 1 (ZO-1) and claudin (Cldn) 1, 3 and 4. In addition, pro-inflammatory cytokines IL-6, IL-1β, IL-1α and IL-8 and alarmin IL-33 will be released after epithelial injury. These cytokines will activate neutrophils and macrophages in the airways which can lead to bronchoconstriction. PM can also activate the epithelial cells via binding to toll like receptor (TLR) 2 or 4 leading to the activation of the NF-κB signaling pathway and the NLRP3 inflammasome. Air pollutants will also generate reactive oxygen species (ROS) which will activate innate lymphoid cells (ILC) and γδ T cells via the NLRP3 inflammasome. Reactive oxygen species can also activate transient receptor potential cation channel A1 (TRPA1) inducing neurogenic inflammation and activating mast cells resulting to airway smooth muscle contraction. Dendritic cells will present antigens from the air pollutants to T-lymphocytes and depending on the costimulatory molecules, a different subset of T cells (Th1, Th2 or Th17 cells) will be activated further increasing the inflammatory mediators and bronchoconstriction.

5. Pollution and Airway Diseases: Cause or Consequence?

In the last decennia, a lot of research was performed investigating the effect of air pollution on both the healthy and diseased respiratory tract. In particular, exposure to air pollution is able to induce bronchoconstriction and has been associated with the development and exacerbation of several respiratory diseases including asthma and COPD. Patients with chronic obstructive diseases such as asthma and COPD are especially vulnerable to the harmful effects of air pollution. Furthermore, special interest exists in exposure during exercise because of the high ventilatory demands resulting in increased air pollutant exposure at the airway epithelium. To assess the human health impact of air pollution, methods are based on recent epidemiological, controlled human exposure, and *ex vivo* studies. The results described below will highlight the impact of air pollution on patients with asthma or COPD, or other respiratory diseases. The quantitative contribution of air pollution to these diseases is still not exactly known in humans. Quantitative disease development risk estimates could be directly used in applications, for example, to evaluate the air quality control strategies to minimize the exposure to indoor/outdoor pollutants and to improve disease burden. Furthermore, limited data exists of the effects of dual or

multiple exposures (e.g., tobacco smoking and other air pollutants or associations between outdoor and indoor air pollutants) on disease outcomes.

5.1. Air Pollution and Asthma

Asthma is a chronic inflammatory disease, which is characterized by airway hyperresponsiveness, remodeling, and reversible airway obstruction [162]. According to WHO, more than 339 million people suffer from asthma [162]. Asthma can be subdivided into several phenotypes, based on the type of inflammation, age of onset, and severity [163]. The strongest risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances that trigger the airways. In the past years, strong epidemiological evidence demonstrated that outdoor pollution does not only affect patients with pre-existing asthma but may also affect the onset of asthma [164]. Air pollution modulates various airway epithelial responses, initiating or contributing to pathological features of asthma.

UFP stimulation of human bronchial epithelial cells from patients with severe asthma but not from nonasthmatics, induced TSLP, CXCL8, and IL-33 release [165]. In addition to air pollution-associated Th2 response, evidence also supports that Th17 responses can be affected. IL-17A expression after high DEP exposure was higher in the epithelium of severe allergic asthma patients than after low exposure [166]. Similarly, cigarette smoking was related to IL-17A expression in patients with asthma [167]. Considering neurogenic inflammation, exposure to a high concentration of DEPs induces increased local levels of neuropeptides like substance P and calcitonin gene-related peptide (CGRP) in asthmatic subjects [168]. In addition, ozone exposure induces a greater number of genes in BAL macrophages, with increased release of inflammatory mediators, in asthmatic patients than in healthy controls [169]. Finally, ozone-induced epithelial permeability was more pronounced in bronchial epithelial cells of asthmatics compared to healthy nonatopic controls [170]. Together these results highlight that the airways of patients with asthma may be more vulnerable to the effects of air pollution.

Allergens and air pollution are two important risk factors for asthma development. DEP is suggested to act as an adjuvant to immune responses and augment allergic inflammation. Inhalation of DEP at environmentally relevant concentrations (300 μg $PM_{2.5}/m^3$) by atopic individuals enhances allergen-induced IL-5 mediated inflammation (eosinophils, IL-5, eosinophilic cationic protein) in BAL. This impact of combined exposure of allergens and DEP was even more pronounced in atopic subjects without normally functioning glutathione S-transferase theta 1 (GSTT1), which is a polymorphism in a gene associated with the metabolism of ROS [171]. Another co-exposure study with allergens and DEP demonstrated elevated $CD4^+$ Th cells, plasma cells ($CD138^+$ cells), and neutrophils (neutrophil elastase 2^+ cells) in the respiratory submucosa of atopic subjects after DEP exposure [172]. To better understand the underlying mechanism of co-exposure to aeroallergens and DEP, regulatory proteins of airway epithelium were investigated. Surfactant protein D (SP-D) levels, which is a soluble pattern recognition receptor, were increased after allergen exposure. This increase was damped by exposure to the whole DEP before the allergen challenge. This dampening effect was not present after exposure to particle-depleted DEP, suggesting that the PM fraction of DEP was responsible for the loss of SPD [173]. In addition, serum CC16 levels were increased after particle-depleted DEP exposure. Environmental epigenetic regulation, including DNA methylation, is recognized as an important mechanism underlying the effects of air pollution on the development of allergic asthma. Similarly, exposure to black carbon (BC) was associated with demethylation of asthma proinflammatory genes, like IL-4 promotor, in asthmatic children [174].

5.2. Air Pollution and COPD

COPD is characterized by progressive chronic inflammation and irreversible airflow limitation. A prevalence of 328 million cases of COPD worldwide has been reported [175]. Smoking is described as the greatest risk factor for the development of COPD, but also

other exposures contribute to the development and progression of the disease [176]. This response to toxic substances induces an impaired tissue repair and a remodeling process characterized by destruction and fibrosis of the small airways, and destruction of the lung parenchyma. Primary COPD epithelial cells demonstrated increased epithelial permeability and reduced levels of adhesive intracellular junctions compared to healthy controls [177]. The chronic inflammatory process further increases during acute exacerbations. Epidemiological and clinical studies reported that an increase in air pollution leads to increases in COPD prevalence, emergency room visits, and hospitalization [178,179]. Most studies are focusing on the association between air pollution and incidence and/or prevalence of COPD and few studies are focusing on the underlying mechanisms [180]. Meta-analyses report at best a suggestive causal role of association between air pollution and COPD, but most studies conclude that there is insufficient evidence to prove a causal relationship [181]. Hence, there is a need for more research on specific at-risk populations such as COPD patients, leading to the formulation of corresponding protective strategies. Current research focuses on oxidative stress, inflammation, and DNA damage.

In vitro studies with primary human bronchial epithelial cells from patients with COPD in relation to healthy control, subjects supported that both genetic and epigenetic events are important players in response to repeatedly $PM_{2.5}$ exposure. In particular, Leclerq et al. (2016) demonstrated that COPD-derived human primary epithelial cells were more sensitive to $PM_{2.5}$ exposure, assessed by decreased DNA methyltransferase activity, decreased telomere length, and modified telomerase activity [182,183].

Recently, mitochondria have been identified as a key player in COPD development. COPD-diseased bronchial epithelial cells were more sensitive to $PM_{2.5}$ exposure, resulting in cytosolic ROS overproduction, mitochondrial function decrease, and NF-kB rise [184]. Mitochondrial ROS will activate NLRP3 inflammasome, increasing cell death pathways leading to remodeling and fibrosis seen in COPD [185].

Ambient air pollution will lead to increased airway inflammation in COPD patients, measured by fractional exhaled nitric oxide (FeNO) levels for eosinophilic and FeH_2S for neutrophilic inflammation respectively [186]. PM exposure to human bronchial epithelial cells showed increased levels of the pro-inflammatory cytokines IL-6 and IL-8 [187,188].

5.3. Air Pollution, Exercise and Bronchial Obstructive Diseases

Regular exercise is beneficial, but it also increases exposure to air pollution. The high ventilatory needs during exercise induce an increase in total exposure to air pollution and deeper deposition of the particles [189,190]. Furthermore, exercise-induced respiratory symptoms are highly prevalent in athletes [191].

On the one hand, exercise has beneficial effects on pulmonary function during exposure to air pollution. Runners showed increased levels of IL-17A in nasal lavage after high PM exposure compared to baseline, demonstrating a different mucosal airway response against PM exposure compared to sedentary subjects [192,193]. The increase in IL-17A can avoid Th2 response, as observed in sedentary subjects. Moreover, exercise can maintain or enhance mucociliary clearance and may help to regulate inflammatory responses in the airways [194]. Regarding lung function, a protective effect of exercise to counterbalance the effect of air pollution was demonstrated in adults and children [195,196]. These results suggest that regular exercise improves the inflammatory status of the airways and lung function after PM exposure. These findings may be linked to altered regulatory T cell (Treg) activity. Physical activity in urban children is associated with lower FOXP3 promoter methylation, a possible indicator of more pronounced Treg function under conditions of high black carbon (BC) exposure [197]. This beneficial effect decreased in higher air pollution concentrations, suggesting a greater need to reduce air pollution exposure during physical activity [198]. Others report no association between air pollutant exposure and lung function after short exposure in small groups [199,200].

On the other hand, the harmful effects of exercise during exposure to air pollution are described in the literature. Especially competitive athletes are vulnerable to training

and competing in adverse environmental conditions, such as high pollution in ice rinks, chlorine derivates, or high vehicular traffic areas [201]. The systematic review of Qin et al. (2019) demonstrated that peak expiratory flow (PEF) decreased after exercise in a polluted region [202]. Moreover, increased risk to airway inflammation was demonstrated after exposure to air pollution during exercise [202]. A significant increase in CC16 and glutathione (GSH) levels was observed in the upper respiratory airways following an 8 km run during heat and O_3 exposure compared to normal conditions [203]. A decrease in lung function was described in cyclists after a ride with high UFP exposure [204].

The impact of air pollution exposure depends on the pollutant levels, species and duration, but also on the intensity of exercise and the studied population. In general, among healthy adult subjects, it is suggested that exercise is beneficial, even during exposure to air pollution [205]. Similarly, Marmett et al. (2020) hypothesized that exercise may cause beneficial effects regardless of the chosen place [206]. Nevertheless, susceptible populations, like the elderly or patients with asthma or COPD will experience the more negative impact of air pollution even with low levels of air pollution or at low-intensity exercise. Furthermore, special consideration needs to be taken for competitive athletes when training and competing in adverse environmental conditions.

Looking at other respiratory diseases such as COVID-19, similar effects of air pollution can be described. Air pollution can increase the susceptibility to COVID-19 and induce further the inflammatory immune response, oxidative stress, and damage to the respiratory epithelium that is already present in the airways of COVID-19 patients as reviewed by Zhao et al. (2021) [207].

6. Conclusions

Pollutant exposure time and particle size determine the inflammatory cascade and the seriousness of the damage in the airways. Its effect might be different in patients with airway diseases when compared to healthy subjects, but whether this is the cause or consequence of the disease is difficult to disentangle. Overall, we can conclude that air pollution leads to adverse effects in the airways of both healthy and diseased lungs such as induction of epithelial damage, production of reactive oxygen species, induction of neutrophilic inflammation, and airway hyperresponsiveness (Figure 2). Intense exercise is considered to be beneficial even when executed in polluted areas, however specific populations will be more vulnerable to higher pollution exposure rates, associated with intense exercise. Additional research is, therefore, necessary to answer the question of how air pollution will affect the human airways either acutely or chronically, especially in the context of obstructive airway diseases and how potential long-lasting damage can be prevented.

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References

1. GHO | by Category | Deaths—By Country. Available online: https://apps.who.int/gho/data/node.main.BODAMBIENTAIRDTHS?lang=en (accessed on 6 April 2021).
2. Ambient (Outdoor) Air Pollution. Available online: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health (accessed on 6 April 2021).
3. Lelieveld, J.; Pozzer, A.; Pöschl, U.; Fnais, M.; Haines, A.; Münzel, T. Loss of Life Expectancy from Air Pollution Compared to Other Risk Factors: A Worldwide Perspective. *Cardiovasc. Res.* **2020**, *116*, 1910–1917. [CrossRef]
4. Air Pollution. Available online: https://www.who.int/news-room/air-pollution (accessed on 29 April 2021).
5. Tiotiu, A.I.; Novakova, P.; Nedeva, D.; Chong-Neto, H.J.; Novakova, S.; Steiropoulos, P.; Kowal, K. Impact of Air Pollution on Asthma Outcomes. *Int. J. Environ. Res. Public Health* **2020**, *17*, 6212. [CrossRef] [PubMed]
6. SDG Indicator 11.6.2 Concentrations of Fine Particulate Matter (PM2.5). Available online: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/concentrations-of-fine-particulate-matter-(pm2-5) (accessed on 6 April 2021).
7. Zawar-Reza, P.; Spronken-Smith, R. Air Pollution Climatology. In *Encyclopedia of World Climatology*; Oliver, J.E., Ed.; Springer: Dordrecht, The Netherlands, 2005; pp. 21–32. ISBN 978-1-4020-3266-0.
8. WHO Regional Publications; World Health Organization, Regional Office for Europe (Eds.) *Glossary on Air Pollution*; Obtainable from WHO Publications Centre: Copenhagen, Denmark; Albany, NY, USA, 1980; ISBN 978-92-9020-109-0.
9. Manisalidis, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Health* **2020**, *8*. [CrossRef] [PubMed]
10. Nieder, R.; Benbi, D.K. Reactive Nitrogen Compounds and Their Influence on Human Health: An Overview. *Rev. Environ. Health* **2021**. [CrossRef]
11. Bhatia, V.; Elnagary, L.; Dakshinamurti, S. Tracing the Path of Inhaled Nitric Oxide: Biological Consequences of Protein Nitrosylation. *Pediatric Pulmonol.* **2021**, *56*, 525–538. [CrossRef]
12. Rouadi, P.W.; Idriss, S.A.; Naclerio, R.M.; Peden, D.B.; Ansotegui, I.J.; Canonica, G.W.; Gonzalez-Diaz, S.N.; Rosario Filho, N.A.; Ivancevich, J.C.; Hellings, P.W.; et al. Immunopathological Features of Air Pollution and Its Impact on Inflammatory Airway Diseases (IAD). *World Allergy Organ. J.* **2020**, *13*, 100467. [CrossRef] [PubMed]
13. Seinfeld, J.H.; Pandis, S.N. *Atmospheric Chemistry and Physics: From Air Pollution to Climate Change*, 3rd ed.; Wiley: Hoboken, NJ, USA, 2016; ISBN 978-1-118-94740-1.
14. Meyerholz, D.K.; Suarez, C.J.; Dintzis, S.M.; Frevert, C.W. 9—Respiratory System. In *Comparative Anatomy and Histology*, 2nd ed.; Treuting, P.M., Dintzis, S.M., Montine, K.S., Eds.; Academic Press: San Diego, CA, USA, 2018; pp. 147–162. ISBN 978-0-12-802900-8.
15. Gibson, P.G.; Simpson, J.L. The Overlap Syndrome of Asthma and COPD: What Are Its Features and How Important Is It? *Thorax* **2009**, *64*, 728–735. [CrossRef]
16. Labaki, W.W.; Han, M.K. Chronic Respiratory Diseases: A Global View. *Lancet Respir. Med.* **2020**, *8*, 531–533. [CrossRef]
17. Kodros, J.K.; Volckens, J.; Jathar, S.H.; Pierce, J.R. Ambient Particulate Matter Size Distributions Drive Regional and Global Variability in Particle Deposition in the Respiratory Tract. *GeoHealth* **2018**, *2*, 298–312. [CrossRef]
18. Glencross, D.A.; Ho, T.-R.; Camiña, N.; Hawrylowicz, C.M.; Pfeffer, P.E. Air Pollution and Its Effects on the Immune System. *Free Radic. Biol. Med.* **2020**, *151*, 56–68. [CrossRef]
19. Losacco, C.; Perillo, A. Particulate Matter Air Pollution and Respiratory Impact on Humans and Animals. *Environ. Sci. Pollut Res.* **2018**, *25*, 33901–33910. [CrossRef]
20. Lippmann, M.; Yeates, D.B.; Albert, R.E. Deposition, Retention, and Clearance of Inhaled Particles. *Br. J. Ind. Med.* **1980**, *37*, 337–362. [CrossRef]
21. Geiser, M.; Kreyling, W.G. Deposition and Biokinetics of Inhaled Nanoparticles. *Part Fibre Toxicol.* **2010**, *7*, 2. [CrossRef]
22. Cooper, D.M.; Loxham, M. Particulate Matter and the Airway Epithelium: The Special Case of the Underground? *Eur. Respir. Rev.* **2019**, *28*. [CrossRef] [PubMed]
23. Michaudel, C.; Fauconnier, L.; Julé, Y.; Ryffel, B. Functional and Morphological Differences of the Lung upon Acute and Chronic Ozone Exposure in Mice. *Sci. Rep.* **2018**, *8*, 10611. [CrossRef] [PubMed]
24. Sokolowska, M.; Quesniaux, V.F.J.; Akdis, C.A.; Chung, K.F.; Ryffel, B.; Togbe, D. Acute Respiratory Barrier Disruption by Ozone Exposure in Mice. *Front. Immunol.* **2019**, *10*. [CrossRef]
25. Liu, Y.; Pan, J.; Zhang, H.; Shi, C.; Li, G.; Peng, Z.; Ma, J.; Zhou, Y.; Zhang, L. Short-Term Exposure to Ambient Air Pollution and Asthma Mortality. *Am. J. Respir Crit. Care Med.* **2019**, *200*, 24–32. [CrossRef] [PubMed]
26. Kim, B.-G.; Lee, P.-H.; Lee, S.-H.; Park, C.-S.; Jang, A.-S. Impact of Ozone on Claudins and Tight Junctions in the Lungs. *Environ. Toxicol.* **2018**, *33*, 798–806. [CrossRef] [PubMed]
27. Roberts, R.A.; Laskin, D.L.; Smith, C.V.; Robertson, F.M.; Allen, E.M.G.; Doorn, J.A.; Slikker, W. Nitrative and Oxidative Stress in Toxicology and Disease. *Toxicol. Sci.* **2009**, *112*, 4–16. [CrossRef]
28. Michaudel, C.; Couturier-Maillard, A.; Chenuet, P.; Maillet, I.; Mura, C.; Couillin, I.; Gombault, A.; Quesniaux, V.F.; Huaux, F.; Ryffel, B. Inflammasome, IL-1 and Inflammation in Ozone-Induced Lung Injury. *Am. J. Clin. Exp. Immunol.* **2016**, *5*, 33–40.
29. Michaudel, C.; Maillet, I.; Fauconnier, L.; Quesniaux, V.; Chung, K.F.; Wiegman, C.; Peter, D.; Ryffel, B. Interleukin-1α Mediates Ozone-Induced Myeloid Differentiation Factor-88-Dependent Epithelial Tissue Injury and Inflammation. *Front. Immunol.* **2018**, *9*. [CrossRef]

30. Xu, M.; Wang, L.; Wang, M.; Wang, H.; Zhang, H.; Chen, Y.; Wang, X.; Gong, J.; Zhang, J.; Adcock, I.M.; et al. Mitochondrial ROS and NLRP3 Inflammasome in Acute Ozone-Induced Murine Model of Airway Inflammation and Bronchial Hyperresponsiveness. *Free Radic. Res.* **2019**, *53*, 780–790. [CrossRef]
31. Che, L.; Jin, Y.; Zhang, C.; Lai, T.; Zhou, H.; Xia, L.; Tian, B.; Zhao, Y.; Liu, J.; Wu, Y.; et al. Ozone-Induced IL-17A and Neutrophilic Airway Inflammation Is Orchestrated by the Caspase-1-IL-1 Cascade. *Sci. Rep.* **2016**, *6*, 18680. [CrossRef]
32. Enweasor, C.; Flayer, C.H.; Haczku, A. Ozone-Induced Oxidative Stress, Neutrophilic Airway Inflammation, and Glucocorticoid Resistance in Asthma. *Front. Immunol.* **2021**, *12*. [CrossRef] [PubMed]
33. Li, F.; Xu, M.; Wang, M.; Wang, L.; Wang, H.; Zhang, H.; Chen, Y.; Gong, J.; Zhang, J.; Adcock, I.M.; et al. Roles of Mitochondrial ROS and NLRP3 Inflammasome in Multiple Ozone-Induced Lung Inflammation and Emphysema. *Respir. Res.* **2018**, *19*, 230. [CrossRef] [PubMed]
34. Michaudel, C.; Bataille, F.; Maillet, I.; Fauconnier, L.; Colas, C.; Sokol, H.; Straube, M.; Couturier-Maillard, A.; Dumoutier, L.; van Snick, J.; et al. Ozone-Induced Aryl Hydrocarbon Receptor Activation Controls Lung Inflammation via Interleukin-22 Modulation. *Front. Immunol.* **2020**, *11*. [CrossRef] [PubMed]
35. Peters, U.; Dixon, A.E. The Effect of Obesity on Lung Function. *Expert Rev. Respir. Med.* **2018**, *12*, 755–767. [CrossRef]
36. Clougherty, J.E. A Growing Role for Gender Analysis in Air Pollution Epidemiology. *Environ. Health Perspect* **2010**, *118*, 167–176. [CrossRef] [PubMed]
37. Shore, S.A. Mechanistic Basis for Obesity-Related Increases in Ozone-Induced Airway Hyperresponsiveness in Mice. *Ann. Ats* **2017**, *14*, S357–S362. [CrossRef]
38. Mathews, J.A.; Krishnamoorthy, N.; Kasahara, D.I.; Hutchinson, J.; Cho, Y.; Brand, J.D.; Williams, A.S.; Wurmbrand, A.P.; Ribeiro, L.; Cuttitta, F.; et al. Augmented Responses to Ozone in Obese Mice Require IL-17A and Gastrin-Releasing Peptide. *Am. J. Respir. Cell Mol. Biol.* **2017**, *58*, 341–351. [CrossRef]
39. Osgood, R.S.; Kasahara, D.I.; Tashiro, H.; Cho, Y.; Shore, S.A. Androgens Augment Pulmonary Responses to Ozone in Mice. *Physiol. Rep.* **2019**, *7*, e14214. [CrossRef] [PubMed]
40. Fuentes, N.; Nicoleau, M.; Cabello, N.; Montes, D.; Zomorodi, N.; Chroneos, Z.C.; Silveyra, P. 17β-Estradiol Affects Lung Function and Inflammation Following Ozone Exposure in a Sex-Specific Manner. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2019**, *317*, L702–L716. [CrossRef] [PubMed]
41. Fuentes, N.; Cabello, N.; Nicoleau, M.; Chroneos, Z.C.; Silveyra, P. Modulation of the Lung Inflammatory Response to Ozone by the Estrous Cycle. *Physiol. Rep.* **2019**, *7*, e14026. [CrossRef] [PubMed]
42. Birukova, A.; Cyphert-Daly, J.; Cumming, R.I.; Yu, Y.-R.; Gowdy, K.M.; Que, L.G.; Tighe, R.M. Sex Modifies Acute Ozone-Mediated Airway Physiologic Responses. *Toxicol. Sci.* **2019**, *169*, 499–510. [CrossRef]
43. Cho, Y.; Abu-Ali, G.; Tashiro, H.; Brown, T.A.; Osgood, R.S.; Kasahara, D.I.; Huttenhower, C.; Shore, S.A. Sex Differences in Pulmonary Responses to Ozone in Mice. Role of the Microbiome. *Am. J. Respir. Cell Mol. Biol.* **2019**, *60*, 198–208. [CrossRef] [PubMed]
44. Last, J.A.; Ward, R.; Temple, L.; Kenyon, N.J. Ovalbumin-Induced Airway Inflammation and Fibrosis in Mice Also Exposed to Ozone. *Inhal. Toxicol.* **2004**, *16*, 33–43. [CrossRef]
45. Liang, L.; Li, F.; Bao, A.; Zhang, M.; Chung, K.F.; Zhou, X. Activation of P38 Mitogen-Activated Protein Kinase in Ovalbumin and Ozone-Induced Mouse Model of Asthma. *Respirology* **2013**, *18* (Suppl. 3), 20–29. [CrossRef]
46. Larsen, S.T.; Matsubara, S.; McConville, G.; Poulsen, S.S.; Gelfand, E.W. Ozone Increases Airway Hyperreactivity and Mucus Hyperproduction in Mice Previously Exposed to Allergen. *J. Toxicol. Environ. Health A* **2010**, *73*, 738–747. [CrossRef]
47. Bao, W.; Zhang, Y.; Zhang, M.; Bao, A.; Fei, X.; Zhang, X.; Zhou, X. Effects of Ozone Repeated Short Exposures on the Airway/Lung Inflammation, Airway Hyperresponsiveness and Mucus Production in a Mouse Model of Ovalbumin-Induced Asthma. *Biomed. Pharmacother.* **2018**, *101*, 293–303. [CrossRef]
48. Hansen, J.S.; Nørgaard, A.W.; Koponen, I.K.; Sørli, J.B.; Paidi, M.D.; Hansen, S.W.K.; Clausen, P.A.; Nielsen, G.D.; Wolkoff, P.; Larsen, S.T. Limonene and Its Ozone-Initiated Reaction Products Attenuate Allergic Lung Inflammation in Mice. *J. Immunotoxicol.* **2016**, *13*, 793–803. [CrossRef]
49. Bromberg, P.A. Mechanisms of the Acute Effects of Inhaled Ozone in Humans. *Biochim. Biophys. Acta* **2016**, *1860*, 2771–2781. [CrossRef]
50. Cheng, W.; Duncan, K.E.; Ghio, A.J.; Ward-Caviness, C.; Karoly, E.D.; Diaz-Sanchez, D.; Conolly, R.B.; Devlin, R.B. Changes in Metabolites Present in Lung-Lining Fluid Following Exposure of Humans to Ozone. *Toxicol. Sci.* **2018**, *163*, 430–439. [CrossRef] [PubMed]
51. Arjomandi, M.; Balmes, J.R.; Frampton, M.W.; Bromberg, P.; Rich, D.Q.; Stark, P.; Alexis, N.E.; Costantini, M.; Hollenbeck-Pringle, D.; Dagincourt, N.; et al. Respiratory Responses to Ozone Exposure. MOSES (The Multicenter Ozone Study in Older Subjects). *Am. J. Respir. Crit. Care Med.* **2018**, *197*, 1319–1327. [CrossRef]
52. Mirowsky, J.E.; Dailey, L.A.; Devlin, R.B. Differential Expression of Pro-Inflammatory and Oxidative Stress Mediators Induced by Nitrogen Dioxide and Ozone in Primary Human Bronchial Epithelial Cells. *Inhal. Toxicol.* **2016**, *28*, 374–382. [CrossRef] [PubMed]
53. Chen, Q.-Z.; Zhou, Y.-B.; Zhou, L.-F.; Fu, Z.-D.; Wu, Y.-S.; Chen, Y.; Li, S.-N.; Huang, J.-R.; Li, J.-H. TRPC6 Modulates Adhesion of Neutrophils to Airway Epithelial Cells via NF-KB Activation and ICAM-1 Expression with Ozone Exposure. *Exp. Cell Res.* **2019**, *377*, 56–66. [CrossRef] [PubMed]

54. Bennett, W.D.; Ivins, S.; Alexis, N.E.; Wu, J.; Bromberg, P.A.; Brar, S.S.; Travlos, G.; London, S.J. Effect of Obesity on Acute Ozone-Induced Changes in Airway Function, Reactivity, and Inflammation in Adult Females. *PLoS ONE* **2016**, *11*, e0160030. [CrossRef]
55. Bleecker, M.L. Chapter 12—Carbon monoxide intoxication. In *Handbook of Clinical Neurology*; Lotti, M., Bleecker, M.L., Eds.; Occupational Neurology; Elsevier: Amsterdam, The Netherlands, 2015; Volume 131, pp. 191–203.
56. Hampson, N.B. Carboxyhemoglobin: A Primer for Clinicians. *Undersea Hyperb. Med.* **2018**, *45*, 165–171. [CrossRef]
57. Decramer, M.; Janssens, W.; Miravitlles, M. Chronic Obstructive Pulmonary Disease. *Lancet* **2012**, *379*, 1341–1351. [CrossRef]
58. Craig, J.M.; Scott, A.L.; Mitzner, W. Immune-Mediated Inflammation in the Pathogenesis of Emphysema: Insights from Mouse Models. *Cell Tissue Res.* **2017**, *367*, 591–605. [CrossRef]
59. Laucho-Contreras, M.E.; Taylor, K.L.; Mahadeva, R.; Boukedes, S.S.; Owen, C.A. Automated Measurement of Pulmonary Emphysema and Small Airway Remodeling in Cigarette Smoke-Exposed Mice. *JoVE* **2015**, e52236. [CrossRef] [PubMed]
60. Serré, J.; Tanjeko, A.T.; Mathyssen, C.; Vanherwegen, A.-S.; Heigl, T.; Janssen, R.; Verbeken, E.; Maes, K.; Vanaudenaerde, B.; Janssens, W.; et al. Enhanced Lung Inflammatory Response in Whole-Body Compared to Nose-Only Cigarette Smoke-Exposed Mice. *Respir. Res.* **2021**, *22*, 86. [CrossRef]
61. Kogel, U.; Wong, E.T.; Szostak, J.; Tan, W.T.; Lucci, F.; Leroy, P.; Titz, B.; Xiang, Y.; Low, T.; Wong, S.K.; et al. Impact of Whole-Body versus Nose-Only Inhalation Exposure Systems on Systemic, Respiratory, and Cardiovascular Endpoints in a 2-Month Cigarette Smoke Exposure Study in the ApoE−/− Mouse Model. *J. Appl. Toxicol.* **2021**. [CrossRef] [PubMed]
62. Shu, J.; Li, D.; Ouyang, H.; Huang, J.; Long, Z.; Liang, Z.; Chen, Y.; Chen, Y.; Zheng, Q.; Kuang, M.; et al. Comparison and Evaluation of Two Different Methods to Establish the Cigarette Smoke Exposure Mouse Model of COPD. *Sci. Rep.* **2017**, *7*, 15454. [CrossRef] [PubMed]
63. Mauderly, J.L.; Bechtold, W.E.; Bond, J.A.; Brooks, A.L.; Chen, B.T.; Cuddihy, R.G.; Harkema, J.R.; Henderson, R.F.; Johnson, N.F.; Rithidech, K.; et al. Comparison of 3 Methods of Exposing Rats to Cigarette Smoke. *Exp. Pathol.* **1989**, *37*, 194–197. [CrossRef]
64. Milad, N.; Pineault, M.; Lechasseur, A.; Routhier, J.; Beaulieu, M.-J.; Aubin, S.; Morissette, M.C. Neutrophils and IL-1α Regulate Surfactant Homeostasis during Cigarette Smoking. *J. Immunol.* **2021**, *206*, 1923–1931. [CrossRef] [PubMed]
65. Huang, Q.; Li, C.D.; Yang, Y.R.; Qin, X.F.; Wang, J.J.; Zhang, X.; Du, X.N.; Yang, X.; Wang, Y.; Li, L.; et al. Role of the IL-33/ST2 Axis in Cigarette Smoke-Induced Airways Remodelling in Chronic Obstructive Pulmonary Disease. *Thorax* **2021**. [CrossRef]
66. Guerrina, N.; Traboulsi, H.; Rico de Souza, A.; Bossé, Y.; Thatcher, T.H.; Robichaud, A.; Ding, J.; Li, P.Z.; Simon, L.; Pareek, S.; et al. Aryl Hydrocarbon Receptor Deficiency Causes the Development of Chronic Obstructive Pulmonary Disease through the Integration of Multiple Pathogenic Mechanisms. *FASEB J.* **2021**, *35*, e21376. [CrossRef]
67. Jiang, L.; Fei, D.; Gong, R.; Yang, W.; Yu, W.; Pan, S.; Zhao, M.; Zhao, M. CORM-2 Inhibits TXNIP/NLRP3 Inflammasome Pathway in LPS-Induced Acute Lung Injury. *Inflamm. Res.* **2016**, *65*, 905–915. [CrossRef]
68. Wang, X.; Qin, W.; Song, M.; Zhang, Y.; Sun, B. Exogenous Carbon Monoxide Inhibits Neutrophil Infiltration in LPS-Induced Sepsis by Interfering with FPR1 via P38 MAPK but Not GRK2. *Oncotarget* **2016**, *7*, 34250–34265. [CrossRef]
69. Huang, K.-C.; Li, J.-C.; Wang, S.-M.; Cheng, C.-H.; Yeh, C.-H.; Lin, L.-S.; Chiu, H.-Y.; Chang, C.-Y.; Chuu, J.-J. The Effects of Carbon Monoxide Releasing Molecules on Paraquat-Induced Pulmonary Interstitial Inflammation and Fibrosis. *Toxicology* **2021**, *456*, 152750. [CrossRef]
70. Lin, H.; Wang, X. The Effects of Gasotransmitters on Bronchopulmonary Dysplasia. *Eur. J. Pharmacol.* **2020**, *873*, 172983. [CrossRef] [PubMed]
71. Lee, C.-W.; Wu, C.-H.; Chiang, Y.-C.; Chen, Y.-L.; Chang, K.-T.; Chuang, C.-C.; Lee, I.-T. Carbon Monoxide Releasing Molecule-2 Attenuates Pseudomonas Aeruginosa-Induced ROS-Dependent ICAM-1 Expression in Human Pulmonary Alveolar Epithelial Cells. *Redox Biol.* **2018**, *18*, 93–103. [CrossRef] [PubMed]
72. Tsoyi, K.; Hall, S.R.R.; Dalli, J.; Colas, R.A.; Ghanta, S.; Ith, B.; Coronata, A.; Fredenburgh, L.E.; Baron, R.M.; Choi, A.M.K.; et al. Carbon Monoxide Improves Efficacy of Mesenchymal Stromal Cells During Sepsis by Production of Specialized Proresolving Lipid Mediators. *Crit. Care Med.* **2016**, *44*, e1236–e1245. [CrossRef] [PubMed]
73. Lee, C.-W.; Chi, M.-C.; Hsu, L.-F.; Yang, C.-M.; Hsu, T.-H.; Chuang, C.-C.; Lin, W.-N.; Chu, P.-M.; Lee, I.-T. Carbon Monoxide Releasing Molecule-2 Protects against Particulate Matter-Induced Lung Inflammation by Inhibiting TLR2 and 4/ROS/NLRP3 Inflammasome Activation. *Mol. Immunol.* **2019**, *112*, 163–174. [CrossRef] [PubMed]
74. Zeglinski, M.R.; Turner, C.T.; Zeng, R.; Schwartz, C.; Santacruz, S.; Pawluk, M.A.; Zhao, H.; Chan, A.W.H.; Carlsten, C.; Granville, D.J. Soluble Wood Smoke Extract Promotes Barrier Dysfunction in Alveolar Epithelial Cells through a MAPK Signaling Pathway. *Sci. Rep.* **2019**, *9*, 10027. [CrossRef]
75. Tatsuta, M.; Kan-O, K.; Ishii, Y.; Yamamoto, N.; Ogawa, T.; Fukuyama, S.; Ogawa, A.; Fujita, A.; Nakanishi, Y.; Matsumoto, K. Effects of Cigarette Smoke on Barrier Function and Tight Junction Proteins in the Bronchial Epithelium: Protective Role of Cathelicidin LL-37. *Respir. Res.* **2019**, *20*, 251. [CrossRef]
76. Wang, M.; Zhang, Y.; Xu, M.; Zhang, H.; Chen, Y.; Chung, K.F.; Adcock, I.M.; Li, F. Roles of TRPA1 and TRPV1 in Cigarette Smoke -Induced Airway Epithelial Cell Injury Model. *Free Radic. Biol. Med.* **2019**, *134*, 229–238. [CrossRef]
77. Larcombe, A.N.; Papini, M.G.; Chivers, E.K.; Berry, L.J.; Lucas, R.M.; Wyrwoll, C.S. Mouse Lung Structure and Function after Long-Term Exposure to an Atmospheric Carbon Dioxide Level Predicted by Climate Change Modeling. *Environ. Health Perspect* **2021**, *129*, 17001. [CrossRef]

78. Schneberger, D.; Pandher, U.; Thompson, B.; Kirychuk, S. Effects of Elevated CO2 Levels on Lung Immune Response to Organic Dust and Lipopolysaccharide. *Respir. Res.* **2021**, *22*, 104. [CrossRef]
79. Schneberger, D.; DeVasure, J.M.; Bailey, K.L.; Romberger, D.J.; Wyatt, T.A. Effect of Low-Level CO2 on Innate Inflammatory Protein Response to Organic Dust from Swine Confinement Barns. *J. Occup Med. Toxicol.* **2017**, *12*, 9. [CrossRef]
80. Shigemura, M.; Lecuona, E.; Angulo, M.; Dada, L.A.; Edwards, M.B.; Welch, L.C.; Casalino-Matsuda, S.M.; Sporn, P.H.S.; Vadász, I.; Helenius, I.T.; et al. Elevated CO_2 Regulates the Wnt Signaling Pathway in Mammals, Drosophila Melanogaster and Caenorhabditis Elegans. *Sci. Rep.* **2019**, *9*, 18251. [CrossRef] [PubMed]
81. Shigemura, M.; Sznajder, J.I. Elevated CO_2 Modulates Airway Contractility. *Interface Focus* **2021**, *11*, 20200021. [CrossRef]
82. Bharat, A.; Angulo, M.; Sun, H.; Akbarpour, M.; Alberro, A.; Cheng, Y.; Shigemura, M.; Berdnikovs, S.; Welch, L.C.; Kanter, J.A.; et al. High CO2 Levels Impair Lung Wound Healing. *Am. J. Respir. Cell Mol. Biol.* **2020**, *63*, 244–254. [CrossRef]
83. Bălă, G.-P.; Râjnoveanu, R.-M.; Tudorache, E.; Motișan, R.; Oancea, C. Air Pollution Exposure—The (in)Visible Risk Factor for Respiratory Diseases. *Environ. Sci. Pollut Res.* **2021**. [CrossRef]
84. Nurmatov, U.B.; Tagiyeva, N.; Semple, S.; Devereux, G.; Sheikh, A. Volatile Organic Compounds and Risk of Asthma and Allergy: A Systematic Review. *Eur. Respir. Rev.* **2015**, *24*, 92–101. [CrossRef]
85. Junge, K.M.; Buchenauer, L.; Elter, E.; Butter, K.; Kohajda, T.; Herberth, G.; Röder, S.; Borte, M.; Kiess, W.; von Bergen, M.; et al. Wood Emissions and Asthma Development: Results from an Experimental Mouse Model and a Prospective Cohort Study. *Environ. Int.* **2021**, *151*, 106449. [CrossRef] [PubMed]
86. Ahn, C.; Jang, Y.-J.; Kim, J.-W.; Park, M.-J.; Yoo, Y.-M.; Jeung, E.-B. Anti-Asthmatic Effects of Volatile Organic Compounds from Chamaecyparis Obtusa, Pinus Densiflora, Pinus Koraiensis, or Larix Kaempferi Wood Panels. *J. Physiol. Pharm.* **2018**, *69*. [CrossRef]
87. Ma, T.; Wang, X.; Li, L.; Sun, B.; Zhu, Y.; Xia, T. Electronic Cigarette Aerosols Induce Oxidative Stress-Dependent Cell Death and NF-KB Mediated Acute Lung Inflammation in Mice. *Arch. Toxicol.* **2021**, *95*, 195–205. [CrossRef] [PubMed]
88. Mandler, W.K.; Qi, C.; Orandle, M.S.; Sarkisian, K.; Mercer, R.R.; Stefaniak, A.B.; Knepp, A.K.; Bowers, L.N.; Battelli, L.A.; Shaffer, J.; et al. Mouse Pulmonary Response to Dust from Sawing Corian®, a Solid-Surface Composite Material. *J. Toxicol. Environ. Health A* **2019**, *82*, 645–663. [CrossRef] [PubMed]
89. Hong, S.-G.; Hwang, Y.-H.; Mun, S.-K.; Kim, S.-J.; Jang, H.-Y.; Kim, H.; Paik, M.-J.; Yee, S.-T. Role of Th2 Cytokines on the Onset of Asthma Induced by Meta-Xylene in Mice. *Environ. Toxicol.* **2019**, *34*, 1121–1128. [CrossRef]
90. Wang, F.; Li, C.; Liu, W.; Jin, Y.; Guo, L. Effects of Subchronic Exposure to Low-Dose Volatile Organic Compounds on Lung Inflammation in Mice. *Environ. Toxicol.* **2014**, *29*, 1089–1097. [CrossRef]
91. Wang, F.; Li, C.; Liu, W.; Jin, Y. Oxidative Damage and Genotoxic Effect in Mice Caused by Sub-Chronic Exposure to Low-Dose Volatile Organic Compounds. *Inhal. Toxicol.* **2013**, *25*, 235–242. [CrossRef] [PubMed]
92. Im, U.; Brandt, J.; Geels, C.; Hansen, K.M.; Christensen, J.H.; Andersen, M.S.; Solazzo, E.; Kioutsioukis, I.; Alyuz, U.; Balzarini, A.; et al. Assessment and Economic Valuation of Air Pollution Impacts on Human Health over Europe and the United States as Calculated by a Multi-Model Ensemble in the Framework of AQMEII3. *Atmos. Chem. Phys.* **2018**, *18*, 5967–5989. [CrossRef]
93. Gostner, J.M.; Zeisler, J.; Alam, M.T.; Gruber, P.; Fuchs, D.; Becker, K.; Neubert, K.; Kleinhappl, M.; Martini, S.; Überall, F. Cellular Reactions to Long-Term Volatile Organic Compound (VOC) Exposures. *Sci. Rep.* **2016**, *6*, 37842. [CrossRef] [PubMed]
94. Alford, K.L.; Kumar, N. Pulmonary Health Effects of Indoor Volatile Organic Compounds-A Meta-Analysis. *Int. J. Environ. Res. Public Health* **2021**, *18*, 1578. [CrossRef] [PubMed]
95. Kwon, J.-W.; Park, H.-W.; Kim, W.J.; Kim, M.-G.; Lee, S.-J. Exposure to Volatile Organic Compounds and Airway Inflammation. *Environ. Health* **2018**, *17*, 65. [CrossRef]
96. Azim, A.; Barber, C.; Dennison, P.; Riley, J.; Howarth, P. Exhaled Volatile Organic Compounds in Adult Asthma: A Systematic Review. *Eur. Respir. J.* **2019**, *54*. [CrossRef]
97. Neerincx, A.H.; Vijverberg, S.J.H.; Bos, L.D.J.; Brinkman, P.; van der Schee, M.P.; de Vries, R.; Sterk, P.J.; der Zee, A.-H.M. Breathomics from Exhaled Volatile Organic Compounds in Pediatric Asthma. *Pediatric. Pulmonol.* **2017**, *52*, 1616–1627. [CrossRef]
98. Choi, H.; Harrison, R.; Komulainen, H.; Saborit, J.M.D. *Polycyclic Aromatic Hydrocarbons*; World Health Organization: Geneva, Switzerland, 2010.
99. Sun, Y.; Shi, Z.; Lin, Y.; Zhang, M.; Liu, J.; Zhu, L.; Chen, Q.; Bi, J.; Li, S.; Ni, Z.; et al. Benzo(a)Pyrene Induces MUC5AC Expression through the AhR/Mitochondrial ROS/ERK Pathway in Airway Epithelial Cells. *Ecotoxicol. Environ. Saf.* **2021**, *210*, 111857. [CrossRef]
100. Yanagisawa, R.; Koike, E.; Win-Shwe, T.-T.; Ichinose, T.; Takano, H. Effects of Lactational Exposure to Low-Dose BaP on Allergic and Non-Allergic Immune Responses in Mice Offspring. *J. Immunotoxicol.* **2018**, *15*, 31–40. [CrossRef]
101. Yanagisawa, R.; Koike, E.; Win-Shwe, T.-T.; Ichinose, T.; Takano, H. Low-Dose Benzo[a]Pyrene Aggravates Allergic Airway Inflammation in Mice. *J. Appl. Toxicol.* **2016**, *36*, 1496–1504. [CrossRef]
102. Wang, E.; Liu, X.; Tu, W.; Do, D.C.; Yu, H.; Yang, L.; Zhou, Y.; Xu, D.; Huang, S.-K.; Yang, P.; et al. Benzo(a)Pyrene Facilitates Dermatophagoides Group 1 (Der f 1)-Induced Epithelial Cytokine Release through Aryl Hydrocarbon Receptor in Asthma. *Allergy* **2019**, *74*, 1675–1690. [CrossRef] [PubMed]
103. Chowdhury, P.H.; Kitamura, G.; Honda, A.; Sawahara, T.; Hayashi, T.; Fukushima, W.; Kudo, H.; Ito, S.; Yoshida, S.; Ichinose, T.; et al. Synergistic Effect of Carbon Nuclei and Polyaromatic Hydrocarbons on Respiratory and Immune Responses. *Environ. Toxicol.* **2017**, *32*, 2172–2181. [CrossRef]

104. Gdula-Argasińska, J.; Czepiel, J.; Totoń-Żurańska, J.; Wołkow, P.; Librowski, T.; Czapkiewicz, A.; Perucki, W.; Woźniakiewicz, M.; Woźniakiewicz, A. N-3 Fatty Acids Regulate the Inflammatory-State Related Genes in the Lung Epithelial Cells Exposed to Polycyclic Aromatic Hydrocarbons. *Pharm. Rep.* **2016**, *68*, 319–328. [CrossRef]
105. Li, F.; Xiang, B.; Jin, Y.; Li, C.; Li, J.; Ren, S.; Huang, H.; Luo, Q. Dysregulation of Lipid Metabolism Induced by Airway Exposure to Polycyclic Aromatic Hydrocarbons in C57BL/6 Mice. *Environ. Pollut.* **2019**, *245*, 986–993. [CrossRef] [PubMed]
106. Oh, S.-Y.; Kim, Y.-H.; Kang, M.-K.; Lee, E.-J.; Kim, D.-Y.; Oh, H.; Kim, S.-I.; Na, W.; Kang, I.-J.; Kang, Y.-H. Aesculetin Inhibits Airway Thickening and Mucus Overproduction Induced by Urban Particulate Matter through Blocking Inflammation and Oxidative Stress Involving TLR4 and EGFR. *Antioxid* **2021**, *10*, 494. [CrossRef]
107. Li, P.; Wang, J.; Guo, F.; Zheng, B.; Zhang, X. A Novel Inhibitory Role of MicroRNA-224 in Particulate Matter 2.5-Induced Asthmatic Mice by Inhibiting TLR2. *J. Cell Mol. Med.* **2020**, *24*, 3040–3052. [CrossRef] [PubMed]
108. Jia, H.; Liu, Y.; Guo, D.; He, W.; Zhao, L.; Xia, S. PM2.5-Induced Pulmonary Inflammation via Activating of the NLRP3/Caspase-1 Signaling Pathway. *Environ. Toxicol.* **2021**, *36*, 298–307. [CrossRef]
109. Dai, M.-Y.; Chen, F.-F.; Wang, Y.; Wang, M.-Z.; Lv, Y.-X.; Liu, R.-Y. Particulate Matters Induce Acute Exacerbation of Allergic Airway Inflammation via the TLR2/NF-KB/NLRP3 Signaling Pathway. *Toxicol. Lett.* **2020**, *321*, 146–154. [CrossRef]
110. Park, S.K.; Yeon, S.H.; Choi, M.-R.; Choi, S.H.; Lee, S.B.; Rha, K.; Kim, Y.M. Urban Particulate Matters May Affect Endoplasmic Reticulum Stress and Tight Junction Disruption in Nasal Epithelial Cells. *Am. J. Rhinol. Allergy* **2021**, 19458924211004010. [CrossRef]
111. Caraballo, J.C.; Yshii, C.; Westphal, W.; Moninger, T.; Comellas, A.P. Ambient Particulate Matter Affects Occludin Distribution and Increases Alveolar Transepithelial Electrical Conductance. *Respirology* **2011**, *16*, 340–349. [CrossRef] [PubMed]
112. Lee, Y.-G.; Lee, S.-H.; Hong, J.; Lee, P.-H.; Jang, A.-S. Titanium Dioxide Particles Modulate Epithelial Barrier Protein, Claudin 7 in Asthma. *Mol. Immunol.* **2021**, *132*, 209–216. [CrossRef] [PubMed]
113. Wang, G.; Xu, Y.; Huang, L.; Wang, K.; Shen, H.; Li, Z. Pollution Characteristics and Toxic Effects of PM1.0 and PM2.5 in Harbin, China. *Environ. Sci. Pollut Res. Int.* **2021**, *28*, 13229–13242. [CrossRef] [PubMed]
114. Yang, C.; Kwon, D.-I.; Kim, M.; Im, S.-H.; Lee, Y.J. Commensal Microbiome Expands Tγδ17 Cells in the Lung and Promotes Particulate Matter-Induced Acute Neutrophilia. *Front. Immunol.* **2021**, *12*, 645741. [CrossRef]
115. Xu, M.; Wang, X.; Xu, L.; Zhang, H.; Li, C.; Liu, Q.; Chen, Y.; Chung, K.F.; Adcock, I.M.; Li, F. Chronic Lung Inflammation and Pulmonary Fibrosis after Multiple Intranasal Instillation of PM2.5 in Mice. *Environ. Toxicol.* **2021**. [CrossRef]
116. Rahmani, H.; Sadeghi, S.; Taghipour, N.; Roshani, M.; Amani, D.; Ghazanfari, T.; Mosaffa, N. The Effects of Particulate Matter on C57BL/6 Peritoneal and Alveolar Macrophages. *Iran. J. Allergy Asthma Immunol.* **2020**, *19*, 647–659. [CrossRef]
117. Estrella, B.; Naumova, E.N.; Cepeda, M.; Voortman, T.; Katsikis, P.D.; Drexhage, H.A. Effects of Air Pollution on Lung Innate Lymphoid Cells: Review of In Vitro and In Vivo Experimental Studies. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2347. [CrossRef]
118. Gao, Y.; Fan, X.; Gu, W.; Ci, X.; Peng, L. Hyperoside Relieves Particulate Matter-Induced Lung Injury by Inhibiting AMPK/MTOR-Mediated Autophagy Deregulation. *Pharm. Res.* **2021**, *167*, 105561. [CrossRef]
119. Li, H.-H.; Liu, C.-C.; Hsu, T.-W.; Lin, J.-H.; Hsu, J.-W.; Li, A.F.-Y.; Yeh, Y.-C.; Hung, S.-C.; Hsu, H.-S. Upregulation of ACE2 and TMPRSS2 by Particulate Matter and Idiopathic Pulmonary Fibrosis: A Potential Role in Severe COVID-19. *Part Fibre Toxicol.* **2021**, *18*, 11. [CrossRef]
120. de Oliveira Alves, N.; Martins Pereira, G.; Di Domenico, M.; Costanzo, G.; Benevenuto, S.; de Oliveira Fonoff, A.M.; de Souza Xavier Costa, N.; Ribeiro Júnior, G.; Satoru Kajitani, G.; Cestari Moreno, N.; et al. Inflammation Response, Oxidative Stress and DNA Damage Caused by Urban Air Pollution Exposure Increase in the Lack of DNA Repair XPC Protein. *Environ. Int.* **2020**, *145*, 106150. [CrossRef]
121. Pang, L.; Yu, P.; Liu, X.; Fan, Y.; Shi, Y.; Zou, S. Fine Particulate Matter Induces Airway Inflammation by Disturbing the Balance between Th1/Th2 and Regulation of GATA3 and Runx3 Expression in BALB/c Mice. *Mol. Med. Rep.* **2021**, *23*. [CrossRef]
122. Grove, K.C.D.; Provoost, S.; Brusselle, G.G.; Joos, G.F.; Maes, T. Insights in Particulate Matter-induced Allergic Airway Inflammation: Focus on the Epithelium. *Clin. Exp. Allergy* **2018**, *48*, 773–786. [CrossRef]
123. Kim, M.H.; Park, S.J.; Yang, W.M. Inhalation of Essential Oil from Mentha Piperita Ameliorates PM10-Exposed Asthma by Targeting IL-6/JAK2/STAT3 Pathway Based on a Network Pharmacological Analysis. *Pharmaceuticals* **2020**, *14*, 2. [CrossRef] [PubMed]
124. Yang, Y.; Li, X.; An, X.; Zhang, L.; Li, X.; Wang, L.; Zhu, G. Continuous Exposure of PM2.5 Exacerbates Ovalbumin-Induced Asthma in Mouse Lung via a JAK-STAT6 Signaling Pathway. *Adv. Clin. Exp. Med.* **2020**, *29*, 825–832. [CrossRef] [PubMed]
125. Ran, Z.; An, Y.; Zhou, J.; Yang, J.; Zhang, Y.; Yang, J.; Wang, L.; Li, X.; Lu, D.; Zhong, J.; et al. Subchronic Exposure to Concentrated Ambient PM2.5 Perturbs Gut and Lung Microbiota as Well as Metabolic Profiles in Mice. *Environ. Pollut.* **2021**, *272*, 115987. [CrossRef]
126. Chen, Y.-W.; Li, S.-W.; Lin, C.-D.; Huang, M.-Z.; Lin, H.-J.; Chin, C.-Y.; Lai, Y.-R.; Chiu, C.-H.; Yang, C.-Y.; Lai, C.-H. Fine Particulate Matter Exposure Alters Pulmonary Microbiota Composition and Aggravates Pneumococcus-Induced Lung Pathogenesis. *Front. Cell Dev. Biol.* **2020**, *8*, 570484. [CrossRef]
127. Lin, C.-H.; Tseng, C.-Y.; Chao, M.-W. Administration of Lactobacillus Paracasei HB89 Mitigates PM2.5-Induced Enhancement of Inflammation and Allergic Airway Response in Murine Asthma Model. *PLoS ONE* **2020**, *15*, e0243062. [CrossRef] [PubMed]

128. Nam, W.; Kim, H.; Bae, C.; Kim, J.; Nam, B.; Lee, Y.; Kim, J.; Park, S.; Lee, J.; Sim, J. Lactobacillus HY2782 and Bifidobacterium HY8002 Decrease Airway Hyperresponsiveness Induced by Chronic PM2.5 Inhalation in Mice. *J. Med. Food* **2020**, *23*, 575–583. [CrossRef]
129. Celebi Sözener, Z.; Cevhertas, L.; Nadeau, K.; Akdis, M.; Akdis, C.A. Environmental Factors in Epithelial Barrier Dysfunction. *J. Allergy Clin. Immunol.* **2020**, *145*, 1517–1528. [CrossRef]
130. Xian, M.; Ma, S.; Wang, K.; Lou, H.; Wang, Y.; Zhang, L.; Wang, C.; Akdis, C.A. Particulate Matter 2.5 Causes Deficiency in Barrier Integrity in Human Nasal Epithelial Cells. *Allergy Asthma Immunol. Res.* **2020**, *12*, 56–71. [CrossRef] [PubMed]
131. Zhao, R.; Guo, Z.; Zhang, R.; Deng, C.; Xu, J.; Dong, W.; Hong, Z.; Yu, H.; Situ, H.; Liu, C.; et al. Nasal Epithelial Barrier Disruption by Particulate Matter ≤2.5 Mm via Tight Junction Protein Degradation. *J. Appl Toxicol.* **2018**, *38*, 678–687. [CrossRef]
132. Wang, C.; Cai, J.; Chen, R.; Shi, J.; Yang, C.; Li, H.; Lin, Z.; Meng, X.; Liu, C.; Niu, Y.; et al. Personal Exposure to Fine Particulate Matter, Lung Function and Serum Club Cell Secretory Protein (Clara). *Environ. Pollut.* **2017**, *225*, 450–455. [CrossRef]
133. Wang, J.; Huang, J.; Wang, L.; Chen, C.; Yang, D.; Jin, M.; Bai, C.; Song, Y. Urban Particulate Matter Triggers Lung Inflammation via the ROS-MAPK-NF-KB Signaling Pathway. *J. Thorac. Dis.* **2017**, *9*, 4398–4412. [CrossRef] [PubMed]
134. Yan, Z.; Wang, J.; Li, J.; Jiang, N.; Zhang, R.; Yang, W.; Yao, W.; Wu, W. Oxidative Stress and Endocytosis Are Involved in Upregulation of Interleukin-8 Expression in Airway Cells Exposed to PM2.5. *Environ. Toxicol.* **2016**, *31*, 1869–1878. [CrossRef] [PubMed]
135. Wang, G.; Zhang, G.; Gao, X.; Zhang, Y.; Fan, W.; Jiang, J.; An, Z.; Li, J.; Song, J.; Wu, W. Oxidative Stress-Mediated Epidermal Growth Factor Receptor Activation Regulates PM2.5-Induced over-Secretion of pro-Inflammatory Mediators from Human Bronchial Epithelial Cells. *Biochim. Biophys. Acta Gen. Subj.* **2020**, *1864*, 129672. [CrossRef] [PubMed]
136. Zhu, X.-M.; Wang, Q.; Xing, W.-W.; Long, M.-H.; Fu, W.-L.; Xia, W.-R.; Jin, C.; Guo, N.; Xu, D.-Q.; Xu, D.-G. PM2.5 Induces Autophagy-Mediated Cell Death via NOS2 Signaling in Human Bronchial Epithelium Cells. *Int. J. Biol. Sci.* **2018**, *14*, 557–564. [CrossRef]
137. Wichmann, H.-E. Diesel Exhaust Particles. *Inhal. Toxicol.* **2007**, *19*, 241–244. [CrossRef] [PubMed]
138. Smyth, T.; Veazey, J.; Eliseeva, S.; Chalupa, D.; Elder, A.; Georas, S.N. Diesel Exhaust Particle Exposure Reduces Expression of the Epithelial Tight Junction Protein Tricellulin. *Part Fibre Toxicol.* **2020**, *17*, 52. [CrossRef]
139. An, Y.-F.; Geng, X.-R.; Mo, L.-H.; Liu, J.-Q.; Yang, L.-T.; Zhang, X.-W.; Liu, Z.-G.; Zhao, C.-Q.; Yang, P.-C. The 3-Methyl-4-Nitrophenol (PNMC) Compromises Airway Epithelial Barrier Function. *Toxicology* **2018**, *395*, 9–14. [CrossRef]
140. Brandt, E.B.; Bolcas, P.E.; Ruff, B.P.; Hershey, G.K.K. IL33 Contributes to Diesel Pollution-mediated Increase in Experimental Asthma Severity. *Allergy* **2020**, *75*, 2254–2266. [CrossRef]
141. De Grove, K.C.; Provoost, S.; Braun, H.; Blomme, E.E.; Teufelberger, A.R.; Krysko, O.; Beyaert, R.; Brusselle, G.G.; Joos, G.F.; Maes, T. IL-33 Signalling Contributes to Pollutant-Induced Allergic Airway Inflammation. *Clin. Exp. Allergy* **2018**, *48*, 1665–1675. [CrossRef] [PubMed]
142. De Grove, K.C.; Provoost, S.; Hendriks, R.W.; McKenzie, A.N.J.; Seys, L.J.M.; Kumar, S.; Maes, T.; Brusselle, G.G.; Joos, G.F. Dysregulation of Type 2 Innate Lymphoid Cells and TH2 Cells Impairs Pollutant-Induced Allergic Airway Responses. *J. Allergy Clin. Immunol.* **2017**, *139*, 246–257.e4. [CrossRef]
143. Daniel, S.; Phillippi, D.; Schneider, L.J.; Nguyen, K.N.; Mirpuri, J.; Lund, A.K. Exposure to Diesel Exhaust Particles Results in Altered Lung Microbial Profiles, Associated with Increased Reactive Oxygen Species/Reactive Nitrogen Species and Inflammation, in C57Bl/6 Wildtype Mice on a High-Fat Diet. *Part Fibre Toxicol.* **2021**, *18*, 3. [CrossRef]
144. Uh, S.-T.; Koo, S.M.; Kim, Y.; Kim, K.; Park, S.; Jang, A.S.; Kim, D.; Kim, Y.H.; Park, C.-S. The Activation of NLRP3-Inflammsome by Stimulation of Diesel Exhaust Particles in Lung Tissues from Emphysema Model and RAW 264.7 Cell Line. *Korean J. Intern. Med.* **2017**, *32*, 865–874. [CrossRef]
145. Kumar, S.; Joos, G.; Boon, L.; Tournoy, K.; Provoost, S.; Maes, T. Role of Tumor Necrosis Factor-α and Its Receptors in Diesel Exhaust Particle-Induced Pulmonary Inflammation. *Sci. Rep.* **2017**, *7*, 11508. [CrossRef] [PubMed]
146. Decaesteker, T.; Vanhoffelen, E.; Trekels, K.; Jonckheere, A.-C.; Cremer, J.; Vanstapel, A.; Dilissen, E.; Bullens, D.; Dupont, L.J.; Vanoirbeek, J.A. Differential Effects of Intense Exercise and Pollution on the Airways in a Murine Model. *Part Fibre Toxicol.* **2021**, *18*, 12. [CrossRef]
147. de Homdedeu, M.; Cruz, M.J.; Sánchez-Díez, S.; Gómez-Ollés, S.; Ojanguren, I.; Ma, D.; Muñoz, X. Role of Diesel Exhaust Particles in the Induction of Allergic Asthma to Low Doses of Soybean. *Environ. Res.* **2020**, 110337. [CrossRef]
148. Zheng, X.; Wang, G.; Bin, P.; Meng, T.; Niu, Y.; Yang, M.; Zhang, L.; Duan, H.; Yu, T.; Dai, Y.; et al. Time-Course Effects of Antioxidants and Phase II Enzymes on Diesel Exhaust Particles-Induced Oxidative Damage in the Mouse Lung. *Toxicol. Appl. Pharm.* **2019**, *366*, 25–34. [CrossRef]
149. Gibbs, J.L.; Dallon, B.W.; Lewis, J.B.; Walton, C.M.; Arroyo, J.A.; Reynolds, P.R.; Bikman, B.T. Diesel Exhaust Particle Exposure Compromises Alveolar Macrophage Mitochondrial Bioenergetics. *Int. J. Mol. Sci.* **2019**, *20*, 5598. [CrossRef] [PubMed]
150. Li, Y.-J.; Shimizu, T.; Shinkai, Y.; Ihara, T.; Sugamata, M.; Kato, K.; Kobayashi, M.; Hirata, Y.; Inagaki, H.; Uzuki, M.; et al. Nrf2 Lowers the Risk of Lung Injury via Modulating the Airway Innate Immune Response Induced by Diesel Exhaust in Mice. *Biomedicines* **2020**, *8*, 443. [CrossRef]
151. Cattani-Cavalieri, I.; da Maia Valença, H.; Moraes, J.A.; Brito-Gitirana, L.; Romana-Souza, B.; Schmidt, M.; Valença, S.S. Dimethyl Fumarate Attenuates Lung Inflammation and Oxidative Stress Induced by Chronic Exposure to Diesel Exhaust Particles in Mice. *Int. J. Mol. Sci.* **2020**, *21*, 9658. [CrossRef]

152. Lee, J.W.; Kim, J.S.; Lee, H.J.; Jang, J.-H.; Kim, J.-H.; Sim, W.J.; Lim, Y.-B.; Jung, J.-W.; Lim, H.J. Age and Gender Effects on Genotoxicity in Diesel Exhaust Particles Exposed C57BL/6 Mice. *Biomolecules* **2021**, *11*, 374. [CrossRef] [PubMed]
153. Deering-Rice, C.E.; Memon, T.; Lu, Z.; Romero, E.G.; Cox, J.; Taylor-Clark, T.; Veranth, J.M.; Reilly, C.A. Differential Activation of TRPA1 by Diesel Exhaust Particles: Relationships between Chemical Composition, Potency, and Lung Toxicity. *Chem. Res. Toxicol.* **2019**, *32*, 1040–1050. [CrossRef]
154. Robinson, R.K.; Birrell, M.A.; Adcock, J.J.; Wortley, M.A.; Dubuis, E.D.; Chen, S.; McGilvery, C.M.; Hu, S.; Shaffer, M.S.P.; Bonvini, S.J.; et al. Mechanistic Link between Diesel Exhaust Particles and Respiratory Reflexes. *J. Allergy Clin. Immunol.* **2018**, *141*, 1074–1084.e9. [CrossRef]
155. Akopian, A.N.; Fanick, E.R.; Brooks, E.G. TRP Channels and Traffic-Related Environmental Pollution-Induced Pulmonary Disease. *Semin. Immunopathol.* **2016**, *38*, 331–338. [CrossRef]
156. Agopyan, N.; Head, J.; Yu, S.; Simon, S.A. TRPV1 Receptors Mediate Particulate Matter-Induced Apoptosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2004**, *286*, L563–L572. [CrossRef] [PubMed]
157. Wooding, D.J.; Ryu, M.H.; Hüls, A.; Lee, A.D.; Lin, D.T.S.; Rider, C.F.; Yuen, A.C.Y.; Carlsten, C. Particle Depletion Does Not Remediate Acute Effects of Traffic-Related Air Pollution and Allergen. A Randomized, Double-Blind Crossover Study. *Am. J. Respir. Crit. Care Med.* **2019**, *200*, 565–574. [CrossRef] [PubMed]
158. Ji, J.; Upadhyay, S.; Xiong, X.; Malmlöf, M.; Sandström, T.; Gerde, P.; Palmberg, L. Multi-Cellular Human Bronchial Models Exposed to Diesel Exhaust Particles: Assessment of Inflammation, Oxidative Stress and Macrophage Polarization. *Part Fibre Toxicol.* **2018**, *15*, 19. [CrossRef] [PubMed]
159. Zarcone, M.C.; Duistermaat, E.; van Schadewijk, A.; Jedynska, A.; Hiemstra, P.S.; Kooter, I.M. Cellular Response of Mucociliary Differentiated Primary Bronchial Epithelial Cells to Diesel Exhaust. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2016**, *311*, L111–L123. [CrossRef] [PubMed]
160. Ozturk, A.B.; Bayraktar, R.; Gogebakan, B.; Mumbuc, S.; Bayram, H. Comparison of Inflammatory Cytokine Release from Nasal Epithelial Cells of Non-Atopic Non-Rhinitic, Allergic Rhinitic and Polyp Subjects and Effects of Diesel Exhaust Particles In Vitro. *Allergol. Immunopathol.* **2017**, *45*, 473–481. [CrossRef] [PubMed]
161. Savary, C.C.; Bellamri, N.; Morzadec, C.; Langouët, S.; Lecureur, V.; Vernhet, L. Long Term Exposure to Environmental Concentrations of Diesel Exhaust Particles Does Not Impact the Phenotype of Human Bronchial Epithelial Cells. *Toxicol. Vitr.* **2018**, *52*, 154–160. [CrossRef]
162. Papi, A.; Brightling, C.; Pedersen, S.E.; Reddel, H.K. Asthma. *Lancet* **2018**, *391*, 783–800. [CrossRef]
163. Wenzel, S.E. Asthma Phenotypes: The Evolution from Clinical to Molecular Approaches. *Nat. Med.* **2012**, *18*, 716–725. [CrossRef]
164. Bontinck, A.; Maes, T.; Joos, G. Asthma and Air Pollution: Recent Insights in Pathogenesis and Clinical Implications. *Curr. Opin. Pulm. Med.* **2020**, *26*, 10–19. [CrossRef]
165. Gras, D.; Martinez-Anton, A.; Bourdin, A.; Garulli, C.; de Senneville, L.; Vachier, I.; Vitte, J.; Chanez, P. Human Bronchial Epithelium Orchestrates Dendritic Cell Activation in Severe Asthma. *Eur. Respir. J.* **2017**, *49*. [CrossRef]
166. Weng, C.-M.; Lee, M.-J.; He, J.-R.; Chao, M.-W.; Wang, C.-H.; Kuo, H.-P. Diesel Exhaust Particles Up-Regulate Interleukin-17A Expression via ROS/NF-KB in Airway Epithelium. *Biochem. Pharm.* **2018**, *151*, 1–8. [CrossRef]
167. Huang, Y.; Lou, H.; Wang, C.; Zhang, L. Impact of Cigarette Smoke and IL-17A Activation on Asthmatic Patients with Chronic Rhinosinusitis. *Rhinology* **2019**, *57*, 57–66. [CrossRef]
168. Sava, F.; MacNutt, M.J.; Carlsten, C.R. Nasal Neurogenic Inflammation Markers Increase after Diesel Exhaust Inhalation in Individuals with Asthma. *Am. J. Respir. Crit. Care Med.* **2013**, *188*, 759–760. [CrossRef]
169. Mumby, S.; Chung, K.F.; Adcock, I.M. Transcriptional Effects of Ozone and Impact on Airway Inflammation. *Front. Immunol.* **2019**, *10*. [CrossRef] [PubMed]
170. Bayram, H.; Rusznak, C.; Khair, O.A.; Sapsford, R.J.; Abdelaziz, M.M. Effect of Ozone and Nitrogen Dioxide on the Permeability of Bronchial Epithelial Cell Cultures of Non-Asthmatic and Asthmatic Subjects. *Clin. Exp. Allergy* **2002**, *32*, 1285–1292. [CrossRef] [PubMed]
171. Carlsten, C.; Blomberg, A.; Pui, M.; Sandstrom, T.; Wong, S.W.; Alexis, N.; Hirota, J. Diesel Exhaust Augments Allergen-Induced Lower Airway Inflammation in Allergic Individuals: A Controlled Human Exposure Study. *Thorax* **2016**, *71*, 35–44. [CrossRef] [PubMed]
172. Hosseini, A.; Hirota, J.A.; Hackett, T.L.; McNagny, K.M.; Wilson, S.J.; Carlsten, C. Morphometric Analysis of Inflammation in Bronchial Biopsies Following Exposure to Inhaled Diesel Exhaust and Allergen Challenge in Atopic Subjects. *Part Fibre Toxicol.* **2016**, *13*, 2. [CrossRef]
173. Ryu, M.H.; Lau, K.S.-K.; Wooding, D.J.; Fan, S.; Sin, D.D.; Carlsten, C. Particle Depletion of Diesel Exhaust Restores Allergen-Induced Lung-Protective Surfactant Protein D in Human Lungs. *Thorax* **2020**, *75*, 640–647. [CrossRef]
174. Jung, K.H.; Lovinsky-Desir, S.; Yan, B.; Torrone, D.; Lawrence, J.; Jezioro, J.R.; Perzanowski, M.; Perera, F.P.; Chillrud, S.N.; Miller, R.L. Effect of Personal Exposure to Black Carbon on Changes in Allergic Asthma Gene Methylation Measured 5 Days Later in Urban Children: Importance of Allergic Sensitization. *Clin. Epigenetics* **2017**, *9*, 61. [CrossRef]
175. Eisner, M.D.; Anthonisen, N.; Coultas, D.; Kuenzli, N.; Perez-Padilla, R.; Postma, D.; Romieu, I.; Silverman, E.K.; Balmes, J.R. Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2010**, *182*, 693–718. [CrossRef]

176. Huang, X.; Mu, X.; Deng, L.; Fu, A.; Pu, E.; Tang, T.; Kong, X. The Etiologic Origins for Chronic Obstructive Pulmonary Disease. *Int. J. Chron Obs. Pulmon. Dis.* **2019**, *14*, 1139–1158. [CrossRef] [PubMed]
177. Nishida, K.; Brune, K.A.; Putcha, N.; Mandke, P.; O'Neal, W.K.; Shade, D.; Srivastava, V.; Wang, M.; Lam, H.; An, S.S.; et al. Cigarette Smoke Disrupts Monolayer Integrity by Altering Epithelial Cell-Cell Adhesion and Cortical Tension. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2017**, *313*, L581–L591. [CrossRef] [PubMed]
178. Liu, S.; Jørgensen, J.T.; Ljungman, P.; Pershagen, G.; Bellander, T.; Leander, K.; Magnusson, P.K.E.; Rizzuto, D.; Hvidtfeldt, U.A.; Raaschou-Nielsen, O.; et al. Long-Term Exposure to Low-Level Air Pollution and Incidence of Chronic Obstructive Pulmonary Disease: The ELAPSE Project. *Environ. Int.* **2021**, *146*, 106267. [CrossRef]
179. Duan, R.-R.; Hao, K.; Yang, T. Air Pollution and Chronic Obstructive Pulmonary Disease. *Chronic. Dis. Transl. Med.* **2020**, *6*, 260–269. [CrossRef] [PubMed]
180. Doiron, D.; de Hoogh, K.; Probst-Hensch, N.; Fortier, I.; Cai, Y.; De Matteis, S.; Hansell, A.L. Air Pollution, Lung Function and COPD: Results from the Population-Based UK Biobank Study. *Eur. Respir. J.* **2019**, *54*. [CrossRef]
181. Berend, N. Contribution of Air Pollution to COPD and Small Airway Dysfunction. *Respirology* **2016**, *21*, 237–244. [CrossRef] [PubMed]
182. Leclercq, B.; Platel, A.; Antherieu, S.; Alleman, L.Y.; Hardy, E.M.; Perdrix, E.; Grova, N.; Riffault, V.; Appenzeller, B.M.; Happillon, M.; et al. Genetic and Epigenetic Alterations in Normal and Sensitive COPD-Diseased Human Bronchial Epithelial Cells Repeatedly Exposed to Air Pollution-Derived PM2.5. *Environ. Pollut.* **2017**, *230*, 163–177. [CrossRef] [PubMed]
183. Leclercq, B.; Happillon, M.; Antherieu, S.; Hardy, E.M.; Alleman, L.Y.; Grova, N.; Perdrix, E.; Appenzeller, B.M.; Lo Guidice, J.-M.; Coddeville, P.; et al. Differential Responses of Healthy and Chronic Obstructive Pulmonary Diseased Human Bronchial Epithelial Cells Repeatedly Exposed to Air Pollution-Derived PM4. *Environ. Pollut.* **2016**, *218*, 1074–1088. [CrossRef] [PubMed]
184. Leclercq, B.; Kluza, J.; Antherieu, S.; Sotty, J.; Alleman, L.Y.; Perdrix, E.; Loyens, A.; Coddeville, P.; Lo Guidice, J.-M.; Marchetti, P.; et al. Air Pollution-Derived PM2.5 Impairs Mitochondrial Function in Healthy and Chronic Obstructive Pulmonary Diseased Human Bronchial Epithelial Cells. *Environ. Pollut.* **2018**, *243*, 1434–1449. [CrossRef] [PubMed]
185. Wiegman, C.H.; Li, F.; Ryffel, B.; Togbe, D.; Chung, K.F. Oxidative Stress in Ozone-Induced Chronic Lung Inflammation and Emphysema: A Facet of Chronic Obstructive Pulmonary Disease. *Front. Immunol.* **2020**, *11*. [CrossRef]
186. Wu, S.; Ni, Y.; Li, H.; Pan, L.; Yang, D.; Baccarelli, A.A.; Deng, F.; Chen, Y.; Shima, M.; Guo, X. Short-Term Exposure to High Ambient Air Pollution Increases Airway Inflammation and Respiratory Symptoms in Chronic Obstructive Pulmonary Disease Patients in Beijing, China. *Environ. Int.* **2016**, *94*, 76–82. [CrossRef]
187. Zhao, J.; Li, M.; Wang, Z.; Chen, J.; Zhao, J.; Xu, Y.; Wei, X.; Wang, J.; Xie, J. Role of PM2.5 in the Development and Progression of COPD and Its Mechanisms. *Respir. Res.* **2019**, *20*, 120. [CrossRef]
188. Hulina-Tomašković, A.; Rajković, M.G.; Jelić, D.; Bosnar, M.; Sladoljev, L.; Grubišić, T.Ž.; Rumora, L. Pro-Inflammatory Effects of Extracellular Hsp70 on NCI-H292 Human Bronchial Epithelial Cell Line. *Int. J. Exp. Pathol.* **2019**, *100*, 320–329. [CrossRef]
189. Daigle, C.C.; Chalupa, D.C.; Gibb, F.R.; Morrow, P.E.; Oberdörster, G.; Utell, M.J.; Frampton, M.W. Ultrafine Particle Deposition in Humans during Rest and Exercise. *Inhal. Toxicol.* **2003**, *15*, 539–552. [CrossRef]
190. Löndahl, J.; Massling, A.; Pagels, J.; Swietlicki, E.; Vaclavik, E.; Loft, S. Size-Resolved Respiratory-Tract Deposition of Fine and Ultrafine Hydrophobic and Hygroscopic Aerosol Particles during Rest and Exercise. *Inhal. Toxicol.* **2007**, *19*, 109–116. [CrossRef]
191. Bonini, M.; Silvers, W. Exercise-Induced Bronchoconstriction: Background, Prevalence, and Sport Considerations. *Immunol. Allergy Clin. N. Am.* **2018**, *38*, 205–214. [CrossRef]
192. Pagani, L.G.; Santos, J.M.B.; Foster, R.; Rossi, M.; Luna Junior, L.A.; Katekaru, C.M.; de Sá, M.C.; Jonckheere, A.-C.; Almeida, F.M.; Amaral, J.B.; et al. The Effect of Particulate Matter Exposure on the Inflammatory Airway Response of Street Runners and Sedentary People. *Atmosphere* **2020**, *11*, 43. [CrossRef]
193. De Santos, J.M.B.D.; Foster, R.; Jonckheere, A.-C.; Rossi, M.; Luna Junior, L.A.; Katekaru, C.M.; de Sá, M.C.; Pagani, L.G.; de Almeida, F.M.; do Amaral, J.B.; et al. Outdoor Endurance Training with Air Pollutant Exposure Versus Sedentary Lifestyle: A Comparison of Airway Immune Responses. *Int. J. Environ. Res. Public Health* **2019**, *16*, 4418. [CrossRef]
194. Cavalcante de Sá, M.; Nakagawa, N.K.; Saldiva de André, C.D.; Carvalho-Oliveira, R.; de Santana Carvalho, T.; Nicola, M.L.; de André, P.A.; Nascimento Saldiva, P.H.; Vaisberg, M. Aerobic Exercise in Polluted Urban Environments: Effects on Airway Defense Mechanisms in Young Healthy Amateur Runners. *J. Breath Res.* **2016**, *10*, 046018. [CrossRef]
195. Laeremans, M.; Dons, E.; Avila-Palencia, I.; Carrasco-Turigas, G.; Orjuela, J.P.; Anaya, E.; Cole-Hunter, T.; de Nazelle, A.; Nieuwenhuijsen, M.; Standaert, A.; et al. Short-Term Effects of Physical Activity, Air Pollution and Their Interaction on the Cardiovascular and Respiratory System. *Environ. Int.* **2018**, *117*, 82–90. [CrossRef]
196. Elshazly, F.A.; Abdelbasset, W.K.; Elnaggar, R.K.; Tantawy, S.A. Effects of Second-Hand Smoking on Lung Functions in Athlete and Non-Athlete School-Aged Children—Observational Study. *Afr. Health Sci.* **2020**, *20*, 368–375. [CrossRef] [PubMed]
197. Lovinsky-Desir, S.; Jung, K.H.; Jezioro, J.R.; Torrone, D.Z.; de Planell-Saguer, M.; Yan, B.; Perera, F.P.; Rundle, A.G.; Perzanowski, M.S.; Chillrud, S.N.; et al. Physical Activity, Black Carbon Exposure, and DNA Methylation in the FOXP3 Promoter. *Clin. Epigenetics* **2017**, *9*, 65. [CrossRef] [PubMed]
198. Laeremans, M.; Dons, E.; Avila-Palencia, I.; Carrasco-Turigas, G.; Orjuela-Mendoza, J.P.; Anaya-Boig, E.; Cole-Hunter, T.; DE Nazelle, A.; Nieuwenhuijsen, M.; Standaert, A.; et al. Black Carbon Reduces the Beneficial Effect of Physical Activity on Lung Function. *Med. Sci. Sports Exerc.* **2018**, *50*, 1875–1881. [CrossRef]

199. Cole, C.A.; Carlsten, C.; Koehle, M.; Brauer, M. Particulate Matter Exposure and Health Impacts of Urban Cyclists: A Randomized Crossover Study. *Environ. Health* **2018**, *17*, 78. [CrossRef]
200. Giles, L.V.; Carlsten, C.; Koehle, M.S. The Pulmonary and Autonomic Effects of High-Intensity and Low-Intensity Exercise in Diesel Exhaust. *Environ. Health* **2018**, *17*, 87. [CrossRef]
201. Rundell, K.W.; Smoliga, J.M.; Bougault, V. Exercise-Induced Bronchoconstriction and the Air We Breathe. *Immunol. Allergy Clin. N. Am.* **2018**, *38*, 183–204. [CrossRef]
202. Qin, F.; Yang, Y.; Wang, S.; Dong, Y.; Xu, M.; Wang, Z.; Zhao, J. Exercise and Air Pollutants Exposure: A Systematic Review and Meta-Analysis. *Life Sci.* **2019**, *218*, 153–164. [CrossRef]
203. Gomes, E.C.; Stone, V.; Florida-James, G. Impact of Heat and Pollution on Oxidative Stress and CC16 Secretion after 8 Km Run. *Eur. J. Appl. Physiol.* **2011**, *111*, 2089–2097. [CrossRef] [PubMed]
204. Park, H.-Y.; Gilbreath, S.; Barakatt, E. Respiratory Outcomes of Ultrafine Particulate Matter (UFPM) as a Surrogate Measure of near-Roadway Exposures among Bicyclists. *Environ. Health* **2017**, *16*, 6. [CrossRef] [PubMed]
205. DeFlorio-Barker, S.; Lobdell, D.T.; Stone, S.L.; Boehmer, T.; Rappazzo, K.M. Acute Effects of Short-Term Exposure to Air Pollution While Being Physically Active, the Potential for Modification: A Review of the Literature. *Prev. Med.* **2020**, *139*, 106195. [CrossRef] [PubMed]
206. Marmett, B.; Carvalho, R.B.; Dorneles, G.P.; Nunes, R.B.; Rhoden, C.R. Should I Stay or Should I Go: Can Air Pollution Reduce the Health Benefits of Physical Exercise? *Med. Hypotheses* **2020**, *144*, 109993. [CrossRef]
207. Zhao, C.; Fang, X.; Feng, Y.; Fang, X.; He, J.; Pan, H. Emerging Role of Air Pollution and Meteorological Parameters in COVID-19. *J. Evid. Based Med.* **2021**, *14*, 123–138. [CrossRef]