

Outdoor Air Pollution and Childhood Respiratory Disease

Subjects: Meteorology & Atmospheric Sciences | Pediatrics | Respiratory System

Contributor: Arianna Dondi, Claudio Carbone, Elisa Manieri, Daniele Zama, Chiara Del Bono, Ludovica Betti, Carlotta Biagi, Marcello Lanari

The leading mechanisms through which air pollutants exert their damaging effects are the promotion of oxidative stress, the induction of an inflammatory response, and the deregulation of the immune system by reducing its ability to limit infectious agents' spreading. This influence starts in the prenatal age and continues during childhood, the most susceptible period of life, due to a lower efficiency of oxidative damage detoxification, a higher metabolic and breathing rate, and enhanced oxygen consumption per unit of body mass. Air pollution is involved in acute disorders like asthma exacerbations and upper and lower respiratory infections, including bronchiolitis, tuberculosis, and pneumoniae. Pollutants can also contribute to the onset of chronic asthma, and they can lead to a deficit in lung function and growth, long-term respiratory damage, and eventually chronic respiratory illness. Air pollution abatement policies, are contributing to mitigating air quality issues, but more efforts should be encouraged to improve acute childhood respiratory disease with possible positive long-term effects on lung function.

Keywords: children ; air pollution ; air quality ; oxidative stress ; respiratory disease ; lung function

1. Main Outdoor Air Pollutants and Their Composition

1.1. Air Pollution and Health Effects

Numerous studies have documented associations between air pollution and mortality and morbidity in adults and children ^[1], with fine PM playing a major role. Nevertheless, fundamental uncertainty and disagreement persist regarding which physical and chemical properties of particles (or unidentified confounding environmental influences) have the most significant impact on health, the underlying pathophysiological mechanisms, and which specific air quality standards should be adopted to minimize risks for public health. This makes causal links between health effects caused by air pollution exposure and identifying proper properties to use as metrics challenging to establish within the scientific community. Moreover, air quality is regulated by most jurisdictions in terms of individual components and using single markers or integrated measurements (for instance, PM₁₀ or PM_{2.5} daily mass), which are now recognized as not ideal for representing the multiple and specific factors involved in the pathogenesis of non-communicable diseases resulting from exposure to air pollution as a whole. The ambient atmosphere is a dynamic system in which the mixture of air pollutants changes quickly over time. The fluctuation of important atmospheric parameters influencing ambient PM concentrations and chemical composition (thus, human exposure), such as particle sources' emission strengths, gaseous precursors, temperature, relative humidity, mixing height, wind direction, and speed, occurs on time scales much shorter than a few hours. For this reason, daily air quality monitoring cannot be adequate to fully assess the physicochemical properties of atmospheric pollution involved in the causal mechanisms associated with the BED. In the last 15 years, there has been a growing literature pointing to potential alternative metrics, and a particular focus has been dedicated to specific health effects in association with cellular oxidative stress initiated by the formation of reactive oxygen species (ROS) at the surface of and within target cells ^{[2][3]}.

1.2. Gases

Highly reactive gaseous pollutants—such as O₃, NO, NO₂, SO, and SO₂—are still being studied for their health effects because they are linked to a cascade of inflammatory processes. They are produced mainly by anthropogenic sources and are thus tracked and regulated by governments and air-quality monitoring agencies. Ground-level O₃ is typically formed by photochemical reactions between solar radiation and other gaseous precursors, such as NO, NO₂, and volatile organic compounds (VOCs), especially in warm summer conditions. NO, and NO₂ are formed primarily by the reaction of O₃ with nitric acid emitted during fossil fuel combustion. The primary sources of SO and SO₂ in the developed world are primary emissions during energy production or industrial processes. Although exposure to SO₂ has been greatly reduced in the developed world through treatment for emissions from coal-fired power plants and energy sources other than coal

combustion, it remains an issue in developing countries (e.g., China). These gaseous pollutants vary substantially in their environmental persistence and oxidizing capacity; whereas O_3 is a potent oxidizing agent, NO_2 is a relatively weak oxidant. Controlled NO_2 exposure appears to have a mild airway inflammatory effect at high levels of exposure that are unlikely to occur in non-experimental settings, but it causes minor lung inflammation at typical ambient concentrations. NO_2 is supposed to have a deeper penetration into the respiratory tree, which could cause microlesions in the respiratory tract and increase susceptibility to infections [4]. However, much debate, the so-called “ NO_2 dilemma”, surrounds whether the epidemiological associations found for fossil combustion-related air pollution are due to direct effects of NO_2 or if it is just a marker and the causes of pulmonary diseases are associated with the broader mixture of correlated components. Indeed, studies report strong associations between NO_x and health outcomes (e.g., pediatric asthma) that mimic other specific properties of traffic PM [5], such as BC and particle number concentrations. Because SO_2 is a reductant, it probably causes pulmonary diseases through a different mechanism. Extensive research has been conducted on the effects of short-term controlled exposure to O_3 and SO_2 at relevant concentrations [6][7]. O_3 exposure results in airway inflammation, airway hyper-responsiveness, and lung function decrees in healthy and fragile individuals, whereas SO_2 causes more prominent bronchoconstriction, mostly in fragile individuals [8].

1.3. Particulate Matter (PM)

PM is the crucial ingredient in polluted air concerning increases in cardiac and respiratory morbidity and mortality. To prevent this staggering loss of life and cost to society, it is essential to understand the characteristics of the toxic particles and gain insight into how they are related to adverse health effects. PM is composed of solid and liquid particles, which can be classified into coarse, fine, or ultrafine (UFPs or $PM_{0.1}$) particles based on their size and mean diameters: coarse particles have a diameter of more than 2.5 μm , fine particles are considered those with diameters in the range 0.1–2.5 μm , and ultrafine particles have diameters $<0.1 \mu m$. Particles are characterized by a myriad of primary and secondary components and complex chemical mechanisms, encompassing both natural and anthropogenic sources. These lead to very heterogeneous physical and chemical properties, varying in relation to the mix of pollutants/components, season, and geography.

It is currently possible to measure many properties of PM populations in the atmosphere. Size-specific mass, surface area, the total number of particles, and the number of particles in different size ranges are all currently measurable, as is the chemical composition of particles in the atmosphere. All these properties, which vary in space and time, can help to describe the multiple characteristics of particle populations and are reported to play a role in the adverse health effects of air pollution, including allergy, asthma, cardiovascular, and respiratory diseases. However, the functional mechanisms explaining the causative relations and mechanisms of interaction on the molecular level remain mostly unclear. There is no conclusive evidence to pinpoint a single pollutant or a limited number of species as the main harmful components/properties of PM, and further research in this area is ongoing to inform policy priorities [9].

Currently, government and air-quality monitoring agencies track and regulate the size-specific mass of 10- μm -diameter (PM_{10}) and 2.5- μm -diameter ($PM_{2.5}$) particles as specified by the Code of Federal Regulations in the US and the European Committee for Standardization (CEN) standard in Europe. As these or equivalent methods are used in routine air quality monitoring networks, they have formed the basis of numerous epidemiological studies. However, the WHO report (2021) [10] review provides an authoritative starting point for considering possible future metrics for regulating particles in the ambient atmosphere. Another mass metric, PM_1 , has been suggested as possibly valuable for managing PM levels in the atmosphere, mainly because it provides better separation of the coarse mode and accumulation mode (and ultrafine) fractions than the 2.5 micron cut-off. Furthermore, WHO prioritized specific types of PM, i.e., Black Carbon (BC), Elemental Carbon (EC), heavy metals, and the concentration of ultrafine particles, but concluded that the quantitative evidence of independent adverse health effects from these pollutants was still insufficient for new air quality guideline levels [10].

In 2021, the WHO [10] recommended lowering the $PM_{2.5}$ annual air quality guideline level from 10 to 5 $\mu g m^{-3}$ to reflect the new evidence about effects occurring at low levels of exposure. Among the reasons possibly explaining the occurrence of health effects even at these very low doses is that these studies are based on $PM_{2.5}$ mass, a metric not ideal for representing the BED of toxic $PM_{2.5}$ [11]. In fact, despite the PM mass being the same, health impacts can vary significantly depending on its chemical composition and size distribution. For instance, the content of relatively small masses of transition metals and organic species increases their intrinsic toxicity, as does the abundance of ultrafine particles (even if they represent a minor contribution to their total mass). These findings led the scientific community to investigate more health-relevant aerosol metrics than PM mass, looking at the link between physicochemical features of the atmosphere and specific relevant health outcomes.

An important new area of research has emerged in the past 15 years or so, undertaken in several different countries, using a range of different approaches, which has demonstrated that the mechanism leading to oxidative stress can be identified as a unifying feature underlying the toxic actions linking PM chemical composition to biological effects [12][13]. Oxidative stress is based on a homeostatic mechanism implying protective responses and can be defined as a change to living cells (and thereby the organs and tissues composed of those cells) caused by reactive oxygen (or nitrogen) species. It is also defined as an imbalance between reactive oxidant species (ROS) generated from the stimulation of pro-inflammatory factors and antioxidants, such as glutathione and antioxidant enzymes, with the former prevailing. Thus, the oxidative potential is recognized as an essential property of PM and has gained growing attention; several now widely used assays and techniques for quantifying particle ROS activity have been developed, and ROS studies have received particular attention. In addition, a wide range of experimental conditions has been explored in the laboratory to assess PM characteristics in terms of toxicological endpoints and mechanisms of ROS formation [14].

Numerous studies have shown a complex relationship between PM oxidative and pro-inflammatory properties and primary combustion aerosol concentrations. They indicate that these are significantly impacted by changes in the particles' size, mixing, and aging state in the real atmosphere. The best candidates for particulate compounds responsible for ROS activity encompass transition metals and specific carbonaceous compounds, such as quinones species and BC [15] or some combination of different physicochemical properties associated with specific PM sources and atmospheric conditions.

For example, during the fall and winter seasons, when common respiratory disease epidemics occur, PM accumulates in many densely populated regions of continental Europe and, more broadly, in many mid-latitude areas, concomitance with the development of high-pressure atmospheric structures. These conditions favor the condensation of semi-volatile species, causing high PM episodes mainly accounted for by carbonaceous matter and ammonium nitrate [16]. Biomass burning for residential heating and fossil fuel combustion dominate as sources of primary organic PM in urban environments, leading to higher risks for detrimental health effects [17]. A higher BC to total organic PM ratio and a higher concentration of ultrafine particles can characterize this PM and are valuable additional air quality indicators to evaluate the health risks of air quality dominated by primary combustion particles [5][18]. A few studies have also highlighted the toxicological potential of secondary organic PM (SOA), demonstrating that ambient PM is responsible for potential impacts on human health and is not only emitted from pollution hotspots [19]. Other authors, comparing ROS assays performed on size-segregated PM samples from six cities on three continents, showed that finer aerosol size fractions tend to have a higher ROS activity and that chemical components determining ROS formation include several transition metals (primarily emitted) and polar organic compounds (likely of secondary origin) [20].

During the CARE experiment carried out in the urban area of Rome (Italy) in wintertime [3], the most significant pro-inflammatory and oxidative responses have been related to a specific ultrafine particle type enriched in BC and associated with new emissions of fossil fuel combustion. Different PM features, characterized by the same levels of BC content but a different mixing of fossil fuel ultrafine particles with background PM, exhibited low oxidative responses, even with higher PM_{2.5} mass concentrations. The mixing state is considered one of the most critical factors determining the impacts of particles not only on the cloud–climate interactions but also on human health [34]. Furthermore, mixing structures of different species or types of change depend on the aerosol source, pollution level, transport distance, and relative humidity, and these changes tend to be more rapid in a more polluted environment [34]. This suggests the importance of considering specific PM features in terms of chemical composition, mixing state, and size distribution associated with specific sources instead of conventional metrics (e.g., PM mass or single pollutant concentrations) that can obscure relevant confounding factors, co-emitted pollutants, and environmental variables, as well as the related health effects of the atmospheric mixture as a whole [35,36].

Recent research indicates that the ROS generated by atmospheric processing significantly impacts the PM oxidative potential, which appears to play an important role in aerosol health effects and provides a direct link between atmospheric and physiological multiphase processes. Consequently, different techniques for its quantification are being tested as an alternative air quality metric in a significant number of studies worldwide. However, it remains the subject of intense research and discussion [37].

1.4. Traffic-Related Air Pollution (TRAP)

Road traffic is a significant source of air pollution in urban environments. In recent decades, many studies linking air pollution and health effects in the urban atmosphere have focused on traffic-related air pollution (TRAP). TRAP is produced by the combustion of fossil fuels and is composed of a complex mixture of pollutants (NO, NO₂) and particles containing both non-volatile and semi-volatile components. The semi-volatile compounds may partition between the gas

and particle phases in ambient conditions depending on their vapor pressure and degree of atmospheric dilution and participate in photochemical reactions in the atmosphere [21].

Consequently, the physical and chemical characteristics of combustion-generated PM change dramatically with background conditions, atmospheric dilution, and processing, which may alter their toxic properties and influence their role in population exposures and public health. Combustion particles also derive from various sources other than motorized road traffic, including wood and coal burning, shipping, and industrial sources, and these sources may contribute significantly to ambient combustion particle concentrations, even in urban areas. As mentioned in the previous section, semi-volatile PM contains a wide variety of organic micropollutants, many of which possess genotoxic and carcinogenic characteristics, such as dioxins, PAHs, and their derivatives. Some of these semi-volatile organic species trigger a chain of biochemical reactions in cells, change their redox state, and exert oxidative stress. Polar organic compounds, such as quinones, oxygenated PAHs, and aldehydes, are reported to induce oxidative stress in cells. BC, also known as soot, is a significant source of combustion PM and has been repeatedly proposed as a PM metric candidate to reflect better the health effects of combustion-related air pollution than PM mass because it is relatively easy and not expensive to measure [18]. Traffic-related PM is characterized by fresh UFPs enriched in BC and micropollutants, making this PM more relevant in terms of PM toxicity per unit mass because of its higher oxidative potential and smaller size. This indicates the potential for particles with high surface reactivity and adsorbed toxic molecules to deposit in the deepest tracts of the respiratory system (more easily with decreasing size) [22]. Additionally, non-tailpipe emissions (pollutants emitted from evaporative emissions of fuel, resuspension of dust, wear of brakes and tires, and abrasion of road surfaces) are reported to exert some relevant effects on health [22].

TRAP is associated, with children, with low birth weight, Intrauterine Growth Restriction (IUGR), preterm birth, asthma exacerbation, chronic asthma, and lower respiratory infections [23]. Moreover, TRAP exposure in pediatric patients is associated with metabolic syndrome (glucose deregulation, blood pressure), oxidative stress [41], and atherosclerosis [24].

2. Health Outcomes: Effects on Childhood Respiratory Health

Air pollution can cause respiratory diseases and affect lung function and growth, depending on the type of pollutant, its concentration, and its dimensions [25]. Pollutants can harm children's respiratory health through various mechanisms, including local and systemic inflammation, oxidative stress damage, immune response modulation, and genetic changes [26][27]. Children are particularly susceptible to the adverse effects induced by air pollution because (1) their respiratory and immune systems are not fully developed [28]; (2) their airway epithelium is more permeable to pollutants [29]; (3) they have higher resting metabolic rate, higher respiratory rate and a higher rate of oxygen consumption because they are growing and because they have a larger surface area per unit body weight; (4) they also have a smaller lung surface area per kilogram, so breathing air reaches a relatively smaller area of the lung; (5) they have smaller airways, so pollutants' irritation can cause a potentially remarkable obstruction; finally, (6) obese children have a higher respiratory rate that causes a higher deposition of fine particles in the lungs; consequently, children with higher body mass indexes might be more vulnerable to air pollution damage [29].

To study the impact of acute exposure to pollutants on the developing lung, Fanucchi and colleagues examined the postnatal lung morphogenesis and function of a group of infant monkeys—which have human-like airway structure and postnatal lung development—subjected to cyclic exposure to O₃. Compared with controls, O₃-exposed monkeys had markedly increased airway resistance at baseline, fewer airway generations, hyperplastic bronchiolar epithelium, and impaired smooth muscle in the terminal and respiratory bronchioles. These results suggest that episodic exposure to environmental pollutants alters postnatal tracheobronchial airway morphogenesis and development [30].

2.1. Local and Systemic Inflammation and Oxidative Stress Damage

Air pollutants trigger pulmonary oxidative stress and inflammation pathways [31]. The defense of the respiratory system against inhaled toxicants consists of innate mechanisms such as aerodynamic filtration, mucociliary clearance, particle transport, and detoxification by alveolar macrophages, as well as innate and acquired systemic antiviral immunity [32]. In experimental models, some of these functions, such as pulmonary inflammation, chemokine expression, and airway hyper-responsiveness, appear to be modified by exposure to pollutants. For example, phagocytosis of pollutant particles by alveolar macrophages produces inflammatory cytokines and chemokines, which are then released into the systemic circulation [33], causing local and systemic inflammation.

The pro-inflammatory state promoted by pollutants is primarily due to the oxidative stress resulting from the production of ROS and the reduction of endogenous antioxidants. Oxidative stress can directly damage cellular proteins and DNA,

create neoantigens by protein oxidation, and activate pro-inflammatory signaling cascades, such as NF- κ B and MAPK pathways. Oxidative stress affects Antigen Presenting Cells (APCs) function and co-stimulation, T helper (Th) lymphocyte imbalance favoring Th2 response, and interferon (IFN)-gamma production [34]. Alveolar macrophages react to exposure by producing ROS, nitrogen species and releasing tumor necrosis factor (TNF)- α and interleukin (IL)-1, which contribute to an imbalance between oxidants and antioxidants [25]. Then free radicals attack local tissue components, causing cellular damage [13].

In response to the inflammatory state, children chronically exposed to high levels of air pollutants show structural changes in the airway mucosa. A study by Calderón-Garcidueñas and colleagues compared by electron microscopy the nasal epithelium of children living in a polluted city with that of peers living in a city with low levels of air pollution [35]. The first group's nasal epithelium revealed metaplastic cells, ciliary dyskinesia, epithelial junction deficiencies, and PM deposited in intercellular spaces. These modifications might result in a lower capacity to protect the lower respiratory tract and make the distal airways more vulnerable to pollutants. O₃, PM, and aldehydes were identified as the most responsible pollutants [35].

Long-term exposure to pollutants leads to a loss of lung function due to progressive airway remodeling and fibrosis of the lung due to oxidative stress, according to several animal model studies [33][36]. Moreover, oxidative stress damage seems to be related to the primary development of asthma and chronic obstructive pulmonary disease (COPD) [31].

2.2. Immune Response Modulation

Cell studies and animal models proved that air pollution could affect both innate and adaptive immune systems (**Table 1**) because the respiratory tract represents the first interface between the immune system and the environment, reducing their ability to limit the spread of infectious agents.

Table 1. Effects of air pollution on the immune system. O₃: Ozone; NO₂: Nitrogen Dioxide; PM: Particulate Matter; PM_{2.5}: Particulate Matter with an aerodynamic diameter of 2.5 μ m; SO₂: Sulphur Dioxide; ROS: Reactive Oxygen Species; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; ICAM-1: Intercellular Adhesion Molecule-1; IFN: interferon; IL: Interleukin; TNF- α : Tumor Necrosis Factor Alfa; \uparrow increase; \downarrow decrease.

		\uparrow Pro-inflammatory cytokines: IL-1, IL-6, TNF α , GMCSF (O ₃ , NO ₂ , PM) \uparrow ICAM-1 expression (NO ₂) \uparrow Leukotriene C4 (NO ₂)	
Innate Immune System	Epithelial cells		
	Monocytes/Macrophages	\uparrow Carbon loading; \downarrow Clearance capacity and phagocytosis; \uparrow Pro-inflammatory cytokine (PM)	
	Neutrophils		\uparrow Migration and activation (PM, O ₃ , NO ₂)
	Eosinophils		\uparrow Migration and activation (SO ₂ , PM _{2.5})
Adaptive Immune System	Immune tolerance		\downarrow T reg function; neo-antigens (ROS); \uparrow antigens immunogenicity (PM); \uparrow immunogenicity of antigens (PM)
	B cells		\downarrow IgA and \uparrow IgE (PM _{2.5})
	T cells		\downarrow Th1 and \uparrow Th2 (NO ₂ , PM); \uparrow Th17 response (PM); Dysregulated IFN-gamma and IL-17A production (PM)

Air pollutants damage epithelial cells, induce granulocyte and mast cell migration and activation, enhance pro-inflammatory cytokines (IL-1, IL-6, and TNF) production, and reduce macrophage phagocytosis and clearance. Pollutants stimulate a pro-inflammatory immune response by triggering several pathways, including Toll-Like Receptors (TLRs), which detect pathogen-associated molecular patterns of infectious microorganisms and analogous injurious triggers, like pollutants. PM, for example, can activate the TLRs pathway because they frequently transport microbial molecules such as lipopolysaccharide and fungal spores, as well as cellular damage products like oxidized phospholipids and nucleic acids [34].

Pollutants enhance the Th2 immune response, IgE, IL-5, IL-13, and leukotriene production, resulting in asthma and allergies exacerbation and an inappropriate antimicrobial environment. Air pollution can also impair anti-viral immune responses by suppressing the Th1 pathway, deregulating IFN-gamma, and reducing macrophage phagocytosis and clearance capacity. For instance, NO₂ increases Th2 cytokines and ICAM-1 (Intercellular Adhesion Molecule-1) epithelium

expression, facilitating respiratory infections since ICAM-1 is a receptor for Rhinovirus and respiratory syncytial virus (RSV) [34].

Pollutants can reduce immune tolerance because pro-inflammatory cytokines reduce regulatory T cell responses. Protein oxidation leads to neo-antigen formation, triggering autoinflammatory and autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes mellitus. PM is proven to act as an adjuvant on APCs, increasing the immunogenicity of antigens [34].

2.3. Genetic and Epigenetic Changes

Epigenetic changes regulate the expression of many genes without changing the DNA sequence itself, including those involved in the inflammatory immune response and lung growth. Environmental factors can alter epigenetic states, and a growing number of studies are looking into the effects of air pollutants on epigenetic mechanisms. DNA methylation, which involves the attachment of a methyl group to the C5 position of cytosine to form 5-methylcytosine, is a crucial epigenetic mechanism that modulates gene expression [37] and seems to act as a mediator between air pollutants and their effects on the respiratory system [38].

The effects of air pollution on DNA methylation have been investigated both in the prenatal and postnatal periods. Several studies analyzed samples obtained from the placenta or cord blood and showed that environmental exposure to air pollutants during pregnancy has a significant impact on DNA methylation in newborns [39], with particular attention to the effects of NO₂ [40], PM_{2.5} [41], and PM₁₀ [42]. In addition, they report differences related to the type of pollutant and the stage of development upon exposure, e.g., PM has been shown to have a more significant impact in the initial period of gestation [42][43]; NO₂ exposure was associated with DNA methylation changes in mitochondria-related genes and antioxidant defense pathways [40].

A systematic review conducted by Isaevska and colleagues showed that prenatal exposure to different pollutants (PM, NO₂, O₃, CO, SO₂, VOC, BC, EC, OC, and PAH) is associated with global methylation loss, telomere reduction, and epigenetic alterations involving genes related to oxidative stress response, mitochondrial function, inflammation, and fetal growth [44].

Exposure to air pollutants may also lead to epigenetic alterations of genes related to the inflammatory pathway [45]. For example, a study on mice that combined inhaled diesel exhaust particles and allergen exposure found changes in the methylation of Th2 cytokines and IgE production in vivo, implying an underlying mechanism that may contribute to the development of asthma [46]. For instance, in infants with severe bronchiolitis, microRNA post-transcriptional regulation could explain the connection between pollution and asthma [47]. Furthermore, DNA methylation plays an essential role in TRAP-induced asthma [48].

3. Focus on Respiratory Diseases

Children's respiratory health is the result of the interaction between environmental influences and genetic susceptibility factors [49]. The respiratory system is the principal interface between air and the organism, so it is a primary target for toxicants such as air pollutants [50]. In recent years, several outdoor air pollutants have been consistently linked to developing and exacerbating pediatric respiratory disorders such as asthma, bronchiolitis, and respiratory infections.

3.1. Asthma

Asthma is the most common chronic respiratory disease in children, and its development seems to result from the interaction between genetic predisposition and environmental factors [51]. Childhood exposure to outdoor air pollution may play an essential role in exacerbating and the onset of chronic asthma [22][52]. A systematic review and meta-analysis by Khreis et al. [53] highlighted the connection between exposure to TRAP and the development of asthma in children. Another systematic review and meta-analysis by Bowatte and colleagues [54] found a link between TRAP exposure and an increased risk of sensitization to common allergens in pediatric patients. An association has been demonstrated between SO₂, NO₂, and PM_{2.5} and a significant decrease in small airway function and an increase in airway oxidative stress in asthmatic children [55].

NO₂ is a significant trigger for pollution-induced asthma exacerbations, mainly because it increases leukotriene production [56]. In addition, several observational and epidemiological studies have shown that air pollutants, mainly O₃, SO₂, NO₂, and UFPs [57], are associated with acute asthma exacerbations [58], and the risk is higher in children

already affected by chronic asthma [59][60][61][62]. Likewise, a meta-analysis showed that exposure to ambient pollutants (especially PM_{2.5}) increases the risk of asthma onset in healthy young children [54].

Furthermore, some studies have shown that the anti-pollution measures adopted during the SARS-CoV-2 pandemic and restrictions on the circulation of motor vehicles during public events can lead to a reduction in the primary environmental pollutants and a consequent decrease in emergency department visits due to asthmatic exacerbations [63][64].

3.2. Bronchiolitis

Bronchiolitis is the most common cause of lower respiratory infection and hospitalization in children younger than one year, and it is characterized by airway inflammation and obstruction of the lower respiratory tract [65][66]. Several studies have investigated the possible relationship between exposure to air pollutants and the incidence and severity of bronchiolitis due to the pollutants' effects on the immune system and viral life cycles, especially that of RSV. A study conducted on a population of 18,595 infants highlighted that sub-chronic (the month preceding hospitalization) and chronic (lifetime) exposures to PM_{2.5} are significantly associated with an increased risk of hospitalization for bronchiolitis and that the risk depends on the concentration of PM (hospitalization risk nearly increased to 9% for each 10 µg/m³ increase in PM_{2.5}) [67]. Another study discovered a link between the risk of hospitalization for RSV bronchiolitis and PM₁₀ exposure, particularly in the two previous weeks [68], because this pollutant can be associated with viral particles and activate endocytic pathways, facilitating viral entry [69]. PM can also increase viral survival and inflammation, inducing IL-6 and IL-8 synthesis [69]. UFPs can increase viral replication and inflammation, enhancing nerve growth factor and chemokine production [69]. Likewise, a study conducted in Hong Kong on 29,688 infants referred to the hospital for acute bronchiolitis showed a link between an increased risk of hospitalization, NO₂ and PM₁₀ exposure, and high temperature, highlighting the combined effect of meteorological factors and air pollutants [18]. PM_{2.5} and PM₁₀ levels are significantly associated with the severity of bronchiolitis [70]. RSV bronchiolitis incidence has a significant correlation with NO, NO₂, PM₁₀, and PM_{2.5} [71][72].

3.3. Respiratory Infections

Exposure to air pollution, especially PM, seems to be linked to upper and lower respiratory infections in children of any age [73][74], likely because polluted air deregulates anti-viral immune responses [56]. These effects disproportionately affect children with other respiratory disease, like asthma [75]. Upper respiratory infections are significantly associated with PM_{2.5}, PM₁₀, SO₂, NO₂, and CO [76], and childhood NO₂ exposure has been linked to persistent cough [77]. A meta-analysis of ten European birth cohorts found relevant associations between air pollution exposure (NO₂, OR 1.47; PM₁₀, OR 1.77; PM_{2.5}, OR 4.06) and pneumonia and identified the first year of life as the most vulnerable period [78]. Glick et al. demonstrated that greater O₃ and PM_{2.5} were associated with more severe pneumonia [79]. A study conducted in Indonesia found that exposure to NO₂ increases children's risk of developing an acute respiratory infection [80]. This evidence is confirmed by other studies, such as the one conducted by Darrow and colleagues, who observed independent effects of O₃ and primary traffic pollutants (NO₂, CO, and the elemental carbon fraction of PM_{2.5}) on hospital admissions for pneumonia and upper respiratory infections among children between 0 and 4 years old; moreover, the study highlights the carbon component in the PM_{2.5} mixture as particularly damaging for respiratory infections in children [81]. Exposure to PM has been shown to facilitate *Streptococcus pneumoniae* infections by improving its ability to adhere to lower airway cells and impair bacterial clearance. However, the role of low PM concentrations, as commonly found in high-income urban environments, on pneumococcal pneumonia is still unclear [82]. A study has shown that PM₁₀ favors the replication of RNA viruses through the inhibition of innate immunity and the upregulation of several genes related to metabolic pathways, supporting the idea that PM₁₀ exposure is associated with increased severity of pulmonary infections [83].

A Chinese study also shows that exposure to highly polluted areas increases the risk of tuberculosis, especially in children exposed to PM₁₀, SO₂, and NO₂ [84].

Furthermore, several studies conducted in adults have linked long-term exposure to air pollutants to novel human coronavirus disease 2019 (COVID-19) infection and mortality rates [85][86]. In particular, a recent English study [87] found that an increase of 1 µg/m³ in PM_{2.5} and PM₁₀ levels increases infection risk by 12% and 8%, respectively, and an increase of 1 µg/m³ in NO and NO₂ levels spreads COVID-19-related mortality risk by 1.5% and 2.5%, respectively. Although the underlying mechanism is unclear, several hypotheses have been proposed, including the inflammatory state promoted by long-term exposure to pollutants and inhibition of the antimicrobial response. However, the relative weight of air pollution in increasing cases of SARS-CoV-2 infection has yet to be definitively determined, due to the several confounding factors and the numerous variables to take into consideration, such as

particles' size and chemical composition, the population's age distribution, density, and social habits, the restrictive measures applied, and the weather conditions [88].

Because of their tiny size, large surface area, and high density, deposition, and penetration, UFPs may be more toxic than larger air pollutants. UFPs are associated with increased access to the emergency department for main respiratory diseases, such as pneumonia (RR 1.2; IQR 1.04–1.38), bronchitis (RR 1.17; IQR 1.03–1.33), and upper respiratory infections (RR 1.14; IQR 1.02–1.28) [57]. The relative risk of such exacerbations is positively correlated with UFP concentration [57].

3.4. Lifelong Effects on Respiratory Function

Injuries to the developing lung, both during pregnancy and in the first years of life, have been shown to have long-term effects on the respiratory system. In the long term, pollution can damage lung function, affecting patterns of growth and causing early function decline, as measured by forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) [89]. A study by Gauderman et al. [90] followed 1759 patients over eight years and demonstrated that lung development (assessed by measuring FVC, FEV₁, and maximum mid-expiratory flow, known as MMEF) was reduced in children exposed to higher levels of air pollution. These deficits have been associated with NO₂, SO₂, PM_{2.5}, and EC, and the authors hypothesized that the main mechanisms involved were a reduction in alveolar growth and airway inflammation. Molter et al. [91] demonstrated that long-term exposure to PM₁₀ and NO₂ is associated with reductions in lung volume growth.

Similarly, pre- and post-natal PM_{2.5} exposure can decrease the number of alveoli in mice [92]. O₃ exposure is associated with acute lung function reduction in healthy and asthmatic children, and toxicologic studies involving animals show that O₃ negatively affects lung development. Similarly, acute and chronic NO₂ exposure can impair lung function [16]. Long-term PM_{2.5} exposure is associated with slower lung function growth in children; on the contrary, the evidence for PM₁₀ is less robust due to the lower availability of long-term models [93]. Some studies even failed to find an association between long-term PM₁₀ exposure and child lung function [94][95].

The exposure during lung development seems to be associated with a negative impact on lung function that may ultimately result in COPD. Low childhood lung function is a risk factor for developing COPD or asthma-COPD overlap syndrome in adulthood, according to a study of 1389 patients who underwent spirometry in childhood and then in adulthood [96]. The main reasons why exposure to air pollutants in early life can lead to COPD in adults are (1) poor lung function; (2) recurrent respiratory illness [97][98]; (3) pro-inflammatory changes in the immune system (enhancement of Th2 and Th17 responses); and (4) dysregulated anti-viral immune responses [56]. Moreover, air pollution is responsible for short stature and stunting, which harm lung development [99].

4. Prenatal Exposure

The development of the human respiratory system is a complex process that begins early during the embryonic stage and lasts long after birth, with complete alveoli development occurring in adolescence. Growth and transcription factors and their interactions with the extracellular matrix coordinate all the steps in lung morphogenesis. During its differentiation and development, the lung is highly vulnerable to exposure to environmental pollutants [91]. Recent evidence has shown that children are harmed not only by direct exposure to pollutants but also by in-utero exposure, which can cause alterations in lung development (pollutants can affect cellular differentiation, morphogenesis, and vascularization) and increase the risk of respiratory illness from childhood into adulthood [15][61]. Most non-human evidence shows that prenatal exposure to PM_{2.5} and PM_{0.1} alters lung and immune system development, increasing the risk of acute and chronic pulmonary diseases (e.g., respiratory infections and asthma, respectively).

Epidemiological studies suggest maternal exposure to environmental hazards, such as combustion-generated PM, is associated with an increased childhood asthma incidence [86]. According to Wang and colleagues [100], pollution appears to cause systemic oxidative stress in pregnant mice and inhibit Th1 lung maturation, leading to asthma in the offspring. The retrospective cohort study by Zhang et al. [87] highlighted strong evidence that early-life exposure to submicrometric PM increases the risk of asthma among preschool children. All size fractions of PM can contribute to asthma, but it was especially notable for PM₁, and the effect of prenatal exposure to PM₁ was more pronounced in males [88]. The study performed by Lavigne et al. found that exposure to UFPs during the second trimester of pregnancy was associated with an increased risk of childhood asthma [85].

Air pollution, particularly TRAP, is recognized to be an important predisposing factor for childhood pneumonia, and the retrospective cohort study performed by Lu and colleagues highlighted that preconception (up to one year before

conception) and prenatal exposure to industrial air pollution play a role in the onset of childhood pneumonia [101]. Similarly, a Spanish study reveals that exposure to NO₂ during pregnancy is associated with an increased risk of respiratory infections in infants [73].

The study by Latzin et al. discovered that prenatal exposure to outdoor air pollution is associated with airway inflammation (NO₂) and higher ventilatory demand (PM₁₀) [81]. Furthermore, maternal exposure to ambient TRAP, especially NO₂, PM₁₀, and PM_{2.5}, was also proven to harm children's lung function and development [61][67]. In addition, prenatal exposure to air pollution is associated with reduced fetal lung growth [16][102] and lower levels of forced mid-expiratory flow (FEF_{25–75}) and FEV₁ [103][104].

Air pollution exposure during pregnancy and after birth can eventually alter the adult lung function trajectory, leading to multimorbidity [105].

Moreover, several meta-analyses show that prenatal exposure to air pollution increases the risk of intrauterine growth restriction and low-birth-weight offspring [106][107], mainly due to PM_{2.5}, PM₁₀, NO₂, and O₃ exposure both in the first and last month of pregnancy [108]. In addition, maternal outdoor air pollution exposure is also associated with the risk of very early and early preterm births [109], which can result in bronchopulmonary dysplasia.

References

1. Schwartz, J. Air Pollution and Children's Health. *Pediatrics* 2004, 113, 1037–1043.
2. Ayres, J.G.; Borm, P.; Cassee, F.R.; Castranova, V.; Donaldson, K.; Ghio, A.; Harrison, R.M.; Hider, R.; Kelly, F.; Kooter, I.M.; et al. Evaluating the Toxicity of Airborne Particulate Matter and Nanoparticles by Measuring Oxidative Stress Potential—A Workshop Report and Consensus Statement. *Inhal. Toxicol.* 2008, 20, 75–99.
3. Costabile, F.; Gualtieri, M.; Ancona, C.; Canepari, S.; Decesari, S. Ultrafine Particle Features Associated with Pro-Inflammatory and Oxidative Responses: Implications for Health Studies. *Atmosphere* 2020, 11, 414.
4. Leung, S.Y.; Lau, S.Y.F.; Kwok, K.L.; Mohammad, K.N.; Chan, P.K.S.; Chong, K.C. Short-Term Association among Meteorological Variation, Outdoor Air Pollution and Acute Bronchiolitis in Children in a Subtropical Setting. *Thorax* 2021, 76, 360–369.
5. Andersen, Z.J.; Loft, S.; Ketzel, M.; Stage, M.; Scheike, T.; Hermansen, M.N.; Bisgaard, H. Ambient Air Pollution Triggers Wheezing Symptoms in Infants. *Thorax* 2008, 63, 710–716.
6. Johns, D.O.; Linn, W.S. A Review of Controlled Human SO₂ Exposure Studies Contributing to the US EPA Integrated Science Assessment for Sulfur Oxides. *Inhal. Toxicol.* 2011, 23, 33–43.
7. Lelieveld, J.; Evans, J.S.; Fnais, M.; Giannadaki, D.; Pozzer, A. The Contribution of Outdoor Air Pollution Sources to Premature Mortality on a Global Scale. *Nature* 2015, 525, 367–371.
8. Guarnieri, M.; Balmes, J.R. Outdoor Air Pollution and Asthma. *Lancet* 2014, 383, 1581–1592.
9. Fuzzi, S.; Baltensperger, U.; Carslaw, K.; Decesari, S.; Denier van der Gon, H.; Facchini, M.C.; Fowler, D.; Koren, I.; Langford, B.; Lohmann, U.; et al. Particulate Matter, Air Quality and Climate: Lessons Learned and Future Needs. *Atmos. Chem. Phys.* 2015, 15, 8217–8299.
10. WHO Global Air Quality Guidelines: Particulate Matter (PM_{2.5} and PM₁₀), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. Available online: <https://www.who.int/publications-detail-redirect/9789240034228> (accessed on 11 April 2022).
11. Mann, J.K.; Lutzker, L.; Holm, S.M.; Margolis, H.G.; Neophytou, A.M.; Eisen, E.A.; Costello, S.; Tyner, T.; Holland, N.; Tindula, G.; et al. Traffic-Related Air Pollution Is Associated with Glucose Dysregulation, Blood Pressure, and Oxidative Stress in Children. *Environ. Res.* 2021, 195, 110870.
12. Nel, A.; Xia, T.; Mäddler, L.; Li, N. Toxic Potential of Materials at the Nanolevel. *Science* 2006, 311, 622–627.
13. Kelly, F.J. Oxidative Stress: Its Role in Air Pollution and Adverse Health Effects. *Occup. Environ. Med.* 2003, 60, 612–616.
14. Shiraiwa, M.; Ueda, K.; Pozzer, A.; Lammel, G.; Kampf, C.J.; Fushimi, A.; Enami, S.; Arangio, A.M.; Fröhlich-Nowoisky, J.; Fujitani, Y.; et al. Aerosol Health Effects from Molecular to Global Scales. *Environ. Sci. Technol.* 2017, 51, 13545–13567.
15. Kelly, F.J.; Fussell, J.C. Size, Source and Chemical Composition as Determinants of Toxicity Attributable to Ambient Particulate Matter. *Atmos. Environ.* 2012, 60, 504–526.

16. Carbone, C.; Decesari, S.; Mircea, M.; Giulianelli, L.; Finessi, E.; Rinaldi, M.; Fuzzi, S.; Marinoni, A.; Duchi, R.; Perrino, C.; et al. Size-Resolved Aerosol Chemical Composition over the Italian Peninsula during Typical Summer and Winter Conditions. *Atmos. Environ.* 2010, 44, 5269–5278.
17. Paglione, M.; Gilardoni, S.; Rinaldi, M.; Decesari, S.; Zanca, N.; Sandrini, S.; Giulianelli, L.; Bacco, D.; Ferrari, S.; Poluzzi, V.; et al. The Impact of Biomass Burning and Aqueous-Phase Processing on Air Quality: A Multi-Year Source Apportionment Study in the Po Valley, Italy. *Atmos. Chem. Phys.* 2020, 20, 1233–1254.
18. Janssen, N.A.H.; Hoek, G.; Simic-Lawson, M.; Fischer, P.; van Bree, L.; ten Brink, H.; Keuken, M.; Atkinson, R.W.; Anderson, H.R.; Brunekreef, B.; et al. Black Carbon as an Additional Indicator of the Adverse Health Effects of Airborne Particles Compared with PM₁₀ and PM_{2.5}. *Environ. Health Perspect.* 2011, 119, 1691–1699.
19. Künzi, L.; Krapf, M.; Daher, N.; Dommen, J.; Jeannet, N.; Schneider, S.; Platt, S.; Slowik, J.G.; Baumlin, N.; Salathe, M.; et al. Toxicity of Aged Gasoline Exhaust Particles to Normal and Diseased Airway Epithelia. *Sci. Rep.* 2015, 5, 11801.
20. Saffari, A.; Daher, N.; Shafer, M.M.; Schauer, J.J.; Sioutas, C. Global Perspective on the Oxidative Potential of Airborne Particulate Matter: A Synthesis of Research Findings. *Environ. Sci. Technol.* 2014, 48, 7576–7583.
21. Robinson, A.L.; Donahue, N.M.; Shrivastava, M.K.; Weitkamp, E.A.; Sage, A.M.; Grieshop, A.P.; Lane, T.E.; Pierce, J.R.; Pandis, S.N. Rethinking Organic Aerosols: Semivolatile Emissions and Photochemical Aging. *Science* 2007, 315, 1259–1262.
22. Daellenbach, K.R.; Uzu, G.; Jiang, J.; Cassagnes, L.-E.; Leni, Z.; Vlachou, A.; Stefenelli, G.; Canonaco, F.; Weber, S.; Segers, A.; et al. Sources of Particulate-Matter Air Pollution and Its Oxidative Potential in Europe. *Nature* 2020, 587, 414–419.
23. Boogaard, H.; Patton, A.P.; Atkinson, R.W.; Brook, J.R.; Chang, H.H.; Crouse, D.L.; Fussell, J.C.; Hoek, G.; Hoffmann, B.; Kappeler, R.; et al. Long-Term Exposure to Traffic-Related Air Pollution and Selected Health Outcomes: A Systematic Review and Meta-Analysis. *Environ. Int.* 2022, 164, 107262.
24. Farzan, S.F.; Habre, R.; Danza, P.; Lurmann, F.; Gauderman, W.J.; Avol, E.; Bastain, T.; Hodis, H.N.; Breton, C. Childhood Traffic-Related Air Pollution and Adverse Changes in Subclinical Atherosclerosis Measures from Childhood to Adulthood. *Environ. Health* 2021, 20, 44.
25. Bălă, G.-P.; Râmnoveanu, R.-M.; Tudorache, E.; Motișan, R.; Oancea, C. Air Pollution Exposure-the (in)Visible Risk Factor for Respiratory Diseases. *Environ. Sci. Pollut. Res. Int.* 2021, 28, 19615–19628.
26. Johansson, K.A.; Balmes, J.R.; Collard, H.R. Air Pollution Exposure: A Novel Environmental Risk Factor for Interstitial Lung Disease? *Chest* 2015, 147, 1161–1167.
27. Havet, A.; Li, Z.; Zerimech, F.; Sanchez, M.; Siroux, V.; Le Moual, N.; Brunekreef, B.; Künzli, N.; Jacquemin, B.; Varraso, R.; et al. Does the Oxidative Stress Play a Role in the Associations between Outdoor Air Pollution and Persistent Asthma in Adults? Findings from the EGEA Study. *Environ. Health* 2019, 18, 90.
28. Oliveira, M.; Slezakova, K.; Delerue-Matos, C.; Pereira, M.C.; Morais, S. Children Environmental Exposure to Particulate Matter and Polycyclic Aromatic Hydrocarbons and Biomonitoring in School Environments: A Review on Indoor and Outdoor Exposure Levels, Major Sources and Health Impacts. *Environ. Int.* 2019, 124, 180–204.
29. Salvi, S. Health Effects of Ambient Air Pollution in Children. *Paediatr. Respir. Rev.* 2007, 8, 275–280.
30. Fanucchi, M.V.; Plopper, C.G.; Evans, M.J.; Hyde, D.M.; Van Winkle, L.S.; Gershwin, L.J.; Schelegle, E.S. Cyclic Exposure to Ozone Alters Distal Airway Development in Infant Rhesus Monkeys. *Am. J. Physiol. Lung Cell Mol. Physiol.* 2006, 291, L644–L650.
31. Anderson, J.O.; Thundiyil, J.G.; Stolbach, A. Clearing the Air: A Review of the Effects of Particulate Matter Air Pollution on Human Health. *J. Med. Toxicol.* 2012, 8, 166–175.
32. Lambert, A.L.; Mangum, J.B.; DeLorme, M.P.; Everitt, J.I. Ultrafine Carbon Black Particles Enhance Respiratory Syncytial Virus-Induced Airway Reactivity, Pulmonary Inflammation, and Chemokine Expression. *Toxicol. Sci.* 2003, 72, 339–346.
33. Gangwar, R.S.; Bevan, G.H.; Palanivel, R.; Das, L.; Rajagopalan, S. Oxidative Stress Pathways of Air Pollution Mediated Toxicity: Recent Insights. *Redox Biol.* 2020, 34, 101545.
34. 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.
35. Calderón-Garcidueñas, L.; Valencia-Salazar, G.; Rodríguez-Alcaraz, A.; Gambling, T.M.; García, R.; Osnaya, N.; Villarreal-Calderón, A.; Devlin, R.B.; Carson, J.L. Ultrastructural Nasal Pathology in Children Chronically and Sequentially Exposed to Air Pollutants. *Am. J. Respir. Cell Mol. Biol.* 2001, 24, 132–138.

36. Sunil, V.R.; Vayas, K.N.; Massa, C.B.; Gow, A.J.; Laskin, J.D.; Laskin, D.L. Ozone-Induced Injury and Oxidative Stress in Bronchiolar Epithelium Are Associated with Altered Pulmonary Mechanics. *Toxicol. Sci.* 2013, 133, 309–319.
37. Moore, L.D.; Le, T.; Fan, G. DNA Methylation and Its Basic Function. *Neuropsychopharmacology* 2013, 38, 23–38.
38. Suhaimi, N.F.; Jalaludin, J.; Abu Bakar, S. Deoxyribonucleic Acid (DNA) Methylation in Children Exposed to Air Pollution: A Possible Mechanism Underlying Respiratory Health Effects Development. *Rev. Environ. Health* 2021, 36, 77–93.
39. Rider, C.F.; Carlsten, C. Air Pollution and DNA Methylation: Effects of Exposure in Humans. *Clin. Epigenetics* 2019, 11, 131.
40. Gruzieva, O.; Xu, C.-J.; Breton, C.V.; Annesi-Maesano, I.; Antó, J.M.; Auffray, C.; Ballereau, S.; Bellander, T.; Bousquet, J.; Bustamante, M.; et al. Epigenome-Wide Meta-Analysis of Methylation in Children Related to Prenatal NO₂ Air Pollution Exposure. *Environ. Health Perspect.* 2017, 125, 104–110.
41. Maghbooli, Z.; Hossein-Nezhad, A.; Adabi, E.; Asadollah-Pour, E.; Sadeghi, M.; Mohammad-Nabi, S.; Zakeri Rad, L.; Malek Hosseini, A.-A.; Radmehr, M.; Faghihi, F.; et al. Air Pollution during Pregnancy and Placental Adaptation in the Levels of Global DNA Methylation. *PLoS ONE* 2018, 13, e0199772.
42. Cai, J.; Zhao, Y.; Liu, P.; Xia, B.; Zhu, Q.; Wang, X.; Song, Q.; Kan, H.; Zhang, Y. Exposure to Particulate Air Pollution during Early Pregnancy Is Associated with Placental DNA Methylation. *Sci. Total Environ.* 2017, 607–608, 1103–1108.
43. Janssen, B.G.; Godderis, L.; Pieters, N.; Poels, K.; Kiciński, M.; Cuypers, A.; Fierens, F.; Penders, J.; Plusquin, M.; Gyselaers, W.; et al. Placental DNA Hypomethylation in Association with Particulate Air Pollution in Early Life. *Part. Fibre Toxicol.* 2013, 10, 22.
44. Isaevska, E.; Moccia, C.; Asta, F.; Cibella, F.; Gagliardi, L.; Ronfani, L.; Rusconi, F.; Stazi, M.A.; Richiardi, L. Exposure to Ambient Air Pollution in the First 1000 Days of Life and Alterations in the DNA Methylome and Telomere Length in Children: A Systematic Review. *Environ. Res.* 2021, 193, 110504.
45. Veras, M.M.; de Oliveira Alves, N.; Fajersztajn, L.; Saldiva, P. Before the First Breath: Prenatal Exposures to Air Pollution and Lung Development. *Cell Tissue Res.* 2017, 367, 445–455.
46. Liu, J.; Ballaney, M.; Al-alem, U.; Quan, C.; Jin, X.; Perera, F.; Chen, L.-C.; Miller, R.L. Combined Inhaled Diesel Exhaust Particles and Allergen Exposure Alter Methylation of T Helper Genes and IgE Production in Vivo. *Toxicol. Sci.* 2008, 102, 76–81.
47. Makrinioti, H.; Camargo, C.A.; Zhu, Z.; Freishtat, R.J.; Hasegawa, K. Air Pollution, Bronchiolitis, and Asthma: The Role of Nasal MicroRNAs. *Lancet Respir. Med.* 2022, 10, 733–734.
48. Ji, H.; Biagini Myers, J.M.; Brandt, E.B.; Brokamp, C.; Ryan, P.H.; Khurana Hershey, G.K. Air Pollution, Epigenetics, and Asthma. *Allergy Asthma Clin. Immunol.* 2016, 12, 51.
49. Lin, W.-W.; Chen, Z.-X.; Kong, M.-L.; Xie, Y.-Q.; Zeng, X.-W. Air Pollution and Children's Health in Chinese. *Adv. Exp. Med. Biol.* 2017, 1017, 153–180.
50. World Health Organization; Regional Office for Europe & European Centre for Environment and Health. Effects of Air Pollution on Children's Health and Development: A Review of the Evidence; WHO Regional Office for Europe: Copenhagen, Denmark, 2005.
51. Toskala, E.; Kennedy, D.W. Asthma Risk Factors. *Int. Forum Allergy Rhinol.* 2015, 5 (Suppl. S1), S11–S16.
52. Jung, K.H.; Hsu, S.-I.; Yan, B.; Moors, K.; Chillrud, S.N.; Ross, J.; Wang, S.; Perzanowski, M.S.; Kinney, P.L.; Whyatt, R.M.; et al. Childhood Exposure to Fine Particulate Matter and Black Carbon and the Development of New Wheeze Between Ages 5 and 7 In an Urban Prospective Cohort. *Environ. Int.* 2012, 45, 44–50.
53. Khreis, H.; Kelly, C.; Tate, J.; Parslow, R.; Lucas, K.; Nieuwenhuijsen, M. Exposure to Traffic-Related Air Pollution and Risk of Development of Childhood Asthma: A Systematic Review and Meta-Analysis. *Environ. Int.* 2017, 100, 1–31.
54. Bowatte, G.; Lodge, C.; Lowe, A.J.; Erbas, B.; Perret, J.; Abramson, M.J.; Matheson, M.; Dharmage, S.C. The Influence of Childhood Traffic-Related Air Pollution Exposure on Asthma, Allergy and Sensitization: A Systematic Review and a Meta-Analysis of Birth Cohort Studies. *Allergy* 2015, 70, 245–256.
55. Liu, L.; Poon, R.; Chen, L.; Frescura, A.-M.; Montuschi, P.; Ciabattini, G.; Wheeler, A.; Dales, R. Acute Effects of Air Pollution on Pulmonary Function, Airway Inflammation, and Oxidative Stress in Asthmatic Children. *Environ. Health Perspect.* 2009, 117, 668–674.
56. Li, H.; Li, X.; Zheng, H.; Liu, L.; Wu, Y.; Zhou, Y.; Meng, X.; Hong, J.; Cao, L.; Lu, Y.; et al. Ultrafine Particulate Air Pollution and Pediatric Emergency-Department Visits for Main Respiratory Diseases in Shanghai, China. *Sci. Total Environ.* 2021, 775, 145777.

57. Fuertes, E.; Heinrich, J. The Influence of Childhood Traffic-Related Air Pollution Exposure on Asthma, Allergy and Sensitization. *Allergy* 2015, 70, 1350–1352.
58. White, M.C.; Etzel, R.A.; Wilcox, W.D.; Lloyd, C. Exacerbations of Childhood Asthma and Ozone Pollution in Atlanta. *Environ. Res.* 1994, 65, 56–68.
59. Smargiassi, A.; Kosatsky, T.; Hicks, J.; Plante, C.; Armstrong, B.; Villeneuve, P.J.; Goudreau, S. Risk of Asthmatic Episodes in Children Exposed to Sulfur Dioxide Stack Emissions from a Refinery Point Source in Montreal, Canada. *Environ. Health Perspect.* 2009, 117, 653–659.
60. Gaffin, J.M.; Hauptman, M.; Petty, C.R.; Sheehan, W.J.; Lai, P.S.; Wolfson, J.M.; Gold, D.R.; Coull, B.A.; Koutrakis, P.; Phipatanakul, W. Nitrogen Dioxide Exposure in School Classrooms of Inner-City Children with Asthma. *J. Allergy Clin. Immunol.* 2018, 141, 2249–2255.e2.
61. Brumberg, H.L.; Karr, C.J. Council on Environmental Health Ambient Air Pollution: Health Hazards to Children. *Pediatrics* 2021, 147, e2021051484.
62. Dondi, A.; Betti, L.; Carbone, C.; Dormi, A.; Paglione, M.; Rinaldi, M.; Gualtieri, M.; Scotto, F.; Poluzzi, V.; Fabi, M.; et al. Understanding the Environmental Factors Related to the Decrease in Pediatric Emergency Department Referrals for Acute Asthma during the SARS-CoV-2 Pandemic. *Pediatr. Pulmonol.* 2022, 57, 66–74.
63. Li, Y.; Wang, W.; Wang, J.; Zhang, X.; Lin, W.; Yang, Y. Impact of Air Pollution Control Measures and Weather Conditions on Asthma during the 2008 Summer Olympic Games in Beijing. *Int. J. Biometeorol.* 2011, 55, 547–554.
64. Baraldi, E.; Lanari, M.; Manzoni, P.; Rossi, G.A.; Vandini, S.; Rimini, A.; Romagnoli, C.; Colonna, P.; Biondi, A.; Biban, P.; et al. Inter-Society Consensus Document on Treatment and Prevention of Bronchiolitis in Newborns and Infants. *Ital. J. Pediatr.* 2014, 40, 65.
65. Silver, A.H.; Nazif, J.M. Bronchiolitis. *Pediatr. Rev.* 2019, 40, 568–576.
66. Karr, C.; Lumley, T.; Schreuder, A.; Davis, R.; Larson, T.; Ritz, B.; Kaufman, J. Effects of Subchronic and Chronic Exposure to Ambient Air Pollutants on Infant Bronchiolitis. *Am. J. Epidemiol.* 2007, 165, 553–560.
67. Carugno, M.; Dentali, F.; Mathieu, G.; Fontanella, A.; Mariani, J.; Bordini, L.; Milani, G.P.; Consonni, D.; Bonzini, M.; Bollati, V.; et al. PM10 Exposure Is Associated with Increased Hospitalizations for Respiratory Syncytial Virus Bronchiolitis among Infants in Lombardy, Italy. *Environ. Res.* 2018, 166, 452–457.
68. Loaiza-Ceballos, M.C.; Marin-Palma, D.; Zapata, W.; Hernandez, J.C. Viral Respiratory Infections and Air Pollutants. *Air Qual. Atmos. Health* 2022, 15, 105–114.
69. Milani, G.P.; Cafora, M.; Favero, C.; Lugini, A.; Carugno, M.; Lenzi, E.; Pistocchi, A.; Pinatel, E.; Pariota, L.; Ferrari, L.; et al. PM2.5, PM10 and Bronchiolitis Severity: A Cohort Study. *Pediatr. Allergy Immunol.* 2022, 33, e13853.
70. Evangelisti, M.; Cangiano, G.; Nenna, R.; Nicolai, A.; Frassanito, A.; Papasso, S.; Alessandrini, C.; Mario, C.D.; Zambonini, V.; Mattia, G.D.; et al. Air Pollution and Bronchiolitis from 2004 to 2014 in Rome. *Eur. Respir. J.* 2015, 46, PA4505.
71. Nenna, R.; Evangelisti, M.; Frassanito, A.; Scagnolari, C.; Pierangeli, A.; Antonelli, G.; Nicolai, A.; Arima, S.; Moretti, C.; Papoff, P.; et al. Respiratory Syncytial Virus Bronchiolitis, Weather Conditions and Air Pollution in an Italian Urban Area: An Observational Study. *Environ. Res.* 2017, 158, 188–193.
72. Jedrychowski, W.A.; Perera, F.P.; Spengler, J.D.; Mroz, E.; Stigter, L.; Flak, E.; Majewska, R.; Klimaszewska-Rembiasz, M.; Jacek, R. Intrauterine Exposure to Fine Particulate Matter as a Risk Factor for Increased Susceptibility to Acute Broncho-Pulmonary Infections in Early Childhood. *Int. J. Hyg. Environ. Health* 2013, 216, 395–401.
73. Gouveia, N.; Fletcher, T. Respiratory Diseases in Children and Outdoor Air Pollution in São Paulo, Brazil: A Time Series Analysis. *Occup. Environ. Med.* 2000, 57, 477–483.
74. Brugha, R.; Grigg, J. Urban Air Pollution and Respiratory Infections. *Paediatr. Respir. Rev.* 2014, 15, 194–199.
75. Liu, Y.; Wang, Y.; Dong, J.; Wang, J.; Bao, H.; Zhai, G. Association between Air Pollution and Emergency Department Visits for Upper Respiratory Tract Infection in Lanzhou, China. *Environ. Sci. Pollut. Res. Int.* 2022, 29, 28816–28828.
76. Esplugues, A.; Ballester, F.; Estarlich, M.; Llop, S.; Fuentes-Leonarte, V.; Mantilla, E.; Vioque, J.; Iñiguez, C. Outdoor, but Not Indoor, Nitrogen Dioxide Exposure Is Associated with Persistent Cough during the First Year of Life. *Sci. Total Environ.* 2011, 409, 4667–4673.
77. Gehring, U.; Gruzdeva, O.; Agius, R.M.; Beelen, R.; Custovic, A.; Cyrys, J.; Eeftens, M.; Flexeder, C.; Fuertes, E.; Heinrich, J.; et al. Air Pollution Exposure and Lung Function in Children: The ESCAPE Project. *Environ. Health Perspect.* 2013, 121, 1357–1364.
78. Glick, A.F.; Tomopoulos, S.; Fierman, A.H.; Elixhauser, A.; Trasande, L. Association Between Outdoor Air Pollution Levels and Inpatient Outcomes in Pediatric Pneumonia Hospitalizations, 2007 to 2008. *Acad. Pediatr.* 2019, 19, 414–

79. Suryadhi, M.A.H.; Abudureyimu, K.; Kashima, S.; Yorifuji, T. Nitrogen Dioxide and Acute Respiratory Tract Infections in Children in Indonesia. *Arch. Environ. Occup. Health* 2020, 75, 274–280.
80. Darrow, L.A.; Klein, M.; Flanders, W.D.; Mulholland, J.A.; Tolbert, P.E.; Strickland, M.J. Air Pollution and Acute Respiratory Infections among Children 0–4 Years of Age: An 18-Year Time-Series Study. *Am. J. Epidemiol.* 2014, 180, 968–977.
81. Grigg, J. Air Pollution and Children's Respiratory Health—Gaps in the Global Evidence. *Clin. Exp. Allergy* 2011, 41, 1072–1075.
82. Mishra, R.; Krishnamoorthy, P.; Gangamma, S.; Raut, A.A.; Kumar, H. Particulate Matter (PM₁₀) Enhances RNA Virus Infection through Modulation of Innate Immune Responses. *Environ. Pollut.* 2020, 266, 115148.
83. Liu, F.; Zhang, Z.; Chen, H.; Nie, S. Associations of Ambient Air Pollutants with Regional Pulmonary Tuberculosis Incidence in the Central Chinese Province of Hubei: A Bayesian Spatial-Temporal Analysis. *Environ. Health* 2020, 19, 51.
84. Cole, M.A.; Ozgen, C.; Strobl, E. Air Pollution Exposure and COVID-19 in Dutch Municipalities. *Environ. Resour. Econ.* 2020, 76, 581–610.
85. Wu, X.; Nethery, R.C.; Sabath, B.M.; Braun, D.; Dominici, F. Exposure to Air Pollution and COVID-19 Mortality in the United States: A Nationwide Cross-Sectional Study. *medRxiv* 2020.
86. Travaglio, M.; Yu, Y.; Popovic, R.; Selley, L.; Leal, N.S.; Martins, L.M. Links between Air Pollution and COVID-19 in England. *Environ. Pollut.* 2021, 268, 115859.
87. Contini, D.; Costabile, F. Does Air Pollution Influence COVID-19 Outbreaks? *Atmosphere* 2020, 11, 377.
88. McGeachie, M.J.; Yates, K.P.; Zhou, X.; Guo, F.; Sternberg, A.L.; Van Natta, M.L.; Wise, R.A.; Szeffler, S.J.; Sharma, S.; Kho, A.T.; et al. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. *N. Engl. J. Med.* 2016, 374, 1842–1852.
89. Gauderman, W.J.; Avol, E.; Gilliland, F.; Vora, H.; Thomas, D.; Berhane, K.; McConnell, R.; Kuenzli, N.; Lurmann, F.; Rappaport, E.; et al. The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age. *N. Engl. J. Med.* 2004, 351, 1057–1067.
90. Mölter, A.; Agius, R.M.; de Vocht, F.; Lindley, S.; Gerrard, W.; Lowe, L.; Belgrave, D.; Custovic, A.; Simpson, A. Long-Term Exposure to PM₁₀ and NO₂ in Association with Lung Volume and Airway Resistance in the MAAS Birth Cohort. *Environ. Health Perspect.* 2013, 121, 1232–1238.
91. de Barros Mendes Lopes, T.; Groth, E.E.; Veras, M.; Furuya, T.K.; de Souza Xavier Costa, N.; Ribeiro Júnior, G.; Lopes, F.D.; de Almeida, F.M.; Cardoso, W.V.; Saldiva, P.H.N.; et al. Pre- and Postnatal Exposure of Mice to Concentrated Urban PM_{2.5} Decreases the Number of Alveoli and Leads to Altered Lung Function at an Early Stage of Life. *Environ. Pollut.* 2018, 241, 511–520.
92. Garcia, E.; Rice, M.B.; Gold, D.R. Air Pollution and Lung Function in Children. *J. Allergy Clin. Immunol.* 2021, 148, 1–14.
93. EPA. Integrated Science Assessment (ISA) for Particulate Matter. Available online: <https://www.epa.gov/isa/integrated-science-assessment-isa-particulate-matter> (accessed on 5 January 2023).
94. Cai, Y.; Hansell, A.L.; Granell, R.; Blangiardo, M.; Zottoli, M.; Fecht, D.; Gulliver, J.; Henderson, A.J.; Elliott, P. Prenatal, Early-Life, and Childhood Exposure to Air Pollution and Lung Function: The ALSPAC Cohort. *Am. J. Respir. Crit. Care Med.* 2020, 202, 112–123.
95. Schultz, E.S.; Hallberg, J.; Bellander, T.; Bergström, A.; Bottai, M.; Chiesa, F.; Gustafsson, P.M.; Gruzdeva, O.; Thunqvist, P.; Pershagen, G.; et al. Early-Life Exposure to Traffic-Related Air Pollution and Lung Function in Adolescence. *Am. J. Respir. Crit. Care Med.* 2016, 193, 171–177.
96. Bui, D.S.; Burgess, J.A.; Lowe, A.J.; Perret, J.L.; Lodge, C.J.; Bui, M.; Morrison, S.; Thompson, B.R.; Thomas, P.S.; Giles, G.G.; et al. Childhood Lung Function Predicts Adult Chronic Obstructive Pulmonary Disease and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Am. J. Respir. Crit. Care Med.* 2017, 196, 39–46.
97. Stocks, J.; Hislop, A.; Sonnappa, S. Early Lung Development: Lifelong Effect on Respiratory Health and Disease. *Lancet Respir. Med.* 2013, 1, 728–742.
98. Soriano, J.B.; Polverino, F.; Cosio, B.G. What Is Early COPD and Why Is It Important? *Eur. Respir. J.* 2018, 52, 1801448.
99. Jedrychowski, W.; Maugeri, U.; Jedrychowska-Bianchi, I. Body Growth Rate in Preadolescent Children and Outdoor Air Quality. *Environ. Res.* 2002, 90, 12–20.

100. Johnson, N.M.; Hoffmann, A.R.; Behlen, J.C.; Lau, C.; Pendleton, D.; Harvey, N.; Shore, R.; Li, Y.; Chen, J.; Tian, Y.; et al. Air Pollution and Children's Health-a Review of Adverse Effects Associated with Prenatal Exposure from Fine to Ultrafine Particulate Matter. *Environ. Health Prev. Med.* 2021, 26, 72.
101. Wang, P.; You, D.; Saravia, J.; Shen, H.; Cormier, S.A. Maternal Exposure to Combustion Generated PM Inhibits Pulmonary Th1 Maturation and Concomitantly Enhances Postnatal Asthma Development in Offspring. *Part. Fibre Toxicol.* 2013, 10, 29.
102. Zhang, Y.; Wei, J.; Shi, Y.; Quan, C.; Ho, H.C.; Song, Y.; Zhang, L. Early-Life Exposure to Submicron Particulate Air Pollution in Relation to Asthma Development in Chinese Preschool Children. *J. Allergy Clin. Immunol.* 2021, 148, 771–782.e12.
103. Peden, D.B. Prenatal Exposure to Particulate Matter Air Pollution: A Preventable Risk for Childhood Asthma. *J. Allergy Clin. Immunol.* 2021, 148, 716–718.
104. Lavigne, E.; Donelle, J.; Hatzopoulou, M.; Van Ryswyk, K.; van Donkelaar, A.; Martin, R.V.; Chen, H.; Stieb, D.M.; Gasparrini, A.; Crighton, E.; et al. Spatiotemporal Variations in Ambient Ultrafine Particles and the Incidence of Childhood Asthma. *Am. J. Respir. Crit. Care Med.* 2019, 199, 1487–1495.
105. Lu, C.; Peng, W.; Kuang, J.; Wu, M.; Wu, H.; Murithi, R.G.; Johnson, M.B.; Zheng, X. Preconceptional and Prenatal Exposure to Air Pollution Increases Incidence of Childhood Pneumonia: A Hypothesis of the (Pre-)Fetal Origin of Childhood Pneumonia. *Ecotoxicol. Environ. Saf.* 2021, 210, 111860.
106. Aguilera, I.; Pedersen, M.; Garcia-Esteban, R.; Ballester, F.; Basterrechea, M.; Esplugues, A.; Fernández-Somoano, A.; Lertxundi, A.; Tardón, A.; Sunyer, J. Early-Life Exposure to Outdoor Air Pollution and Respiratory Health, Ear Infections, and Eczema in Infants from the INMA Study. *Environ. Health Perspect.* 2013, 121, 387–392.
107. Latzin, P.; Rössli, M.; Huss, A.; Kuehni, C.E.; Frey, U. Air Pollution during Pregnancy and Lung Function in Newborns: A Birth Cohort Study. *Eur. Respir. J.* 2009, 33, 594–603.
108. Morales, E.; Garcia-Esteban, R.; de la Cruz, O.A.; Basterrechea, M.; Lertxundi, A.; de Dicastillo, M.D.M.L.; Zabaleta, C.; Sunyer, J. Intrauterine and Early Postnatal Exposure to Outdoor Air Pollution and Lung Function at Preschool Age. *Thorax* 2015, 70, 64–73.
109. Usemann, J.; Decrue, F.; Korten, I.; Proietti, E.; Gorlanova, O.; Vienneau, D.; Fuchs, O.; Latzin, P.; Rössli, M.; Frey, U.; et al. Exposure to Moderate Air Pollution and Associations with Lung Function at School-Age: A Birth Cohort Study. *Environ. Int.* 2019, 126, 682–689.
110. He, B.; Huang, J.V.; Kwok, M.K.; Au Yeung, S.L.; Hui, L.L.; Li, A.M.; Leung, G.M.; Schooling, C.M. The Association of Early-Life Exposure to Air Pollution with Lung Function at ~17.5 years in the “Children of 1997” Hong Kong Chinese Birth Cohort. *Environ. Int.* 2019, 123, 444–450.
111. Agustí, A.; Faner, R. Lung Function Trajectories in Health and Disease. *Lancet Respir. Med.* 2019, 7, 358–364.
112. Parker, J.D.; Rich, D.Q.; Glinianaia, S.V.; Leem, J.H.; Wartenberg, D.; Bell, M.L.; Bonzini, M.; Brauer, M.; Darrow, L.; Gehring, U.; et al. The International Collaboration on Air Pollution and Pregnancy Outcomes: Initial Results. *Environ. Health Perspect.* 2011, 119, 1023–1028.
113. Li, C.; Yang, M.; Zhu, Z.; Sun, S.; Zhang, Q.; Cao, J.; Ding, R. Maternal Exposure to Air Pollution and the Risk of Low Birth Weight: A Meta-Analysis of Cohort Studies. *Environ. Res.* 2020, 190, 109970.
114. Liu, Y.; Xu, J.; Chen, D.; Sun, P.; Ma, X. The Association between Air Pollution and Preterm Birth and Low Birth Weight in Guangdong, China. *BMC Public Health* 2019, 19, 3.
115. Chen, Q.; Ren, Z.; Liu, Y.; Qiu, Y.; Yang, H.; Zhou, Y.; Wang, X.; Jiao, K.; Liao, J.; Ma, L. The Association between Preterm Birth and Ambient Air Pollution Exposure in Shiyang, China, 2015–2017. *Int. J. Environ. Res. Public Health* 2021, 18, 4326.