Air Pollution in Infancy, Childhood and Young Adults

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10.1 Background

Air pollution remains a major concern for the health of younger people: their different physiology and lifestyles can affect them deeply and in different terms when compared to the adults. Studies on the effect of air pollution on children can be dated as early as the eighteenth century: not surprisingly one of the first epidemiological studies in oncology, which is linked to the onset of cancer [1, 2] with the exposure to pollutants of children hired as chimney sweeper. Today we are far from the level of pollution of the industrial revolution, and children's labour is not welcome anymore as in the past. Yet, in urban area children are constantly exposed to air pollution in their everyday activities. Those that live in less polluted or in greener areas commute to schools exposed to pollution. Extra-scholastic activities take children around the city; most of those are outdoor activities that take place when the concentration of pollutants in the air is higher. In poor-income areas, where the number of children in the population is higher, air pollution is often out of control and exacerbated by routine activities. In those same settings, there is no awareness of the risk to air pollutions, and there are basic or no procedures to reduce exposure to pollutants.

The risk on children health is somehow of more concern compared to the ones in adults: children can have lifelong consequences that can also deeply affect their wellbeing and their choices and consequently the same quality of life. Early exposures, besides, mean an increased risk for chronic outcomes for those pollutants that have cumulative effects.

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The effect of air pollution on respiratory system in children is nowadays well-known. Recent studies show how other systems and organs are affected [3] and how exposure to pollutant can become a risk factor for developing chronic non-communicable disease in the adulthood [4]. But as we will see, every aspect of the developing process can be affected by air pollution. This is not an unpredictable observation: a child's organism grows rapidly and undergoes to a number of changes over the months or the years. This process can be easily altered by external influences. These involve behavioural and affective stimuli, microorganisms, physical and chemical interactions as well as the combinations of those.

For these reasons, lately scientists are becoming more aware of the implications of air pollution in childhood. They promoted a new set of studies that helped to better understand how air pollution can compromise the natural growing of a child and how it can affect both his or her everyday life and his or her adult life.

10.1.1 Why Children Differ from Adults When Exposed to Air Pollution

As we have briefly seen, children are normally more vulnerable than adults to the effect of air pollution. This is not an idea that can be given for granted, as children can otherwise be less affected than adults to other pathological processes: children do not normally have chronic and multiple conditions, can have more healing resources when exposed to acute injuries and infections, do not normally take medicines for long-term or lifelong treatments or do not have consolidated habits that can be risk factors for the development of diseases.

But from a different point of view, children are more fragile than adults. They are more vulnerable because their body is developing and changing rapidly over the months or the years. And children comprise a wide category of individuals that range from few days of life to the teenage.

When it comes to air pollution, besides, environmental, behavioural and physiological factors deeply affect the way children are exposed to pollutants compared to adults [3, 5–12]. The main characteristics are synthetized in Table 10.1.

Some of these factors are peculiar only for children. Others may be in common with adults but can result in more harmful or long-term effect in children. Others affect children as well as adults, but children can proactively change the circumstances that cause them to be exposed to pollutants. Passive smoking, for instance, is an environmental factor but also a behavioural factor. While adult can decide to quit smoking or avoid smoking at home, children normally cannot take similar decisions. Thus, smoking is a relatively non modifiable circumstance that could affect children, while it is a potentially easily modifiable factor when individual adults are considered.

Other behavioural factors are more related on children's activities and have to be considered: children spend more time outside. Children engaged in physical outdoor activities are exposed to outdoor pollution which in urban areas is strongly associated with traffic. Because of the increase in the respiratory rate and to bronchodilation secondary to the exercise, the amount of pollutant inhaled has increased.

Table 10.1 Susceptibility of children to air pollution when compared to adult exposure to environmental factors

Behavioural	Environmental	Physiological
• More time spent outside • More physical activities done outside • Ingestion of dust and soil (pica behaviour) • Time spent commuting (walking, biking, car, public transport) • Less awareness and proactive preventive behaviours • Children labour (in selected settings) • Malnutrition and selective micronutrient deficiency (in selected settings) • Mouth breathing • More time spent outside in summer time when the level of pollution is higher • Different timing when compared to adults in terms of daily or seasonal exposure to pollutants • Time spent at school (are often closer to busy roads when compared to residential areas) normally at daily traffic pollution peak • Different behaviours across the life stages • Active smoking during adolescence, as part of normal challenging behaviour of the teenage • Pica behaviour (ingestion of dust on object contaminated by air pollution) • Poor control of cough and expectoration in smaller children • More engagement in increased physical activities as children are normally more active than adults, that results in increased oral breathing and respiratory rate	• Indoor pollution • Household air pollution and cooking fumes • Time spent in school (the quality of indoor and outdoor air cannot be controlled by children/parents) • Frequent respiratory infection (community-acquired respiratory tract infections) • Exposure during antenatal life also results in possible congenital conditions (like newborns small for gestational age) that increase the risk of exposure to air pollution later in life • Low-income settings (both in urban and in rural areas) • Exposure to passive smoking • Exposure to different pollutant in relation also to their socioeconomic status • Level of education of parents • Air pollutants type and concentration vary during the day/year resulting in different exposure depending on children's activities that differ from the ones of the adults	• Small stature: children breathe air closer to the ground that can be potentially more contaminated • Higher respiratory rate • Poor filtering through the nose • Oral breathing (predominant in infants and in small children) • Higher volume of air per minute compared to the smaller body size • Smaller airways that result in a higher impact on the lung function • Limited metabolic detoxification • Maturation and growth of organ and apparatus, including lungs, brain, immune system • Different susceptibility across the life stages • Children develop in spurts • Dosing/toxicity changes according to weight and surface area • Change in the homeostasis during later childhood, puberty and adolescence • Interference of pollutants with sexual maturation • Cumulative effects of the pollutants: toxins remain in the lungs for more time • More time to develop tumours for cells affected by carcinogenic pollutants • Blood-brain barrier not fully developed • Immaturity of the immune system

Children attending school are also exposed to community-acquired respiratory tract infection that easily spread among crowded indoor areas, like a classroom. Air pollution augments the risk of respiratory infection, and respiratory infections reduce the protection against microorganism (e.g. compromising the ciliary motility in the respiratory tract, hence reducing the mucociliary clearance [13]).

Small children that do not attend nursery and those that live at home during the entire childhood can be also affected by environmental exposure. This is especially observed in very-poor-income area where children are constantly exposed to household air pollution. This can be controversial as in very rural locations, children do not necessarily spend time inside houses, or houses are often open so that there are no clear boundaries in terms of the microenvironment between the inside and the outside. In some settings, infants and toddlers spend the whole of their times with their mums, often tied to them, also during household activities like cleaning and cooking. That could expose children from high to toxic concentration of chemicals, exhaust or fumes. The same considerations can be applied to children who spend most of their time inside a house also in higher-income countries, when the quality of the indoor air is poor.

In a developing body, in which organs and systems are not mature, any possible harm can result in long-term consequences.

It had to be noted that children can be exposed to air pollution starting from their antenatal life. This can have important implications, as pre-birth exposure lower the threshold and increases susceptibility later in childhood to the harmful effects of air pollution in an already susceptible population, namely the children (see also Chap. 26).

10.2 Epidemiology and Impact

10.2.1 Exposure

As we have seen, children can be exposed at home or at school, while commuting or when engaged in other inside and open-air activities. It implies that they can be exposed to indoor and outdoor pollution or to a mixture of both. Growing evidences link the areas in which children live or go to school with short- or long-term health problems or developing impairments. Traffic-related pollution seems accountable of most of the health effects during the time children spend at school, especially when school is located near busy roads. But effect on health can be noted also in children coming from different urban areas with different level of pollutants and attending the same school [14]. This gives a picture of the complexity in mapping the risk of air pollution exposure. It has been noted that in big cities the areas with a lower socioeconomic level are normally more polluted and children living in those neighbours are the ones that are mostly affected by air pollution [6, 15, 16]. Nonetheless children can have a more dynamic lifestyle when compared to adults: it means that they can more frequently move to different areas of a city spending several hours of the weeks in more or less polluted zones.

Although regions with a high level of industrialization are allegedly more polluted, the rate of urbanization has also a role especially in rapidly developing countries, meaning that children living in low- and middle-income areas are potentially at higher risk [4]. In those same settings, there may not be policies in place for air pollution contention; at the same time, the percentage of children in the population is higher.

The amount, the length of exposure and the type of pollutants children can be exposed to, for those reasons, can vary. Individual exposure can hardly be measured, but a map of exposure can be estimated. This can be done by monitoring the quality of the air near the places a child spend most of the time (like home, school, playground, sport field), monitoring the average of pollutants concentration in a study area, mapping the nearest busy roads, monitoring the ambient with ad hoc measurements and placing pollutant monitor outside and inside schools or at home. Personal exposure can be also measured with the use of personal equipment that children can carry (mainly for a limited time) everywhere they go. Biomarkers as well have been studied in order to establish whether they can be used as expression of early effects and exposure to given pollutants [17].

It is however difficult to establish which pollutants are more dangerous for children. Particulate matter (PM), ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides (NO_x) and lead [3–5] have been identified as a major cause of health problem in children. Carbon monoxide, PM2.5, nitrogen oxides, hydrocarbons, other hazardous air pollutants (HAPs) and ozone are related to traffic pollution. In rural areas fumes from combustion can be a major cause of indoor and outdoor air pollution.

The concentration of those pollutants can change among micro- and macro-areas, during season and during different times of the day or of the week. Exposure can consequently change according to daily, weekly and seasonal routines in children's lives.

10.2.2 Age and Gender

Children are an inhomogeneous group of people whose characteristics vary according to age. Because children grow over the years, the same individual changes more or less quickly, altering his or her personal features and evolving to new and different stages. Those simple assumptions cause two major consequences:

1. Air pollution can affect the way children grow.
2. Air pollution can have different effects in different stages of life.

The number of study assessing the possible implications is still limited; although it appears clear that air pollution can have effect on the antenatal life and on the early stage of life, the response to different pollutants in the different stage of life is still unclear, as well as the long-term implications that exposure to toxic substance can have in small children when compared to the most grown-up.

As we will see, evidences suggest that the whole developing process can be nonetheless put at risk, with the maturation of every organ and system potentially involved. Besides, early exposures seem to increase the risk of adverse outcomes as they (a) affect very immature systems that are rapidly changing, (b) affect systems that do not have mature protective systems, (c) compromise the normal developmental pathways, (d) create cumulative effects and (e) affect systems with peculiar physiology also related to their smaller size.

Boys and girls can have different response to the effect of air pollution, because of differences in terms of exposure and of response to pollutants. Again behavioural, environmental and physiological factors have to be considered. During puberty the differences become more clear, when the effect of growth clearly differentiates the two sex also in terms of behaviour and activities. Some studies suggest still different effects of air pollution also in younger children, especially when respiratory symptoms and allergies are considered [18, 19], with healthy boys being more affected than girls and already symptomatic girls being more at risk for relapses [20]. Those preliminary results however do not clarify the physiopathology underneath the observed effect and cannot exclude that behavioural factors alone can justify those differences. Thus, further studies are needed to proper assess the risk of air pollution in children of different ages and sex.

10.2.3 Air Pollution and Healthcare

The effects of air pollution are not always so straightforward. Most of the time, the request for help is secondary to the effects that are not clearly related to air pollution or that apparently have no link to it. So it is difficult to estimate the real impact of air pollution in children although is likely very underestimated. Although some pathologies are more frequently observed according to seasonal patterns, air pollution is not normally monitored when it comes to emergency department attendance or hospital admission.

Another limitation to assess the real impact of air pollution on the healthcare is the fact that different organs and systems can be directly or indirectly affected, and most of the time, the spatial and temporal association is difficult to understand even for those that analyse epidemical data. Primary care and hospital statistics therefore cannot easily correlate the incidence of a disease with the environmental factors.

For this reason, most of the data related to hospital admission and the consequent burden of air pollution for the health systems are based on study designs that study the effect of air pollution on hospitalization and respiratory symptoms that are more easily associated with environmental triggers.

Data strongly suggest that the number of admission and relapsed strongly related to the exposure to air pollutants and traffic-related air pollution [21].

It is in any case reasonable to think that a high number of admission to children's wards, even when apparently not directly linked to air pollution exposure, can be nonetheless been caused by environmental factors.

Those are fundamental data, for the implementation of efficient and cost-effective health policies.

10.2.4 Hospitalization

Although it is becoming clear that there is a strong association between the level of exposure to air pollution and the children's health, it is difficult to make real estimates of its burden in terms of hospitalization and expenditure for the different health systems. A main reason is the fact that some of the effects cannot be directly linked to single episodes; in other cases, acute episodes can or cannot be an expression of a chronic exposure to air pollutants or may be triggered by other factors (e.g. virus or bacteria) in children chronically exposed to the effect of air pollution. Besides, in some children the quality of the air they are breathing can increase the frequency of relapses of chronic diseases that need medical attention.

For those reasons, the exact impact on hospitalization is largely unknown. Most of the studies in addition focus on respiratory causes only of hospitalization, as those are the ones that more clearly can be related to acute exposure—or to variations in terms of exposure—to air pollutants. Even in these cases, the association is still unclear: although some studies show strong evidences that support the idea that air pollution increases the number of hospitalizations and visits to emergency departments in children [22, 23] especially for those exposed to traffic-related pollution [21] and those with a diagnosis of asthma [24, 25], others found no significant association between exposure to some particulate and hospital admissions [26]. This same study suggests that exacerbation of respiratory symptoms may reflect more on primary care or outpatients' interventions, rather than in admission, and that different mechanism and different pollutants can directly or indirectly affect the health conditions of children, meaning that only in some cases a hospital intervention may be needed. That increments the difficulty in planning epidemiological studies that can help to understand the real impact of air pollution on the health systems.

10.2.5 Morbidity and Mortality

Being the medium- and long-term effects of air pollution on children's health difficult to evaluate, it is still not clear what are the numbers in terms of morbidity and mortality directly or indirectly related to air pollution. Children respond to environment differently; they can be more vulnerable during the first months or years of life; the cumulative effect can show its signs in the adult life; air pollution can cause the exacerbation of an underlying condition and that can, in turn, result in serious or lethal damages. In the latter case, it may be difficult to ascribe disability or death to air pollution.

In particularly polluted environment, nonetheless, a substantial increment of mortality under the age of five and in neonates has been noted [27–29], although in the same settings, other studies find a more significant association with mortality and older age [30]. On the other hand, different pollutants may be more or less poisoning and have effects on children's health that are comparable to the ones on the adults; for some of them, the hazards are known [3], and it has been possible to evaluate the adverse outcomes (viz. disability and mortality) also in terms of cost for the society [31].

In selected cases, the toxic effects of air pollutants are more clear, especially when indoor pollution is considered: for instance, the household solid fuel used in low-income areas is strictly related to acute respiratory infections, chronic obstructive pulmonary disease, tuberculosis, asthma, lung cancer, ischaemic heart disease, blindness and death [32].

Further assessments are needed to better understand the real impact of air pollutants on short- and long-term disabilities and deaths in children.

10.2.6 Quality of Life

Social and health factors affect the quality of life for children that live in polluted areas. We have seen that, even if probably underestimated, the effect of air pollution on health conditions is clear and children may live with disabilities, have exacerbation of chronic conditions, experience acute events or develop morbidities that eventually impact on their growth and on their future adult life. The burden in terms of direct effect is difficult to establish, but the relationship remains clear.

The resulting effect then is not different from the one created by similar health and medical conditions in children.

On the other hand, to survive in a polluted environment, families and children have to adopt different lifestyles or take precautions that may result in an impairment of the overall quality of life. Those families that are particularly aware may decide to change neighbourhood or school, and that may result in more time spent commuting. Children may be asked to remain at home in the afternoon or during summertime not only when the level of pollution can be higher but also when children are more likely to be engaged in outdoor and recreational activities. Time spent indoor may not be necessarily safer: inactivity can be associated with risky or unhealthy behaviour in children and can influence relationships and children's social lives [33].

Behavioural changes may be fostered, but taking action against air pollution can be also stressful for children that do not necessarily understand the implications and the need for change. This is particularly true when they are asked to wear active protection equipment or to avoid particular outdoor or indoor areas.

10.2.7 Society

Estimating the impact of air pollution on society is challenging. At the same time, it is hard to understand how the exposure to air pollution and its related effects on human health depends on the differences in society and in the socioeconomic status of families and individuals.

Some studies in fact suggest that ethnicity and social background can have a role in terms of exposure and outcomes on children's health [6, 16, 34]. It remains unclear if the relationship is related to genetics, to the air quality in poorer neighbourhoods (that is supposedly worse when compared to greener or residential zones) or to lifestyles. Those are also to be considered confounding factors in designing a study to evaluate the consequences of air pollution on children's health [15].

When it comes to children, the burden of air pollution has to consider a number of factors: the direct cost for the evaluation, investigation and treatment of medical conditions directly or indirectly interrelated to the exposure to air pollutants; these impact on the expenditure of the different health systems and on the available resources. Some reports give an idea of the impact on economy of air pollution-related disease in children: selected conditions due to toxins in the environment in the sole United States are responsible of about 3% of the whole US care cost [31]. This of course largely underestimates the problem, as long as diseases not directly attributable to air pollution are not included in the surveys.

Pollution-related health problems also represent a direct cost for families, in terms of money used to reach the health centre, to pay for healthcare and for investigation and treatment. The indirect costs that in children involve the same child and his or her adult carers; for the child a possible esteem can be based on school attendance and on the number of missed days of school that is significantly increased in children exposed to air pollution especially when they suffer of respiratory conditions [31, 35, 36]. Parents are also involved in terms of days of work lost in order to provide care for ill children.

As we have seen, the quality of life as well can be compromised. It results in costs for family and the society and in the use of resources that could be used for other aims.

10.2.8 Developing Countries

Two major issues are related to the effect of air pollution on children in very poor settings: first, the percentage of children in the population is generally higher in developing countries, where on the other hand the level of assistance for families and underage people is lower. Second, although rural area may be less polluted when compared to high-income countries, in developing countries' metropolitan areas, the quality of the air is poorer secondary to a number of factors. Besides, the awareness of the problem is lower, and people are less concerned and less interested in taking personal precaution or in advocating changes. In addition, children suffer often of chronic selective malnutrition or acute malnutrition ranging from mild to severe; nutritional status can reduce the level of protection to air pollutants, especially in these areas where environmental conditions are poorer [37].

In rural areas, the level of indoor pollution, especially secondary to the use of household solid fuel mainly for cooking, is a serious concern. The smoke coming from combustion produces a number of toxins that are known to provoke damage on human health and particularly on children that are the most vulnerable ones [38]. Among them are volatile organic compounds (VOCs), carbon monoxide (CO), carbon dioxide (CO_2), nitrogen dioxide (NO_2), ozone (O_3), hydrocarbons, particulate matter (PM) and dust particles [39, 40]. Very young children in these settings spend most of their time with mums or adults engaged in household activities, often on their lap or tied on their backs. The effects are mainly respiratory symptoms, but they can range up to life-threatening conditions and death [40].

The quality of outdoor air should be supposedly better, but combustion-related pollutants come from wood or manure's fires especially where livestock are hold and fumigation is constant. In addition, the level of dust in the air can be higher, as well as the concentration of biological pollutants; even if the level of traffic is very low when compared to urban settings, the use of outdated vehicle increases the level of pollutants in those area close to the main roads.

Unfortunately, it is very difficult to assess the level of exposure in these settings [41–43], and consequently developing a strategy to reduce the health effects of air pollution on children may be extremely challenging. More studies are therefore needed to better understand the entity of the problem and to correctly address it [43], in order to produce effective policies also in those countries with a low level of awareness in the government and in the population.

10.3 Effect of Air Pollution on Organs and Systems in Children

Most of the studies on the effect of air pollution on children's health focused in the past on respiratory diseases. This was due both to the logic link among air toxins and respiration, as well as the empiric observation of exacerbation of respiratory symptoms in children with chronic conditions as asthma and exposure to pollutants. As we have seen, children can be particularly exposed to air pollutants, and the rising awareness that all the systems can be potentially affected by air pollution created new lines of investigation in the last decade. Research therefore focused as well on other health issues, more related to the growing processes which naturally are typical for children. New and consistent findings demonstrate that the whole development can be affected, starting from the antenatal life up to the puberty and the teen years. These studies gave new insights to the problem. The peculiarities of children's organism in fact made them particularly vulnerable to pollutants, so that is today difficult to separate the different health effect on system and organs.

It is reasonable to think that the whole body can be affected by air pollution especially the rapidly evolving one of children. Yet, most of the consequences are largely unknown, also because of the limited number of studies undertaken so far. It is nonetheless reasonable to think that the problem in children is largely underestimated. What we know so far is that pollutants play a decisive role in the developing of diseases in children starting from weight at birth and perinatal harms up to life-threatening events and chronic life-changing conditions.

The analysis of the possible diseases that follows is not meant to be exhaustive, because of the limited number of studies in childhood. Nonetheless it gives a thorough overview of what today we know about air pollution and diseases in children and supposedly opens the doors to further lines of research.

10.3.1 Birth Weight and Antenatal Exposure to Air Pollution

The weight at birth is a reliable marker of foetal development, as every harm received during the antenatal life can present itself with a slow rate of growth [44]. This of course is not the only feature of damages occurred during pregnancy, but it is easy to observe, to measure and to compare. In addition, children small for gestational age and foetus with intrauterine growth restriction can present with serious consequences at birth and potentially life-threatening complications during delivery and the first minutes or hours of life.

Children with a low weight at birth consequently are at higher risk; it is therefore essential to ascertain if air pollution can be among its cause: a low weight could become expression of exposure to pollutants during pregnancy, at the same time can predict possible complication or damages to the foetus due to pollution and predict possible developmental issues or chronic conditions later during childhood.

The association of inhaled toxins and antenatal development is already known, as the many studies on maternal smoke and birth weight or weight for gestational age show. In fact, observation of the effect of smoking on maternal health has been noted as early as the mid-30s of the twentieth century [45]. A number of potentially harmful molecules that can pass the placental barrier are present in tobacco's smoke, and those may be similar to chemicals that can be retrieved in indoor or outdoor polluted places. What remained unclear thus was the relationship with environmental pollutants passively breathed by mums during pregnancy and their effects on the newborn. Furthermore, changes in the antenatal grow rate may or may not correlate to long-term medical conditions or to processes that could affect the normal development of a child. A new body of evidence demonstrated that air pollution even in outdoor concentrations can affect the normal development of the foetus and consequently his or her weight at birth. Physiological mechanisms are still not clear, but causality correlation has been found for different pollutants as PM_{10}, NO_2, SO_2 and CO [46–49] and low weight at birth or preterm deliveries [49].

Other effects—mainly respiratory ones—on later childhood also have been observed with a correlation with adverse outcomes later in children's lives and maternal contact or inhalation of air toxins during pregnancy [47, 50]. Some surveys seem to confirm in fact that exposure to indoor and outdoor pollutants (pesticides, polycyclic aromatic hydrocarbon, environmental tobacco smoke, PM, NO_2, O_3, CO, airborne endotoxins, dust, SO_4, NO_3, NH_4, CI, acid vapour as HNO3, formic, acetic) in the gestational life does not affect only the same pregnancy outcomes but also has a role in later onset of neurodevelopment, cognitive, asthma, obesity and pubertal development issues [51] as well as on the birth deformities, sudden infant death syndrome, cognitive impairment and reproductive outcomes [52] and autism spectrum disorder [53, 54]. It is unclear, yet, how the timing, the amount and the acute/high versus constant/low exposure to pollutants during pregnancy lead to the development of diseases in childhood and adolescence.

The number of studies is limited, so definitive associations are difficult to describe, but it is becoming clear that air pollution can be particularly harmful in pregnancy, and adequate measure in terms of prevention and reduction of the exposure should be undertaken.

10.3.2 Growth

The development process is a key issue in children. Children change dramatically during a time span of months and years. Growth and weight gain are consequently a reliable marker of a child's wellbeing. Nevertheless, evaluating the way children are growing and establish relations between grow rate and external or environmental stimuli is extremely challenging. The main reason is that every child follows an own growth curve that can be only partially estimated with the different models of growth charts currently available. Because exposure to pollutants changes over the years and goes through phases of acute exposure to likely more modest chronic background exposure, understanding what and in which amount causes discrepancies between the normal/expected growth curve of a child and the actual rate of growing. Moreover, the number of confounders that can influence the development of a child is incredibly high and varies from family to family. Creating cluster of children that could be included in longitudinal studies is challenging, and because of the confounders, there are no guarantees that the children in a comparer group could give a reliable model in terms of exposed and not exposed group.

As long as children are quickly growing, it is reasonable to think that childhood may be a critical exposure time, and it would be logical to speculate that toxins could interfere with this rapidly ongoing process.

Very few studies for these reasons focused on the effects of air pollution on the physical development of children; most of them however agreed, even with some limitation, that children exposed to air pollution have a slower growing rate [55–57], although is not clear when, for how long, how many times and what type of exposure can be considered cause of that.

To partially overcome those issues, to assess possible growth's delay or impairment in children exposed to air pollution, the makers of bone turnover have been also used. Osteocalcin and the C-terminal telopeptide of type I collagen are related to reduction in mineral bone density, and the increase of the level of these substances is a reliable marker of increased bone turnover. Children exposed to air pollution show an increase of both, meaning a negative effect of environmental toxins on their bone turnover [58].

Bone age as well can be compared with chronological age to demonstrate delay or discrepancy in the growth rate in children. Some findings suggest that the peak bone mass can be prejudiced by air pollutants [59].

This is no surprise as growth in children is determined mostly by modification of the musculoskeletal system; the same adult height depends on the lengthening of bones during childhood, puberty and adolescence. Skeletal problems secondary to the exposure to air pollutant can therefore affect the physical development of children, as bones are still maturing and rapidly changing.

Ozone pollution seems to negatively influence the cutaneous production of vitamin D; O_3 works as a screen on sunrays, reducing the level of ultraviolet B (UVB) photons that can reach the skin [59, 60]. Besides, children that live in polluted areas are less likely to spend more time outdoor, meaning a reduced exposure to sun light. UVB have a prominent role in the production of cholecalciferol that is crucial for the development of healthy bones in children and for the prevention of rickets.

Skeletal fluorosis—a chronic metabolic condition that depends mainly on an excessive absorption of fluoride and that can lead to osteosclerosis, osteomalacia, osteoporosis and secondary hyperparathyroidism, with in some cases severe deformation—seems to have a strong relationship with indoor pollution, in those areas where burning coal is used as household solid fuel [61, 62].

Although mainly ingested with food, elemental toxicants are also present in air pollution and in environmental tobacco smoke. Among them lead, cadmium and aluminium are known to influence the skeletal metabolism, damaging directly the bone tissue or indirectly due to renal toxicity or acting on the metabolism of calcium and vitamin D. Long-term exposure and cumulative effect are related to osteodystrophy and bone disease [63–66] that eventually lead to growth impairment and disruption of the physiological physical development of children.

10.3.3 Neurological Development

Growing evidences correlate the exposure to air pollution and brain functions in children. Not surprisingly the toxic effects of environmental pollutants interact with the physiological development of the particularly plastic nervous system of children.

Air pollution in fact can affect the brain development as early as the antenatal age as long nervous cells' multiplication and structural organization are particularly active in this stage of life, while the immaturity of the barrier makes the central nervous system more exposed to toxins; exposure to different gestational ages is supposed to lead to different outcomes in terms of cognitive development later in childhood [67, 68].

The mechanism of neuro damage in children and the consequences later in the adult life are still under study, and also in this field, it is still unclear what type and what timing of exposition are mainly related to impairment of the cognitive function and the physiological maturation of the brain. A major role may have the diffuse neuro-inflammation; children chronically exposed to pollutants have been noted an increment of the oxidative stress and an increase of the inflammatory response, also expressed in terms of change in the modulation of serum cytokines and chemokines [69]. That seems to be related to modification of the central nervous system structural and volumetric responses [70].

The inflammation response in the lungs, which are the organs primarily affected by air pollutants, also produces circulating cytokines that act on the cyclooxygenase 2 in the vessels of the brain endothelium, leading eventually to central nervous system inflammation [68].

The accumulation of misfolded proteins, the harmful effect of pollutants on the neurovascular unit and the production of autoantibodies to neural and tight-junction proteins are another possible mechanism of damage. Those findings have been observed in children chronically exposed to air pollution. Particulate matter ($PM_{2.5}$ and PM_{10}), O_3 and NO exposure in childhood may be linked to development of multiple sclerosis and Parkinson's and Alzheimer's disease in adulthood [71, 72]. This is mainly due to the oxidative stress and to the brain inflammatory imbalance, also involving the gene responsible for the inflammatory response in the central nervous system, and the reduced protective response of prion protein that is altered by chronic exposure to air pollutants [69]. That processes could lead to neurodegenerative process, as well as to psychological distress and psychiatric conditions, able to give short- and long-term consequences, affecting also the performance of children at school and their behaviour.

Interestingly, some of the studies that tried to evaluate the progresses at school of children constantly exposed to pollutants (at home, during commuting, at school or in a combination of those) gave alarming results. Also when confounding factors (environmental and behavioural variables that are commonly associated with air pollution and that are known to interfere with cognitive maturation in children as social environment at home and at school; parental psychological status; parents' education, unemployment and occupation; breastfeeding; diet; parental smoking at home and/or during pregnancy; and noise [73]) were excluded, children studying in more polluted schools show a significant reduction of the cognitive development particularly affecting working memory, superior working memory and inattentiveness [74], while children exposed to black carbon levels show a deterioration in their vocabulary, composite intelligence, memory construct and learning [75].

Cognitive delay can potentially lead to life-changing consequences especially during primary school age; if air pollution compromises the process of learning, it is unclear if brain impairment can be recovered in a later stage of life. Besides, at this age, children receive key information and develop mental abilities that are crucial in their future educational life. Aside from the clinical manifestations that related air pollution to brain health, youngsters would miss opportunities that are part of their wellbeing and impact on their future quality of life.

10.3.4 Psychological Effect

Living in a polluted environment can be a cause of stress for a number or reasons. For those families that are aware of the problem, pollution can impose behavioural changes aimed to protect. Life change in itself nowadays is not considered a source of emotional concern; starting new, healthy routine can result on the contrary in an improved mood and better attitude towards life. Undesirable events, yet, are more likely to produce distress, and in this sense a change in the routine can result in psychological distress [76]. Reducing the hours spent in outdoor activities, keeping windows or doors closed even during the warmest months, avoiding busy road or travelling during rush hours and wearing personal protective equipment are some of possible behaviours that can affect children's quality of life. What may be useful to prevent environmental damages, in this case, can impact on the mental wellbeing of a child. In addition, air pollution can be a cause of physiological concerns in adults also resulting in change in personal behaviours [77], and that ultimately can lead to distress in children.

Although it is difficult to evaluate the psychological burden of air pollution (because of the many confounders that often are associated with it and that can be cause of psychological distress in themselves and because "psychosocial stress can cause symptoms similar to those of organic mental disorders" [78]), organic causes have been investigated and correlated with mental health issues in children exposed to air pollutants.

A direct link between oxidative stress in nervous tissues and brain inflammation—that can be also attributable to air pollution (see Sect. 10.3.3)—are possible findings in patients affected by anxiety. In adults short-term exposure to $PM_{2.5}$ was strongly correlated to exacerbation of anxiety [79]. Higher concentration of interleukin-6 as the one that can be found in children chronically exposed to air pollution can cause the reduction of the volume of hippocampus that has been observed in major depressive disorders [69]. Some findings suggest an increment of the use in children under the age of 18 of medication for psychiatric disorder, including sedative, sleeping pills and treatments for schizophrenia and severe acute psychosis, during increment of the level of PM_{10} and NO_2 [80]. Exposure to airborne toxins and traffic-related pollution is also correlated with onset of autism spectrum disorder [81]. Moreover, air pollution can aggravate underlying chronic condition, creating an indirect cause of stress and possible mental disorders [78] like anxiety or depression.

Because of the high number of confounders, the relationships between air pollution and behavioural problems in children or organic causes that can be attributable to those remain also unclear. Yet, exposure to traffic-related pollutants during the early childhood and the perinatal life has been allegedly associated with higher hyperactivity scores in children, as well as anxiety, depression, attention disorder and antisocial/delinquent behaviours [12, 82, 83].

10.3.5 Immunity and Infections

Although it is becoming clear that air pollution can increase the risk of respiratory infections (see Sect. 10.3.10), it remains unclear whether air toxins can act on the active and passive immunological mechanisms in children, so to lead to higher risk of infections from other focuses. Airborne toxins are known to interact with the immune system on the human body and to trigger the inflammatory response [8, 84, 85]. Air pollution is known to increase level of IgA, IgM and C3c, to reduce level of IgG and to contribute to the weakening of the immune system [86], which can eventually lead to the development of systemic infections.

Pollutants impair the activity of the cilia and reduce the normal clearance of secretions from the airways and inhibiting the activity of the macrophages in the alveoli [87, 88], increasing the likelihood of penetration of microorganisms in the respiratory tree. Although this mechanism is among the causes of air pollution-related respiratory infections, it opens also the doors to microorganisms, like the mycobacterium species, responsible of systemic infections in immunocompetent and immunosuppressed individuals.

Air pollution increases also the risk of infections related to the upper respiratory tract like tonsillitis, pharyngitis, eustachian tube dysfunction and otitis media [89–91]; those are very common conditions in children and among the first causes of medical interventions in paediatrics. The mechanisms are still unknown although it has been hypothesized that chemical irritation, the impairment of the mucociliary clearance secondary to exposure to toxins, the allergic inflammation and the immunosuppressive effect of airborne pollutants may have a major role. [92].

Another possible cause can be the alteration of the normal oral bacterial flora [93] that eventually leads to the development of pathological strains that increased the number of carriers and of individuals with active symptoms of upper respiratory infection. In fact, studies suggest that air pollution can be associated with an increased colonization of bacteria in the upper airways like the *Staphylococcus* species [94] and group A *Streptococcus* [95]. The latter one can indirectly lead to systemic diseases in children as rheumatic fever, postinfectious nephritis and sepsis.

10.3.6 Gastroenterological

Poorly soluble contaminants are ubiquitous in polluted environment. These pollutants can deposit in the oral cavity and in the upper respiratory tract. In adults and older children, cough and expectoration reduce the systemic adsorption of chemical and particulate matter. Part of these particles however is swallowed into the gastrointestinal tract as part of their clearance process. This is particularly true in small children that are not able to control the cough reflex, to cough out the sputum coming from expectoration or to properly blow the mucus out of their nose, resulting in an increased swallowing of secretion from the respiratory tract.

Pollutants can interfere with the natural homeostasis of the bowel and of the other organs of the human digestive system, resulting in an increased level of gastrointestinal disorders.

The association between ingestion of pollutants and diseases in children remains unclear. However, some studies suggest an increased number of episodes of gastroenteritis and gastrointestinal disorders in children exposed to air pollution [96, 97] and an impairment of the liver detoxification function in children coming from heavily polluted areas [98].

It is reasonable to think that children can be more affected than adults, as the effects of gastroenteritis are normally more severe in this age group that is normally at higher risk of dehydration and metabolic imbalances as ketosis. Besides the higher concentration of pollutants that can be swallowed or inhaled by small children can results in an increased level of toxins, whose clearance is reduced by the allegedly changed detoxification capacity of the liver.

Chemicals and particulate coming from air pollution deposit in the soil. Pica behaviours—common in children—can increase the risk of gastrointestinal exposure to these toxins and therefore of gastroenteritis, both by augmenting the overall amount of air pollutants ingested and increasing the likelihood of enteric infections secondary to microorganism ingestion.

10.3.7 Cardiovascular

Although the effects of air pollution on the cardiovascular system in the generic population are well known, the effect on children has not been exhaustively studied. Cardiovascular diseases are not common in this age group, and the long-term effects of minor alteration of heart and vessels are difficult to assess. A major predictor for future cardiovascular damages in children is blood pressure. Increments in the normal values of blood pressure in children are unusual and are mainly due to secondary causes as renal or endocrine diseases.

Children exposed to air pollution seem to present with higher values of systolic pressure. The number of studies available is limited, and some results are controversial [99]. This may be related also to the fact that the type of pollutants considered varies, as well as the timeframes considered in the studies. However, children exposed to ultrafine particles (UFP), PM_{10}, SO_2, NO_2, O_3 and

CO seem to be associated with increased level of arterial blood pressure and with hypertension [100, 101], both secondary to short/same-day exposure and chronic/long-term exposure.

Alterations of the cardiovascular system due to exposure to air pollution, which can potentially lead to major diseases in the adulthood, have not been proven. Nonetheless, some indirect indicators as the carotid arterial stiffness [102], increase in the level of plasma endothelin-1 [103] and endothelial dysfunction [104, 105] have been observed in children subjected to air pollutants. The presence of other risk factors as obesity can amplify the effect of air pollution on children's blood pressure [106].

Besides, as the association between long-term exposure to air pollution and cardiovascular conditions is known [107], it is reasonable to think that exposure starting from the early life can augment the risk of heart diseases in the future life of exposed children, triggering as well the same process of atherogenesis since childhood [108, 109] (see also Chap. 17).

10.3.8 Metabolism, Endocrinology and Obesity

The oxidative stress secondary to exposure to air pollutants and the poisoning interferences of toxins inhaled with pollution can alter the fine balance of the endocrine system. Because of the complexity and the heterogeneity of the hormonal signals, disruptions can happen at any level. Although the endocrinological effect of air pollution is known and well documented (see Chaps. 20, 21, and 22), there are a limited number of studies in children.

On the other hand, children are particularly affected by the effect of hormones that regulate the different phases of growth, from the first stages of life up to the transformations that happen during puberty and the transition to the adulthood. In particular, the sexual maturation of children depends on a series of chemical signals that can be easily disrupted. Interestingly one of the few studies available in children demonstrates the effect of air pollution on the adrenal cortex function [110] in schoolchildren, which may be related to a reduced spermatogenesis later in life, suggesting a possible correlation with disorder of the reproductive tract later and air pollution exposure during childhood. The same adrenal hormones are involved in the bone metabolism and mineral accumulation, suggesting possible effect on the bone resorption that may be crucial in a rapidly developing body.

The same response to insulin in children can be affected by air pollution. Insulin is mainly known to be involved in the regulation of carbohydrates and lipids metabolism, but its effects indirectly shape and design the architecture of the human body. Insulin resistance has been proven in primary schoolchildren exposed to long-term effect of NO_2, $PM_{2.5}$ and PM_{10} [111]. Although it is difficult to establish the real connection with growth restriction and insulin resistance, this finding may suggest an increased risk of development of diabetes later in life. A similar association has been observed in children with new onset of type 1 diabetes [112], suggesting a role of ozone and SO_4 in the triggering of this disease. As diabetes is a multifactorial disease, such associations are difficult to establish, and the number of studies is still

Table 10.2 Mechanism that could lead to obesity in children exposed to air pollution and road traffic

Direct	Indirect
– Direct obesogenic effect of air pollutants – Direct endocrine effect of air pollutants (can trigger obesogenic pathways) – Systemic inflammation (can trigger obesogenic pathways)	– Reduction of physical activities • Less time spent outdoor because of air pollution • Chronic disease related to air pollution • Stress related to air pollution – Reduction of walking or bicycling for transportation • Increased perceived danger coming from Traffic accidents Effect of air pollution – Change in diet • Higher intake of carbohydrates secondary to stress

limited. However, some papers point out how pollution can deteriorate the control of glucose metabolism and the insulin sensitivity secondary to oxidative stress and inflammation, although the effect on metabolic control in children has not been proven so far [113].

On the other hand, air pollution can indirectly lead to alteration of the diet and of food assumption (see Table 10.2) and to reduced physical activities that can eventually lead to increment of the body weight and of BMI in children [114]. Overweight and obesity are a known risk factor for metabolic dysfunctions and a possible cause of type 2 diabetes.

Moreover, studies suggest that some pollutants can have a direct role in the onset of obesity in children: some toxins as the phthalates can be directly obesogenic [115], while others can affect the endocrine system creating disruptions that can eventually lead to obesity.

To close the circle, obesity can worsen the respiratory symptoms of respiratory conditions (as wheeze or respiratory tract infections) triggered or caused by air pollution [116]. These pathways are highly demonstrative of the complex interaction between air pollution and the endocrine system in children, as well as the multitude of factors that can affect their growth and the development of diseases in the adult life.

10.3.9 Haematology

Impact on air pollution in schoolchildren has been described as early as the second half of the 1970s [117]. Although the relationship between exposure to pollutants and changes in the cells line in the bloods remains unclear, some studies suggest a possible reduction of the level of red cells and haemoglobin, with an increment of the number of white cells and platelets in the blood [118]. This may be in line with an inflammatory response secondary to air pollutants or to an increased incidence of respiratory, non-respiratory or systemic infections. On the other hand, it has been observed that exposure to lead in ambient air can increase the level of lead in children's blood and it has been associated in this age group with anaemia [119, 120].

Black smoke, NO_2 and SO_2 have also been considered possible causes of anaemia in children [121].

Although the data are limited, the observed association with air pollution and leukaemia in children [122–124] suggests that all the cell lines can be affected by air pollutants.

Haematological diseases can have a strong impact on young people affecting their growth and their quality of life; further studies in this field are therefore needed.

10.3.10 Respiratory

The respiratory system is a major target for air pollutions at all ages. The combination of environmental air, chemicals and particulate is actively inhaled in the pulmonary system. Gases are exchanged in the alveoli lumen; soluble and insoluble substances can be absorbed or can be deposited in the respiratory tract. Toxic components can cause damages and inflammation locally or can enter the bloodstream and diffuse systemically. Those same toxins can interact with the normal physiology, genetic expression, biochemical reactions and metabolism of the organism.

Children's lungs are physiologically more exposed to air pollutants because of the immaturity of their respiratory system and because of the higher exchange rate secondary to the higher respiratory frequency. It means that they are at higher risk for respiratory symptoms and conditions related to air pollution and for systemic diseases related to inhalation of air pollutants.

The effect of air pollution in children has been largely investigated [3, 5, 8, 9, 12, 84, 125–137]. The major effects and the possible mechanisms are summarized in Table 10.3.

The main effects observed in children are on development and exacerbation of asthma, on airway inflammation, on lung development and function and on frequency and recurrences of chest infection. Children can be exposed to outdoor and indoor pollution; different toxins seem to be associated with respiratory outcomes. In addition, respiratory symptoms in children strongly correlate with the type of exposure. The number of studies available in this field allows a grossly classification secondary to the different parameters considered:

a. *Early-life exposure*: It considers mainly the level of pollution at the birth address and at the time of birth.
b. *Long-term exposure*: It considers the overall exposure in children that lived for in a polluted area for a long period. The timeframe varies in the different studies and can be associated with the exposure since birth, differentiating those children that have been always exposed to air pollution from those that moved from a less polluted area to a more polluted area and vice versa. It is normally associated with a continuous exposure to pollutants, although in most studies, where continuous/daily monitoring of the pollution was not available, it may refer to annual, seasonal, monthly or weekly mean of exposure.

Table 10.3 Effects of air pollution on the respiratory system in children

Respiratory conditions or symptoms	Alleged responsible pollutants	Alleged type of exposure
Asthma onset	NO_2	Early life
	SO_2	
	$PM_{2.5–10}$	
	O_3	
	Traffic-related air pollution	Continuous
	$PM_{2.5–10}$	Short exposure
	O_3	
Wheeze and exacerbation of asthma[a]	NO_2	Higher peak in previous hours/day/week
	NO_x	
	SO_2	
	$PM_{2.5}$	
	O_3	
	CO	
	NO_2	Facilitate viral infections to trigger exacerbation after 1 week from exposure
Nonallergic asthma	Traffic-related air pollution	Early exposure
Airway inflammation	$PM_{2.5}$	
Progression to adult COPD	$PM_{2.5}$	Chronic
	O_3	
Decrease in lung function	SO_2, NO_2, NO_x, $PM_{2.5–10}$, $PM_{2.5}$ absorbance, O_3	Current and long-term exposure
	$PM_{2.5}$	Subchronic exposure
	O_3	
	Black smoke, PM_{10}, NO, CO	Acute exposure, affecting baseline function
	O_3	Acute exposure
Respiratory tract infection	NO_2	Short-term exposure
	$PM_{2.5}$	
	O_3	
	Solid and biomass fuel	Indoor, continuous/recurrent
	NO_2	Long-term exposure, annual average
	$PM_{2.5}$	
	$PM_{2.1}$	
Otitis media	Tobacco smoke	Passive environmental smoke; continuous (recurrent episode of otitis and earache)
Pharyngitis	Fungi	Indoor, short term
	Tobacco smoke	Passive and active smoking
Rhinitis and olfactory function	NO_2	Early life
	SO_2	
	PM_{10}	

[a]Include increased use/frequency of relief medication

c. *Short-term exposure*: It refers to children exposed to air pollution for a limited number of hours, days or months, according to different studies. It can refer also to children partially exposed to air pollution as those that commute from a non-polluted area to a highly polluted area (e.g. school, outdoors activities) and therefore are exposed to pollutants only for few hours per day/week.

d. *Same-day exposure*: It considers the immediate effects of air pollution on the respiratory system. Respiratory symptoms in this case are expression of an acute exposure to pollutants
e. *Home address exposure*: Consider the exposure at home. Children are likely to spend evenings, nights and weekend at home, when the level of pollution is normally lower. However, the number of hours spent at home is normally considered more than the one spent in other locations. Most studies consider the level of pollution in the different neighbour to evaluate the baseline exposure, especially when outdoor and school's hours' exposure is considered. It also helps to differentiate among those children that are constantly exposed to pollution (at home, because their home is in a polluted area, and at school) from those exposed to pollution only for a limited number of hours a day (at school and in other activities, because they live in a less polluted area). A common parameter to evaluate traffic-related air pollution is the distance from a busy road, while different monitoring techniques are considered to evaluate the mean exposure in different town's areas
f. *Commuting exposure*: Evaluate the time children spend commuting. Children living and going to school in relatively non-polluted areas can be even so exposed to pollution while moving on the traffic (car or public transport) or while walking or biking.
g. *School address exposure*: Children spend a considerable number of hours at school; children that attend school located in more polluted areas are more likely exposed to the effects of outdoor air pollution. In addition, the quality of indoor air in schools can be poor, because of the possible contaminants in the air (e.g. chalk's powder, fumes from the kitchen, heating), the number of people attending the building (increase the formation of dust, the spreading of respiratory infections) and the spreading of chemicals (e.g. cleaning solutions, printers' toners). Schools are more likely located near busy road than residential areas.
h. *Change of address*: Children can change address one or more times over the year. Most studies consider whether children included in their research have constantly lived in the same area for a given amount of time. It can help to differentiate from those children that have been constantly exposed to the same mean amount of pollution to those subjected to different concentrations of pollutants over the time.

Respiratory symptoms easily related to the different exposure to pollutants, as they are mainly expression of a direct damage of air pollution on the respiratory tract. Those same typologies of exposure are possibly linked also to other medical conditions associated with air pollution in children. However, the restricted number of studies in children limits this possible conclusion.

10.3.10.1 Asthma and Airway Inflammation

Asthma is a chronic inflammation of the respiratory tract characterized by reversible airway obstruction and hyper-responsiveness of the airways. The main symptoms of asthma are wheeze, increased work of breathing, dyspnoea, cough and increased secretion and mucus production. It is a relatively common condition in children even if its clinical presentation can be mismatched with other common cause of wheeze especially in infants and toddlers.

Air pollution is known to create a persistent inflammation of the respiratory tract, with an increment of the indicators of airway inflammation and oxidative stress, like pH, 8-isoprostane and cytokines [138]. Although the molecular mechanisms remain unclear, the correlation of chronic inflammation induced by indoor-, outdoor- and traffic-related air pollution with asthma is strong and consistent.

The burden of asthma in children is substantial. Symptoms can deeply affect the quality of life; asthma can affect school attendance, curricular and non-curricular activities, impacting thus on a child's career development; symptoms can present at night disrupting the sleep and therefore the daytime life; parents taking care of children with asthma may neglect their social and work life or other children not affected [139].

Asthma is a multifactorial condition. Genetic predisposition has a major role, but environmental triggers remain a key factor in its onset and relapses. Any cause of inflammation or irritation of the airways can potentially trigger exacerbations of asthma, including viral and bacterial infection and exposure to chemicals.

Considering the number of possible confounders, the real impact of air pollution on the development and exacerbation of asthma remains unclear, despite the number of studies available on this subject. Yet, although complex, the association with inhalation of air pollutants and asthma in children remains clear.

The complexity depends on the several factors that must be considered, as different pollutants and types of exposure can act on the different mechanisms involved in the onset and exacerbation of asthma in children: oxidative stress, IgE-mediated sensitisation, airway inflammation, lung function, airflow obstruction, airway responsiveness and the use of medications and preventers [133, 140, 141]. On the other hand, cleaner air seems to be associated with a reduction of the airway inflammation and to an improvement of the lung function [142].

From a clinical point of view, it may be difficult to isolate a single chemical or particulate related to asthma: exposure to air pollution is rarely selective in children, and specific prophylactic measures able to reduce the exposure to single cadre of pollutants are limited.

However, understanding the cause of onset and exacerbation of airway inflammation and asthma could help clinicians in their clinical management of children with wheeze improving: the likelihood of diagnosis, the decision to start a pharmaceutical prophylaxis, the management of acute asthma also in community-based health facilities, the health education of children affected or presumably affected by asthma and the lifelong consequences of asthma like the development of chronic obstructive pulmonary disease in adulthood, which may be aggravated, caused or accelerated by the same air pollutants [143].

Onset of Asthma

Small children presenting with recurrent wheeze may represent a clinical challenge for paediatricians who should decide if and how to treat acute symptoms and whether to start a chronic treatment and prophylaxis.

As a multifactorial disease, asthma may remain latent in children or may present with blurred clinical symptoms that may mimic—especially in the youngest—other common clinical conditions as upper and lower respiratory tract infections. Children presenting with wheeze may or may not be affected by asthma, and children with asthma can present with wheeze with or without a common viral infection. For this reason, it is difficult to evaluate the effect of air pollution in children below the age of three when studying the incidence and prevalence of asthma [144] and consequently the role of air pollution in the onset of new cases.

Many studies however show a possible association with air pollution exposure and onset of asthma in susceptible children. Early-life exposure to NO_2, SO_2, $PM_{2.5–10}$ and O_3, early-life [145] and continuous exposure to traffic-related air pollution [146, 147] and maternal smoking during pregnancy where the foetus is successively exposed to air pollutants [148] may be the major factors, with an association of 1.5–2-fold increased risk of lifetime asthma for children exposed to NO_x [127], with children living close to busy road and freeways being at higher risk [134].

New onsets of asthma in children coming from lower-income urban areas consequently to early-life exposure to NO_2 [149] and to short exposures to high concentration of O_3 and $P_{2.5}$ have been also noted [150]. However, exposure to NO_2 remains a major suspected cause for the development of asthma observed in schoolchildren [151].

These findings suggest that environmental hygiene remains a key factor in the prevention of the onset of asthma in children [152, 153]. Moreover, studying and monitoring [154] the type and amount of exposure to air pollution can help to map the population of children at higher risk to develop asthma and to create individualized risk profiles.

An environmental anamnesis is crucial, and clinician should consider information coming from a child's social history and from public health sources when considering a diagnosis of asthma and in designing a therapeutic and prophylactic plan for their little patients.

Exacerbation of Asthma

Several studies underline the relation among short-term and chronic exposure to air pollution with the relapses of episodes of acute asthma [125], highlighting how acute exposure is a stronger cause of exacerbations than long-term and early-life exposure [155]. Children with asthma already suffer from a chronic inflammation of the respiratory tract and for this reason are more vulnerable to the irritant, inflammatory and oxidant effects of air pollutants. Air pollution contributes to increment the level of airways inflammation, lowering the threshold of bronchi response and increasing the likelihood of relapses: pollution can adjuvate external or internal stimuli known to trigger asthma like viral infections or exercise. In addition, fluctuations of the concentration of chemicals and particulate in the indoor or outdoor air can trigger per se asthma attacks in children.

As genetic polymorphism may be related to lifetime asthma [156], it is not surprising that children with concomitant conditions can be at higher risk of relapses: in fact, children with atopy seem to be more prone to develop wheeze secondary to short-term exposure to air pollution [157].

Exacerbations of asthma in children known to be asthmatic are mainly correlated with short-term exposure to pollutants and with an increase of the concentration of chemicals and particulate in the air. Interval symptoms or chronic symptoms of bronchitis—namely, daily cough for three consecutive months and congestion or phlegm for at least three consecutive months—have been reported in children exposed to air pollution [158], suggesting a stretching of the acute effects related to short-term exposure and exacerbation of asthma, possibly related to the oxidative stress and continuous inflammatory response.

Thus, children constantly subjected to pollution may present a chronic inflammation of the airways, but fluctuations from baseline concentration of toxins are likely the main cause of acute episodes of asthma: studies show that daily high peak of NO_2, NO_x, SO_2, $PM_{2.5–10}$, O_3 and CO is related to an increment of relapses of the symptoms of asthma the days following the exposure [159], increments of CO, NO_2 and partially SO_2 concentration are often related to episodes of exacerbation 2–3 days after the exposure [160–162] and a cumulative effect lasting over the days after the exposure has been described [163].

Seasonal variations of the concentration of pollutants also relate to an increment of acute cases and hospitalizations [164, 165]. Seasonal and short-term rise of pollutants results in a higher number of emergency department visits and also in big cities with normally low level of pollution [166]; the overall number of relapses, asthma medication use and hospital admissions for acute asthma remains higher in children acutely or chronically exposed to air pollution [160, 162, 167–169].

Other factors influence the reactivation of the disease in asthmatic exposed children, as the use of preventers. Children using inhaled or nebulized corticosteroids may be at higher risk of exacerbation secondary to acute (daily or hourly) increment of concentration of $PM_{2.5}$, PM_{10} and O_3 [170]; NO_2-facilitated viral infections [171], seasonal climate variation, air pollen concentration and second-hand smoke are known to trigger acute asthma [172, 173], the latter being outdoor and indoor air pollutants themselves.

For these reasons, environmental prophylaxis can reduce the number of relapses, emergency departments and hospital admissions. Health education in primary care settings can help to reduce the risk of indoor pollution that may lead to acute cases of asthma. Public health policies can help in reducing the fluctuation of air pollutants, decreasing the chance of inhaling higher concentrations of toxins. Mapping and monitoring the time and areas with peak in concentration of pollutants can help in creating forecast of request of medical attention in primary, secondary and tertiary care for acute asthma—grading from mild to severe. This can be useful both to plan and optimize resources and interventions and to develop public health policies aimed to reduce the number of relapses and hospitalizations.

10.3.10.2 Respiratory Tract Infections

Respiratory tract infection is a group of very common medical conditions in children. Those are communicable diseases directly caused by microorganisms. Some like pneumonia or bronchiolitis are strongly related to increments in hospital admissions and emergency departments' visits, ranging from mild to severe and life-threatening presentations. Several factors contribute to the development of a disease following a contact with the pathogens, among which are the type of organism, its virulence, the concentration of pathogens that enter in contact with the host and the active and passive defences of the host.

Although the microorganism in itself by definition is the sole direct cause of an infectious disease, these factors can act on the chain of events that lead from exposure to a pathogen to the development of an infectious disease in the host; those are indirect causes of the disease and may be the precipitating factors that lead to the clinical manifestation of the contagion. In other words, some pathogens may infect the host, which overcome its active and passive defences and have clinical manifestations, because of an external concomitant synergic cause.

Traffic-related air pollution and indoor fumes coming from the use of solid biomasses have been related to increased risk of upper and lower respiratory tract infection [5, 131, 171, 174–181]. The exact mechanisms are not known, although the most likely factors are listed in Table 10.4.

As discussed in Sect. 10.3.10.2, viral infections have been observed in children exposed to air pollution shortly before the onset of the symptoms, in some cases leading to secondary effects as exacerbation of asthma in sensitized subjects, being the two conditions strictly related.

Table 10.4 Possible mechanisms that contribute to the development of infectious diseases in children exposed to air pollution

Most likely factor	Possible mechanism or causing condition
Increment of the virulence	Pathogens as part of air pollution in themselves (e.g. fungi)
	Pollutants acting as carrier for pathogens
	Poor environmental hygiene leading to increased concentration of pathogenic organisms and strains
	Pollutants selecting pathogenic organisms' strains
	Selection of resistant and multiresistant pathogenic strains secondary to the dissemination of chemicals in the air (e.g. disinfectants)
Increased likelihood of contagion	Increased indoor activities with poor ventilation in crowd locations (schools, recreational areas) secondary to high outdoor pollution
Impairment of passive defences in the host	Irritation of the upper airways
	Reduced or impaired ciliary motility caused by pollutants
	Thickening of airways secretions
	Impairment of the clearance of the airways
	Exacerbation of asthma or other subacute condition that facilitates penetration and expression of the pathogen
Impairment of active defences in the host	Impairment or reduction of the immune system response (cellular and humoral mediated) in children exposed to the effect of air pollution
	Interaction with the immune response pathway in the epithelial cells of the respiratory tract
	Impaired activity of alveolar macrophages as reduced adherence to surfaces, ability to phagocytize bacteria and intracellular bactericidal processes
	Increased inflammation response
	Increased oxidative stress

Atypical infections related to air pollution as well have been described: this is relevant as microorganisms like *Mycoplasma pneumoniae* causing this type of disease are resistant to first-line drugs normally used in children to treat chest infections. *M. pneumoniae* is supposed to interact with metals present in fine particulate ($PM_{2.5}$), activating the inflammatory pathway and increasing the oxidative stress [182], which eventually lead to a defective response of the immune response. Therefore, children exposed to air pollution may be at higher risk, and second and third lines of treatment have always to be considered in symptomatic patients with poor clinical response to standard antibiotics.

Chronic exposure to traffic-related pollution and household pollution can be also at higher risk of opportunistic infections: tuberculosis has been positively associated with exposure to CO and NO_2 and solid fuel fumes in adults [183, 184] and in children exposed to tobacco smoke [87]. This is not surprising as tuberculosis can take advantage of the impairment of immune response in people exposed to air pollutants; it also means that in patients with latent or subclinical tuberculosis infection, air pollution can trigger relapse and acute up to life-threatening exacerbations of the disease. On the other hand, tobacco smoke can reduce the activity of pulmonary alveolar macrophages that are a major barrier to *Mycobacterium tuberculosis* infection.

Fungi can be also a component of air pollution, and higher concentration can be observed in areas with poor environmental hygiene like schools [185], especially those with a higher concentration of dust and mould like the ones with carpeted floors [186]. This can lead to minor symptoms as stuffy sinuses, sore throats, respiratory illnesses, lethargy, itchy eyes and runny noses [187] to a higher rate of serious pulmonary infections in susceptible children.

For these reasons, children at high risk for opportunistic infection, as *HIV*-positive patients, should be particularly monitored and protected from air pollution exposure.

10.3.10.3 Lung Function

Organs and tissues belonging to the airways are the more exposed to air pollutants and to their negative effects, in terms of growth and development. As we have seen, a chronic inflammation of the respiratory tract secondary to early, long-term and short-term exposure may be responsible for chronic obstruction and hyper-responsiveness, leading to increased episode of wheeze, cough and respiratory symptoms in general. However, long-term exposure may be responsible of permanent or long-lasting effects, in terms of maturation of the respiratory tract, like lung growth and alveoli differentiation [188].

The study of lung function in children gives reliable information on the development of the respiratory system in children. Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF) are the parameters most commonly used to measure the lung function in children [130]; their modification from reference range or from previous individual baseline recordings in children exposed to air pollution can demonstrate acute and chronic changes.

Several studies agree that exposure to outdoor and traffic-related pollution, as well as indoor pollution, produces negative effects in terms of lung function and consequently on respiratory tract development and maturation both in asthmatic and in non-asthmatic children, with some evidences of worse outcomes in children with concomitant conditions as atopy [126, 127, 130, 135, 189–203].

Because of the heterogeneity of the studies, the possible confounders and the different type of pollutants and exposure, the real extent of the damages on developing airways remains unclear.

Further studies are needed to evaluate: what are the population at higher risk; what chemicals and particulate are more likely to interact with a developing respiratory system; what damages are caused by which toxin; which damages are permanent and which are reversible and by which extent and what type of exposure to the single component (e.g. high peak, short term, long term, continuous, sporadic, early) causes permanent or reversible damage.

As the respiratory effect of air pollution in childhood can persist in the adult life increasing also the risk of respiratory disease of the older age [5], these information are crucial. Especially in children, they can be useful to establish which actions—in terms of individual prevention and public health interventions—can be more effective to reduce the risk of lifelong effects on the respiratory tract.

10.3.10.4 Upper Respiratory Effects: Otitis, Rhinitis and Olfactory Function

The upper airways are directly exposed to the higher concentration of pollutants in the breathed air; moreover, the mechanic defences like nasal cilia and mucous, although preventing the deep inhalation of particulate and toxins, increase the chance of prolonged interactions between toxins and tissues in nose, throat and ears.

As we have seen (see Sect. 10.3.5), children exposed to ambient air pollution and particularly to indoor passive tobacco smoke show an increased risk of eustachian tube disorders that can lead to recurrent episodes of earache and otitis media, one of the commonest requests for medical attention in children. Chemical irritation as well as the effect of biological pollutants like fungi of the upper respiratory tract can also result in acute episodes of pharyngitis, while environmental tobacco smoke has been associated with chronic sinusitis, chronic disease of tonsils and adenoids and chronic laryngitis [204].

Irritation of nose and throat mucosae is a common and widely experienced effect. However, a growing body of evidence link the early-life exposure to pollutants as NO_2, SO_2 and PM_{10} to the onset of lifelong allergic rhinitis [205] and olfactory dysfunction. Moreover, the neurological damages of air pollution (see also Sect. 10.3.3) have been observed also in the olfactory bulbs, which may represent a main target for pollutants. Olfactory bulbs exposed to pollutants present endothelial hyperplasia and accumulation of ultrafine particles in the endothelial cytoplasm and basement membranes [206]; these findings are consistent with a damage of the olfactory function in children and support the idea of severe neurological damages in subject exposed to air pollution since early life.

10.3.11 Allergies

As we have seen (see Sect. 10.3.10.1), air pollution is strongly associated with asthma onset and exacerbation of asthma, particularly in children with atopy. Allergic asthma is a relatively common condition, and it is often associated with other allergic conditions in the youngest as rhinitis, hay fever, eczema and dermatitis. Airborne particles, like pollens, spore and fungi, can cause allergic reactions. Although most of them come from natural source, biological contaminants are pollutants in themselves; human activities can increase their concentration [207] in urban and rural areas or increase the chances of contact for sensitive children. Example of that are cultivation and agriculture or industrial food processing up to the alleged climate changes due to the same human activities and demographic expansion.

Pollutants can bind pollens and airborne biological allergens, working as carriers and increasing their effects on human beings; air pollution on the other hand can increase the allergenicity of pollens, secondary to morphological changes, increased allergenic proteins release and exposure and pollen release in the atmosphere as a response of the vegetation to environmental conditions [208–210] that facilitate the IgE-mediated reaction in sensitized children.

Allergens coming from natural sources are directly linked to allergic response, but there is also a strong association between long-term exposure to chemicals and air pollutants like particulate matter, NO_2, SO_2 and ozone and atopic diseases like asthmatic bronchitis, bronchial hyper-responsiveness, rhinitis, hay fever, eczema and sensitization [211–213].

Air pollutants cause airway mucosal damage and impaired mucociliary clearance increasing the concentration of inhaled allergens and therefore their presentation to the cells of the immune system, promoting consequently airway sensitisation. Particulate matter and ozone are also related to oxidative stress that leads to airway inflammation, hyperreactivity and reduction of the mechanisms that are known to prevent allergies. In addition, diesel exhausts coming from traffic-related air pollution seem to directly stimulate the IgE synthesis, which is the basis of the allergic reactions [132, 212, 214, 215].

It is still unclear if air pollutants can increase the chance of allergies' onset in children not known to have atopy, directly causing the development of the allergic sensitization [216], although strong association has been found [211, 217]. Some children may be more susceptible to the oxidative effects of air pollution secondary to their genotypes [84]; that may explain why some individuals develop allergic diseases later on in life, but it also explicates why the effect of air pollutants on the modulation of the immune response is so complex and difficult to ascertain.

10.3.12 Cancer

The mutagenic action of some of the many components of air pollution is well known and well documented, as well as the link with carcinogenesis (see Chap. 23).

Several airborne chemicals and particulate matter have been associated with respiratory and non-respiratory malignancies; for some of them, the causal effect has been demonstrated, while exposure to others shows an increased risk and odd ratio for the development of cancer.

Yet, it remains unclear whether the exposition to air pollutants during early life and infancy can increase the risk of developing cancer in later childhood and in adulthood. Most of the studies try to link traffic-related air pollution or environmental tobacco smoke exposure in childhood to some types of cancer. Although the data are extremely limited, there are mild indications of second-hand tobacco smoke and lung cancer in adult life and non-respiratory childhood cancers, particularly leukaemia, lymphoma, brain and central nervous system tumours, Wilms' tumours, acute lymphatic leukaemia and central nervous system cancers [5, 218]. The strongest correlation seems to be related to motor traffic emissions, which may be involved in the aetiology of childhood leukaemia [124, 219], Hodgkin's disease [220] and other childhood cancers [123], although results are still controversial due to the partial information available and the possible confounders [220, 221].

On the other hand, inhalation of chemicals and particulate matter is only a possible way of exposure, and some of the toxins present also in air pollution may give cancer in children or adults otherwise exposed. This assumption implies also that air pollutants deposited on surfaces can enter in contact with exposed children (e.g. skin contact, ingestion) potentially leading to DNA damages and mutations during the same childhood or later in life.

For some components of air pollution, a possible mutagenic activity has been observed, with increased level of biomarkers of genotoxic substances exposure, even if no clear association with cancer in childhood has been found [222].

However, epidemiological studies in this field are defective, as the complex mixture of toxins presents in air pollution represents a major limitation. The sole products of combustion are representative of the complexity in studying correlation between pollutants and cancer development [223], as identifying critical components in the mixture, their source and their exposure and the related effects is a challenge. This is particularly true when exposition happens during childhood, and the effects are observed decades later, when an assessment of all the possible confounders is not always possible or reliable.

Further studies are therefore needed, to better clarify the role of the numerous pollutants and their possible short- and long-term carcinogenic effects in children and young adults.

10.4 Diagnosis

From a clinical point of view, because of the numerous implications of early-life, short- and long-term exposure to air pollution in children and the possible effect on health both during childhood and later in the adult life, it may be crucial to evaluate which children are or have been exposed to pollutants and in which terms. There are no clear models at the moment that can be used in clinical scenarios and in clinical settings. The different methods used in observational studies may be appropriate in research, but can be difficult to use in the clinical practice.

Continuous monitoring of air pollution with station in proximity of residential areas and schools can offer a possible source of information, but data should always be available, and paediatrician may not be able to use that information in clinical decision-making. Community doctors should nonetheless be able to access to environmental data and to crosscheck individual demographic information to assess risk of individual exposure in single children.

As we have seen, this information may be critical in clinical practice to better define profiles of risk, to assist doctors and paediatricians in differential diagnosis, to promote a proactive approach aimed to prevention and prophylaxis of selected conditions, to promote healthy lifestyles and reduce the burden of air pollution and air pollution-related diseases in children.

Further information may come to laboratory tests, able to determine if a child has been exposed to air pollution and to specific pollutants, as well as the entity of that same exposure.

10.4.1 Possible Markers of Air Pollution Exposure in Children

The definition of markers of air pollution exposure could open a whole new chapter in the clinical practice, especially in children. As it is becoming more clear that air pollutants are involved or are direct cause of several and severe medical conditions, the assessment of exposure should become a common practice in clinical settings.

However, although the effects of pollution on human health have been known or suspected for a long time, this is a relatively new field of medicine, in terms of clinical and practical applications. The different time and form of exposures to air pollutants in children are a further limitation, also because of the many possible ways in which children can get in touch with toxins (see also Table 10.1).

For some pollutants, it may be possible to have a direct or indirect reading of the level of contamination, as the measure of concentration of heavy metals in water or in food commonly ingested by children of specific population, of the actual individual exposure to given pollutants or of the tissue or blood concentration in living individuals. While the first gives an esteem of the absorption and interaction with toxins, the former can give a direct reading of the level of contamination and therefore of the possible health effects.

Other approaches try to find those markers—as product of catabolism or effect-related molecules—that may be dosed in bloods and other body sources or samples and that may be direct or indirect expression of dose-related exposure to air pollutions and to specific toxins.

A number of chemicals and techniques have been studied; some are summarized in Table 10.5 [69, 83, 91, 98, 138, 141, 154, 224, 225].

It should be noted that some markers may result sensitive but not specific, as they merely represent the final effect of the exposure; this is particularly true for the marker of inflammation or of immune response or of oxidative stress.

Table 10.5 Some of the markers of exposure that may be used in research and in the clinical practice to ascertain if a child has been exposed to air pollution or to its effects

Marker or technique	Source	Pollutants and effect
Cotinine concentration	Serum	Environmental tobacco smoke exposure
Interleukin-6	Whole blood	Traffic-related air pollution exposure
Interleukin-8		
Interleukin-10		
Monocyte chemotactic protein-1		
Tumour necrosis factor-alpha		
Interferon-gamma		
Apolipoprotein E ε4 allele	Genetic test	Increased risk of brain function impairment in children with the allele exposed to air pollution
pH	Breath	Airway inflammation secondary to traffic-related air pollution
8-Isoprostane	Breath	Oxidative stress secondary to traffic-related air pollution
Interleukin-1	Cerebrospinal fluids	Oxidative stress, inflammation, innate and adaptive immune responses in the central nervous system of children exposed to urban air pollution
Interleukin-1 receptor antagonist		
Interleukin-2		
Macrophage inhibitory factor	Serum	Inflammation in the central nervous system of children exposed to urban air pollution
Cellular prion protein	Cerebrospinal fluids	Accumulation of misfolded proteins in the central nervous system of children exposed to urban air pollution
Polycyclic aromatic hydrocarbons–DNA adducts	Umbilical cord white blood cells	Behavioural effects on children exposed to airborne polycyclic aromatic hydrocarbons
Lung radiology (X-ray and computed tomography)	Radio-imaging	Non-specific modifications in children chronically exposed to urban air pollution
[15N]Methacetin test	Urine	Reduction of liver detoxification capacity in children exposed to urban air pollution

This data, therefore, should be merged with information coming from individual demographic records and local epidemiological measurements.

10.5 Management and Prevention

The identification of those subjects at higher risk for air pollutant exposure is crucial in the management of the air pollution-related diseases in children, as well as the assessment of the type and level of exposition. For this reason, paediatricians should always consider the possible effect of air pollution when dealing with their little patients and ask about environmental anamnesis when taking a medical history. The number of tests available so far to routinely evaluate the level and the effect of exposure to air pollutants is limited, and as we have seen, they are not specific for given pollutants. Data on local level of pollution are available only in selected areas and that same information may not be useful to properly evaluate the individual exposure.

The use of mobile devices may be useful to map the daily changes in exposure, tracking children movement in the different urban areas (e.g. home, school, playground) and the air quality index in that same places. That would give a punctual picture of the hour-by-hour individual exposure, provided that children can carry smartphones and technologies with them and that a reliable monitoring of the quality of air is obtainable. Those technologies are already potentially available, but a widespread use of them is still far to reach and has practical implications that need to be overcome.

On the other hand, children living or studying in metropolitan areas, in urban areas and in places with a high level of emissions (urban, rural or semirural areas close to factories or plants) should always be considered potentially at risk.

Because of the number of acute, chronic and lifelong consequences of air pollution, the patient at risk has to be monitored during the time, and the correct information should be obtained and given in order to reduce the health risk associated with air pollution. In a patient-centred approach, doctors should improve the level of communication with children and families, aiming to a long-term relationship that could help to improve the outcome of health education.

The role of prevention, in fact, is essential, as some of the effect of air pollution may not be reversible, while others may emerge later in the adult life, when the damage has already been done.

Besides, prophylaxis and prevention at the moment are the real clinical measure that paediatrician can use to reduce the risk of adverse health effect secondary to air pollution in children.

In order to achieve that, the key actions for the management of air pollution-related diseases in children are:

a. Detecting, measuring and monitoring air pollution
b. Protecting children from pollutants
c. Cleaning up of the areas where children live or spend most of their time
d. Reducing indoor and outdoor exposure promoting behavioural changes and public health interventions

The monitoring of outdoor and indoor air pollution in those areas where children live, study and play [154] is essential. As we have seen, children are peculiar and are particularly exposed to air pollution and to its effects when compared to adults. Detection of sources of air pollution and of the characteristics of the pollutants and their diffusion in the air should be taken in account, to produce reliable information to assess individual exposures. For those reasons, specifically designed tools, tailored to children's social, behavioural and physiological specificities, should be engendered. Indoor and outdoor detectors for the main pollutants should be in use at home and at school, and those data should be available to community paediatricians, public health doctors and policy-makers. Children at higher risk as the ones with atopy or respiratory conditions should be constantly monitored so to create individualized plan of intervention aimed to reduce the chance of relapses and severe exacerbations. Alerts on individual bases should be sent during peaks of concentration of chemicals, particulates and biological pollutants. Those same alerts should take into account the place where the child lives, where he or she attends school and extra-scholar activities and the route he or she follows while commuting. The average level of exposure (weekly, monthly and annually) should be known and recorded on personal files.

In children at high risk and in those acutely or chronically exposed to high level of air pollution, personal protection devices should be considered. Face masks are a possible option, provided that their technical specificities are adequate so to effectively block fine and ultrafine particulate and hazardous chemicals. Because they may be not well tolerated by children, this equipment has to be specifically designed for children, taking in account their behavioural and physiological peculiarities.

Schoolrooms and bedrooms at home can also be screened to reduce the amount of pollutants coming from outdoor sources. At the same time, the ventilation of those ambient where children spend most of their time, especially schools [187], has to be adequate, so that clean air can clear the ambient reducing individual exposure and therefore the need of personal protection devices.

Because of the many health hazards secondary to indoor pollution, the best prevention in this sense is to reduce the source of pollutants. Second-hand tobacco smoke is a major cause of indoor pollution, and for this reason, adults should never smoke in places with children, should avoid smoking at least 10 min before entering a place where children are and should not wear or bring in clothes they had on while smoking (exposure to third-hand smoke) [226–228].

Cleaning up the air in ambient where children live, reducing the level of pollutants and consequently the amount of chronic and acute/peak exposure, is proven to improve the health condition of children and their quality of life reducing at the same time school absences, the number of hospital admission and medical intervention [136]. The reduction even of small level of air pollution indeed reduces the burden and the respiratory symptoms in children [229]. This can be achieved locally with the implementation of air cleaner devices that may be mounted at school and those indoor places where children spent their time. Personal devices can also be used at home, especially at night to guarantee a clean ambient during sleeping time. Home-based devices can be used in single rooms, like children's bedrooms, to assure a good quality of air especially for those houses close to busy road even in the night-time or near industrial areas.

Although social, extra-scholar and sport activities are extremely important in children, the amount of pollutants that they can inhale during the time they spend outdoor can have dangerous consequences on their health. Reducing the exposure, limiting the hours spent outdoor when the level of traffic and of pollutants in general is higher, should be considered. This also implies that traffic and emission should be strongly regulated in areas where children study, play or practise outdoor activities, especially during the time of the day and the year when those places are busier.

Conclusions

Air pollution is a major issue in children as they are particularly exposed to its effects when compared to adults. Although several studies highlight the damages of air pollutants to the airways, little is known about the other effect on children's health and on the lifelong consequences of early exposures to these elements.

A growing body of evidences yet show how the damages are not limited to the respiratory system and some of the effects can cause serious and permanent damages.

As children grow, the cumulative effect of toxins present in air compound can emerge developing chronic conditions that may not be treated in the adult age.

Because of the peculiarities of children's lifestyles, the chance of outdoor and indoor exposure spreads across the different areas where they live, study or play, across the different times of the night or the day and across the different seasons of the year. In other words, children can be continuously exposed to background pollution and the effect of short-term peak in concentration of toxins. Some children may be more vulnerable than others because of underlying pathologies, sensitization, responsiveness to pollutants or genetic profile. On the other hand, every child can be seriously affected by the effect of air pollution, and it is currently not possible to estimate which level of exposure to which children and to which component can bring to acute, subacute or chronic consequences in susceptible and in healthy children. That has practical consequences in paediatrics and in public health, resulting in an increased number of hospital and emergency department admissions, help-seeking behaviours and ultimately health policies development and implementation.

Changes in air quality should be monitored, and individual exposure should be estimated for every child living in highly polluted areas or in places close to source of pollution like busy road, plants or industrial areas.

For these same reasons, information on air quality should be easily accessible to doctors, as peak of concentration may result in an augmented request of intervention and hospitalization; those same children known to have recurrent relapses should be alerted, so that adequate precautions can be taken to reduce the risk of exacerbation of chronic or subacute diseases.

Because any organ or system can be potentially affected also with serious and lasting consequences, doctors should always consider air pollution exposure while taking medical history in children; at the same time, children and families should be sensitized on the effect of pollution on health, and effective measure should be suggested and taken to reduce the chance of exposure.

A number of factors contribute to an increased vulnerability in children. Some are physiological, and no individual action is possible. Others can be modified in order to reduce the risk on health: behavioural changes are important, and health education can help to reduce the children's exposure to air pollution. Nevertheless, decision-makers should engage themselves in policies aimed to radically improve the quality of the air that children breathe in residential areas, at school and outdoor.

Besides, actions to reduce the impact of air pollution on children's health have been proven to be cost-effective [136], reducing the burden for families and for the society and diminishing the costs of acute medical interventions and those secondary to the management of chronic and potentially lifelong conditions.

These considerations are not limited to high-income countries with an elevated technological development profile. The burden in developing countries is still not completely known, although the high growth rate of big cities and small centres are likely to produce a poorly regulated level of pollution that may primarily impact on children which remain a major component of those societies. In addition, even in rural areas, children may be particularly subjected especially to indoor pollution, and action to reduce the exposure had to be fostered: behavioural changes in fact can highly reduce the devastating effects of these highly poisoning mixtures on children's health [230].

Policy-makers, paediatricians, emergency department and public health doctors have to be aware of the clinical consequences of air pollution in children, so that programme of prophylaxis and prevention can be planned on individual and community level. Families as well have to be informed of the risks of air pollution on their children's health and the potential sources of exposure, which are not limited to busy or undeveloped urban areas or to external factor on which they are unable to act. Parents should be in fact aware that outdoor pollution can affect also the quality of the air in their homes and of children's bedroom during the hours of sleep. Health education programmes should also emphasize the role of indoor air pollution and of second- and third-hand smoke, so that behavioural changes can reduce the chance of exposure to toxins coming from everyday activities.

Children should be protected when appropriate with personal protection equipment, and parents and educators should always make sure that the air children are breathing is good and the ambient in which they live, study and play cleaned up from pollutants.

Simple local actions, as well as major change in policies at national and international level, are needed in order to ensure a reduction of emission and of exposure, improving the air and the ambient where children live, their health and wellbeing and eventually their quality of life and of that of their families.

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