Ambient Environmental risk factors for childhood wheezing illness

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1. ABSTRACT

   It is a great consensus in the scientific community that environmental factors, such as weather conditions and ambient air pollution, have vital impacts on respiratory diseases. Further, these factors imply the potential to have many significant impacts on aeroallergens, and therefore related diseases such as asthma and allergic rhinitis. The impacts are more pronounced in sensitive groups of population, such as children and elderly, living in urbanized areas. Over the last three decades, studies have shown changes in production, dispersion and allergen content of pollen and spores, which may be region- and species-specific. In addition, these changes may have been influenced by air pollutants interacting directly with pollen. It is not easy to evaluate the impact of climate change and air pollution on the prevalence of asthma in general and on the timing of asthma exacerbations. However, the global rise in asthma prevalence and severity suggests that air pollution and climate changes could be contributing. The objective of this review is to summarize the environmental impacts on pulmonary diseases in children based on recent literature over the world.

2. INTRODUCTION

   Climate changes affect many physical and biological systems, including the immunologic and respiratory systems that are critical to human health, and it is foreseeable that environmental risk factors will have a stronger effect in the coming decades (1). Studies on the effects of climate change on human health respiratory allergy are still lacking and current knowledge is provided by epidemiological and experimental studies on the relationship between asthma and environmental factors,
such as meteorological variables, airborne allergens and air pollution. Asthma is the most common chronic disease among children (2). Its prevalence is up to 10% of the general paediatric population in Europe (3). Despite advances in asthma management, asthma exacerbations continue to occur and the frequency varies depending on the severity and the degree of control (4). The majority of asthma exacerbations are usually preceded by viral upper airway infections (5). Other exacerbation triggers are also: allergen exposure, weather conditions, and air pollutants (4). There is a link between climatic agents, air pollution and children’s exposure to aeroallergens (6). The impacts of environmental factors on aeroallergens, and in particular pollen, include impacts on pollen production and atmospheric pollen concentration, pollen season, plant and pollen spatial distribution, pollen allergenicity, and similar impacts on mould spores (7). Furthermore, the aforementioned clinically important allergens are particularly sensitive to changes in air pollutants (8). Hence, asthma presentation in children may be significantly dependent on environment, even though probably there is globally no single sufficient factor. The purpose of this review was to detect links between environmental factors - weather and ambient air pollution - and anticipated increases in prevalence and severity of asthma and related allergic disease mediated through worsening ambient air pollution and altered local and regional pollen production. Original research studies published in English between 1985 and 2014 were selected (PubMed and Scopus). Computer searches used combinations of Key Words relating to “environmental conditions”, “asthma” and “allergy”. In addition, the reference lists of the retrieved articles helped in the search for other relevant articles which were not found during the searching initial procedure. Thus, relevant interdisciplinary studies with respect to environmental impacts on childhood wheezing illness (including cross-sectional, case control and population based studies) were selected and discussed in this review, focusing mainly on recent literature. The potential factors which may bias the findings of this review are restriction articles in English, together with database, and citation bias.

3. WEATHER CONDITIONS AND WHEEZING ILLNESS

There has been an increasing concern about the effect of weather conditions on human health in recent years, considering that many human diseases such as cardiovascular problems (9-12), pulmonary diseases, mortality (13) and even though psychological symptoms (14) are linked to climate fluctuations (Table 1). In addition weather conditions are a significant driver of respiratory infections (15). Bronchial asthma is the most common chronic respiratory illness in childhood, which is characterized by symptomatic periods. The symptoms are characterized by wheezing, breathlessness, chest tightness and coughing. The symptomatic periods are created mostly by atmospheric conditions, and they reveal the clinical picture of asthmatic patient.

In Western Europe (57 centers in 12 countries), asthma symptoms have been increased by 2.7.% (95% CI 1.0.% to 4.5.%) with an increase in the estimated annual mean of indoor relative humidity of 10%. The correlation between altitude and the annual variation of temperature and relative humidity outdoors were negatively associated with asthma symptoms (16). The day to day change in weather patterns contribute to the total variability of respiratory diseases. These changes can be provided by the changes of meteorological parameters such as mean, maximum and minimum air temperature, air temperature range, relative and absolute humidity, sunshine, surface atmospheric pressure, wind speed and the day to day changes of these parameters. In Athens the respiratory infections are mostly influenced by the decrease from higher barometric pressure, air temperature and absolute humidity (17).

Young children having reduced regulating mechanism against extreme bio-climatic conditions are exposed at high risk (18). A previous study made in Buenos Aires found an increase in lower respiratory infections (LRI) in children under 5 years old, during wintertime (19). Similarly, Goncalves et al. 2005 (20) in Sao Paulo found a decrease in respiratory morbidity under hot and dry weather conditions. In agreement, another study in Cordoba, Argentine, by Amarillo and Carreras 2012, (21) showed that the highest risk for upper respiratory infections (URI) was during winter, fall and spring, but also they found a significant risk during spring for LRI. Numerous studies have proved that upper respiratory infections (URI) are affected by low temperature. However the reasons for this seasonality are still controversial because many different social and biological factors contribute to the increase incidence of these diseases during the winter months, such as the crowding promotes the transmission, breathing cold air causes drying of the mucosal membrane and even low temperatures favor the survival of pathogens (21). Study in Izmir, Turkey has showed that there is correlation between atmospheric conditions and asthmatic symptoms in children between ages of 5 to 14 and it was investigated using peak expiratory flow rate (PEFR) as the respiratory function test. Asthmatic symptoms were increased by low temperatures in all asthmatic children (22).

Furthermore, Beer et al. have studied the effect of the weather on acute exacerbations of bronchial asthma in children. The effect of meteorological parameters in respiratory diseases showed that acute asthma and acute laryngitis are correlated with the afternoon decrease of air temperature, heat content, but not correlated with the absolute values of air temperature and water content. In addition bronchopneumonia/pneumonia and URI are correlated with the absolute values of the meteorologic
parameters (air temperature, water content, and modified heat content factor), but not with their afternoon gradients. The admission rates of acute exacerbation of bronchial asthma in childhood are linked both to the afternoon weather gradients and to some of the acute respiratory infections (23).

3.1. Temperature

Higher temperature and a rapid decrease of temperature within a 3-day period were positively associated with an increase in emergency visits. Although over short (day-to-day) time periods, low temperatures have a direct effect resulting in acute exacerbations of asthma; warmer average temperatures are associated with an increase in asthma prevalence. In contrast, the abrupt cooling of air temperature can trigger an asthma attack directly or indirectly through some viral infection in the airway (24). The lower ambient temperatures coincided with the higher detection of respiratory syncytial virus at week 28 (September), moment in which the demand for consultations or hospital admissions was descending (25). In Tokyo, the risk of children asthma, between the ages 2-15, is increased during autumn and spring, seasons that characterized by unstable weather conditions, because of a rapid decrease of barometric pressure, temperature and humidity (24).

In Canada stratified analyses by season found no association in any of the four calendar intervals between the number of asthma visits and visibility, change in relative humidity and change in temperature. There were considerable variations in observed differences by season. For example, the mean 6:00 a.m. temperature was significantly lower on high asthma visit days relative to other days during the spring (April to June) (P<0.001) and fall (September to November) (P=0.002) periods, but not for other parts of the year. Similar results were found on days with lower daily mean temperatures (26).

In addition two studies have shown that the childhood asthma admissions in Athens appear seasonal with a peak in winter, spring and autumn periods. These periods the weather condition is characterized by low temperature, high low water vapor pressure and cold anticyclonic presence, which were significantly correlated with an increase in the number of asthma admissions among children in Athens. The impact of these specific weather conditions on asthma exacerbation should be interpreted by the asthmogenic effect of humid weather per se or the association with respiratory viral infection, mold’s and mites’ allergy (14, 27).

3.2. Humidity

Humidity and its decreased level were positively associated with respiratory infections (P<0.0.01), and on other hand wind speed and vapor pressure were negatively associated with asthma attack (P<0.0.01) (24). This is consistent with reports that weather conditions such as a decrease in wind speed and an abrupt rise in relative humidity might be important factors in the increased incidence of asthma attacks. Hashimoto et al. found that decreasing humidity from a high humidity level is a risk factor for asthma attack. Also, higher barometric pressure is connected with the incidence of asthma attack (24).

The incidence of asthma exacerbations among children is influenced by air temperature and absolute humidity. Specifically the lower air temperature (T≤10.9°C) and absolute humidity (es≤7.1.g/m³) leads to increase of hospitalizations (p=0.5). Cold weather associated with windy conditions could be the precursor of childhood asthma exacerbations (28).

3.3. Wind speed

There is a well-established relationship between weather conditions and hospitalizations of asthmatic children aged 0-4 years in Greece. The wind speed from the meteorological parameters and the cooling power from the biometeorological indices examined could be the precursors of worsening the health of asthmatic children, namely an increase of 1m/sec in the mean monthly wind speed is associated with a 20% increase in Childhood Asthma Admissions (28). Also, higher wind speed was observed on days with high asthma counts from April to June (P<0.001), and September to November (P=0.02), but not during the other periods examined in Ottawa, Canada. (26).

Another research in Alaska showed that cold air is one of the main reason causing asthma (was cited by 36% of respondents as causing asthma and by 48% as being a trigger for asthma) in children (aged 3-18 years), that it may affect a child directly by exposure to cold air during time spent outdoors (29). Also in Indramayu, Indonesia the most common cause for acute respiratory infections (ARI) in children aged under five years was air entering the body through some type of chill, exposure to change of weather (30).

3.4. Mist / Fog

Many studies have explores the association between asthma admissions and mist, fog, thunderstorms. One recent study in Ottawa, Canada has evaluated the association between those meteorological parameters and counts of emergency room visits for asthma among children between 2 and 15 years of age, which reveal that the occurrence of fog or liquid precipitation was associated with an increased number of asthma visits, while snow was associated with a reduced number (P<0.05), namely on days with fog increased visits were observed, while fewer visits were observed on days with thunderstorms and snow (26).

Kashiwabara et al. examined whether or not the presence of mist or fog affects respiratory conditions in asthmatic children in Kyushu, the southernmost large
island in Japan and they evaluated the relation between meteorological data and the number of emergency room visits of asthmatic children. The mean number of asthmatic children who visited the emergency room was higher on misty or foggy nights than on clear nights (1.2. +/- 1.2. people/night vs. 0.8. +/- 0.9. people/night, p<0.0.001). Mist and fog had an increased odds ratio (OR) of emergency room visits of asthmatic children (1.7.4, p<0.0.01). In addition, increased (odds ratio) OR was found for high atmospheric temperature (4.3.9, p<0.0.001). Multivariate analysis showed mist and fog (p<0.0.001), average atmospheric temperature (p<0.0.001), and day-to-day change of temperature (p<0.0.5) were related to the number of asthmatic children (1.7.4, p<0.0.01). In addition, increased (odds ratio) OR was found for high atmospheric temperature (4.3.9, p<0.0.001).

4. AMBIENT AIR POLLUTION AND WHEEZING ILLNESS

4.1. Sources of exposure

Asthma can be defined as a diffuse, hyper-reactive airway, obstructive lung disease with hyper-reactivity of the airways to a variety of stimuli and a high degree of reversibility of the obstructive process, that cause difficulty with the mechanics of breathing. Nearly all asthmatic individuals have some degree of family history of allergy. Furthermore, asthma in childhood can go in many different directions. Some children with asthma continue to have the disease for their entire lives. Other children find that their symptoms decrease or even disappear during adolescence (24).

The International Study of Asthma and Allergies in Childhood (ISAAC) was formed in 1991 to facilitate research into asthma, allergic rhinitis and eczema around the world and it shows that the highest asthma prevalence occurred in industrialized and westernized countries. The highest 12month asthma prevalence rates were in the United Kingdom, New Zealand, Australia, and the Republic of Ireland, followed by North, Central, and South America. The highest adolescent asthma prevalence was 36.8.%% in UK (ISAAC Steering Committee, 1998). A community-based epidemiological study of asthma incidence rates in the USA from 1964 to 1983 showed that the rise in asthma incidence was entirely accounted for by the increased incidence rates in the age range of 1–14 years (32,33). It is known that children may be more vulnerable to the effects of air pollution than adults, because children’s lung development is not complete at birth but lung development proceeds through proliferation of pulmonary alveoli and capillaries until the age of 2 years. Thereafter, the lungs grow through alveolar expansion until 5-8 years of age (34).
The epidemiology and basic science literature indicates that both air pollutants and allergens are independently associated with increased in hospital admission and mainly in respiratory symptoms, the effects of the combined insult have not been elucidated. This combined insult may help to explain the differential asthma burden between inner-city and non-inner-city children. Specifically one study in Baltimore showed that asthmatic children aged 6-12 years are exposed to allergens and indoor pollutants, particularly PM2.5. (35).

Ambient air pollutants can come from many sources and include both gaseous and particulate pollution. Air pollution arises in 2 ways: as primary pollutants emitted directly into the air from sources (including the gaseous pollutants NO\textsubscript{2} and SO\textsubscript{2}, as well as PM, such as soot), and as secondary pollutants formed from the primary pollutants in the atmosphere in the co-presence of sunlight, moisture, or both (including O\textsubscript{3} and secondary particles, such as sulfates). The dominant anthropogenic origin of all these pollutants is the combustion of fossil fuels. In most urban areas, and increasingly in suburban areas, traffic-related emissions are a major source of air pollution. Truck, car, and bus traffic produces a complex mixture of toxic chemicals (e.g., benzene from unleaded gasoline and the organic chemicals in diesel exhaust), PM, and a variety of irritant gases (including nitrogen dioxide (NO\textsubscript{2}), SO\textsubscript{2}, and O\textsubscript{3}). Ambient air pollutants such as nitrogen dioxide (NO\textsubscript{2}), ozone (O\textsubscript{3}), particulate matter (PM) and its components including organic carbon are associated with increased allergic disease and asthma.

In addition the air quality is being influenced by dust episodes, which can effect locally, regionally and globally (36). Dust storms carry different geogenic and anthropogenic particles, which - depending to their size - penetrate into the airways and lungs causing different pulmonary diseases. One recent review article suggests that dust storms can serve as carriers for the pathogens and microbial products, promoting infections upon inhalation and causing neutrophilic pulmonary inflammation (37).

The primary route of exposure to air pollutants is through inhalation, but the substances can also contaminate water and soil through atmospheric deposition and precipitation and some of the pollutants can accumulate and persist in the soil and sediments of streams because they do not degrade quickly. Children, the elderly, and persons with preexisting respiratory conditions, such as asthma, are among those most affected by air pollution. It is known that air pollution episodes are related to long-range transport from the east occurred in Western Europe, such as Germany, Netherlands increasing the mortality and hospital admissions with changes in lung functions (38).

Infants and young children are at increased risk to environmental exposures. They spend more time outdoors and exercise more, and therefore they breathe a greater amount of pollution per pound of body weight than adults. Furthermore, they have a higher resting metabolic rate and rate of oxygen consumption per unit body weight than adults, because their surface per unit body weight is larger and they are growing rapidly. So their oxygen demand is higher and their respiratory rates higher per unit body weight than adults and their exposure to any air pollutant may be greater. Also, their bodies are growing and can be more affected by pollutants that impair organogenesis and other developmental processes. Since the vast majority of air pollution’s effects on children are mediated through inhalation, this review is limited to the childhood health effects that result from this way. Chronic exposure to ambient air pollutants has been linked to deterioration of normal lung growth and development of diseases such as asthma (39).

4.2. The effects of individual pollutants on wheezing illness

Epidemiological research on the health effects of air pollution on children has mainly focused on particles, which have been associated with upper and lower respiratory symptoms in children (40, 41), the most frequently occurring illness in childhood. Though viral respiratory tract infections are reported as the major trigger for asthma exacerbations in children, an additive or synergistic effect with ambient air pollutants has been considered (42).

The environmental pollution with respirable particles and gasses affect on different parts of the respiratory tree of adults and children depending upon their characteristics (relative solubility, size), causing mainly rhinitis and infectious bronchitis (43). In Greece, schoolchildren 8-10 years of age living in urban environment have increased non-specific respiratory symptoms, such as cough, in comparison with the children living in rural area (44). Another study in Athens, Greece has revealed that Childhood Asthma Admissions are associated with ambient air pollution at different seasons of year. Younger children (0-4 years) present increased admission rates during on winter air pollution. On the other hand, older children (5-14 years) seem to be more vulnerable to the exposure of primary air pollutants mainly during late spring. In Athens the air pollution episodes appeared mainly during spring during the development of sea breeze maximizing the pollutant’s concentrations in the greater Athens area and affect the health of asthmatic children (45). Moustris et al, 2012 examined the period 2001-2004, found that the mean daily number of childhood asthma admissions regarding the children’s age group 0-4 years is 2 admissions per day; while for the children’s age group 5-14 years are approximately 3 admissions per day (46).
Sometimes relationships between more routine levels of air pollution and adverse health outcomes are not as obvious, but recent epidemiologic studies (47) revealed statistically significant associations between multiple individual pollutants, such as particles with aerodynamic diameter less than 10 micrometer, NO\(_2\) and inorganic acid vapor and a wide range of significant adverse and preventable sequence at present-day pollutant levels in the United States (California), sometimes even in areas with pollution levels less than current air pollution standards. The acute adverse health effects of air pollution have been shown to include reduced lung function (lung function growth rate specifically in children), inflammation in the lung, increased numbers of asthma attacks, excess respiratory and cardiac hospital admissions, and even premature death (39). 

### 4.3. Ozone

Ozone (O\(_3\)) is a highly reactive gas that results primarily from the action of sunlight on hydrocarbons and NO\(_x\) emitted in fuel combustion. It is an ambient ground level pollutant and represents a great challenge to anyone concerned with its health effects. It oxidizes lung tissues on contact, acting as a powerful respiratory irritant at the levels frequently found in most of the nation’s urban areas during summer months (48). Epidemiologic and clinical studies have shown that O\(_3\) within the first few hours after the start of the exposure is associated with worsening of athletic performance, reductions in lung function, shortness of breath, chest pain with deep inhalation, wheezing and coughing, and asthma exacerbations among those with asthma (49). Exposure to O\(_3\) and particulate matter of aerodynamic diameter of 2.5 mic or less (PM\(_{2.5}\)) is a risk factor for respiratory symptoms in children with asthma (48) (US EPA).

Other cohort study showed that playing multiple team sports in a high ozone environment is associated with development of physician-diagnosed asthma and generally respiratory diseases. The results are consistent with a large increased risk both for new-onset asthma and for exacerbation of previously undiagnosed asthma, because playing multiple sports was associated with asthma in children with no lifetime history of wheezing at baseline and children with a previous history of wheezing. The larger effect of high activity sports than low activity sports, and an independent effect of time spent outdoors, also only in high ozone communities, strengthens the inference that exposure to ozone may modify the effect of sports on the development of asthma in some children. Exercise-induced asthma by itself is unlikely to have been an explanation for these results, because asthma onset was associated with exercise only in polluted communities (50).

One recent study has found that ozone significantly predicted increased risk of respiratory symptoms and rescue medication use among children using asthma maintenance medication. There is an immediate (same-day) effect of O\(_3\) on wheeze (with the 1-hour ozone metric), chest tightness, and shortness of breath (with both the 1-hour and 8-hour ozone metrics). The authors also found that previous-day levels of O\(_3\) (both metrics) were significantly associated with increased risk of chest tightness and shortness of breath (51). This finding is supported by another study of 13.246 hospital admissions for asthma in Brisbane, Australia, that showed a strong association between hospital admissions for respiratory diseases— with little evidence of a threshold and O\(_3\) in the absence of aerosolized sulfate, strengthening the causative link between O\(_3\) exposure and asthma exacerbations. The ozone effect was relatively unaffected by the control for high levels of other pollutants (52).

McConnell et al. suggest that long-term O\(_3\) exposure can increase the chances that children will have asthma and affect on theirs lung growth. However, children exercising outside receive greater doses of outdoor pollutants to the lung than those who do not and thus would be more susceptible to any chronic effects of air pollution. In high ozone communities, children playing at least one high activity sport have increased risk of asthma in comparison with children playing no sports. The California Children’s Health Study carefully tested the hypothesis that air pollution (with high and low particulate matter) can cause asthma by investigating the relation between newly diagnosed asthma and team sports in a cohort of children exposed to different concentrations of air pollutants. The relative risk of asthma development in children playing three or more sports in the 6 more polluted communities was 3.3. (95% CI, 1.9-5.8.) compared with children in these areas playing no sports. Sports had no effect in areas of low O\(_3\) concentration areas (relative risk, 0.8.; 95% CI, 0.4-1.6.), but time spent outside was associated with a higher incidence of asthma in areas of high O\(_3\) (relative risk, 1.4.; 95% CI, 1.0-2.1.). Exposure to pollutants other than O\(_3\) did not alter the effect of team sports (50).

### 4.4. Nitrogen oxides

The main sources of ambient nitrogen oxides (NO\(_x\)) emissions are diesel- and gasoline-powered vehicular engines and coal- and oil-fired power plants, which typically result from the fixation of nitrogen in the air during high-temperature combustion and it is considered to be a good marker of traffic-related air pollution. The available epidemiologic studies are often difficult to interpret and evaluate the effects of NO\(_2\) because of his synergistic role by other outdoor air pollutants such as SO\(_2\) in mediating lower respiratory tract illnesses among children (39). Many studies have shown the relationship between NO\(_2\) – PM\(_{10}\) and the frequency of asthma symptoms and with lung function decrements in children on a day-to-day scale (53).
Recent studies suggest that exposure to high levels of NO\textsubscript{2} can be a contributory factor in the aggravation of childhood asthma and respiratory symptoms generally. The study concluded that even “acceptable” airborne O\textsubscript{3} levels might be associated with worsening of asthma in children. However, the situation is not necessarily so clear-cut. There is a detrimental effect of NO\textsubscript{2} on symptoms or lung function and another study in southern California had found that the relative risk for asthma development was increased considerably in children aged 9-10, 12-13 and 15-16 years exposed to high levels of O\textsubscript{3} environment during outdoor team sports (54). In London and in Japan the findings revealed the association of outdoor NO\textsubscript{2} and asthma and other lower respiratory disease in children (55,56).

Many epidemiological researches indicate a positive association of outdoor pollution (high levels O\textsubscript{3}, NO\textsubscript{2}, SO\textsubscript{2}) with increasing respiratory diseases of children and chronic respiratory symptoms. In Greece, recent epidemiological data have shown that asthma and asthma-like symptoms are common in children and in adults. A consistent negative association of higher levels of particles with evening Peak Expiratory Flow (PEF) was observed, which became evident after one day in the urban panel. A relatively consistent negative association between NO\textsubscript{2} and PEF was also observed and was especially evident also when the 7 day average was used in the urban panel. A significant positive association was found between morning PEF and black smoke lag 0 day. The results of NO\textsubscript{2} effects are difficult to interpret because they are associated at extended lags and report for longer lags is needed in panel studies to better judge the effect of monitored outdoor NO\textsubscript{2}. However a prolonged exposure on NO\textsubscript{2} and SO\textsubscript{2} affect on symptoms incidence (57).

Also many studies show the association of wheezing problems with indoor exposures of NO\textsubscript{2}. So the Yale Childhood Asthma Study (51, 58, 59) enrolled 1,002 families who had a newborn infant and an older child with physician-diagnosed asthma. The infants exposed to high NO\textsubscript{2} concentrations (17.4 ppb) inside their homes (cooking stoves, unvented gas heaters) are at high risk of developing cough, shortening of breath, asthma and wheezing illness just in the first year of their life, considering the fact that 49% of them have a parent with asthma, and 77% a parent with allergies (58). These data support the hypothesis that children with atopy or asthma may be more sensitive to NO\textsubscript{2} exposure. Although the concentrations of air pollutants stay below the official limit, CO and NO\textsubscript{2} affect the health of the child population of the Urban Area of Guadalajara (60)

4.5. Sulfur Oxides

Sulfur dioxide (SO\textsubscript{2}) is emitted primarily by coal- and oil-fired plants and by industrial processes involving fossil fuel combustion, as sulfur is a natural contaminant of these fossil fuels. Air pollutants including SO\textsubscript{2} and other particles are directly regulated under the Clean Air Act whereas the possibility of a standard for acid aerosols has only recently been considered by the U.S. EPA. These particles and acid aerosols are released by fossil fuel fossil fuel combustion processes and are usually present together as components of a complex mixture, causing increase in mortality and airway resistance – especially with oral breathing (61).

SO\textsubscript{2}, in contrast with the others pollutants, is a respiratory irritant that does not cause substantial acute or chronic adverse effects in human beings exposed to ambient concentrations (62, 63), but because it is 50 times more soluble than CO\textsubscript{2} in water at 30\textdegree C, it can in one hand absorb in the upper airways at rest and on another hand increase the deposition in deeper parts of the lung (61). Controlled human studies of healthy subjects exposed to SO\textsubscript{2} at rest or with exercise have failed to demonstrate effects on respiratory mechanics at levels up to 10 ppm (64-67). In contrast, exposure to low levels of SO\textsubscript{2} does alter the lung function of asthmatics (68,69).

Air pollution was associated with an increase in reports and duration of asthma attacks and asthma-like symptoms in mild asthmatic children in Paris. The strongest association was the risk of asthma attack for an increase of 50 microg x m\textsuperscript{-3} of sulphur dioxide (SO\textsubscript{2}) on the same day (odds ratio (OR)=2.8,6). Maximum reduction in morning peak expiratory flow (PEF) (5%) and maximum increase in PEF variability (2%) were observed at a lag of 3 and 4 days for an increase of 50 microg x m\textsuperscript{-3} of SO\textsubscript{2} in the subgroup of mild asthmatics receiving no regular inhaled medication (70). Other study in the Netherlands showed that SO\textsubscript{2} was associated with increased prevalent episodes of wheeze and bronchodilator use and decreased morning and evening PEF (71).

4.6. Particle Matter

Particle matter (PM) is a widespread air pollutant, consisting of a mixture of solid and liquid particles suspended in the air. PM are relevant to health refer to the mass concentration of particles with a diameter of less than 10\mu m (PM\textsubscript{10}) and less than 2.5\mu m (PM\textsubscript{2.5}), so the deposition in the respiratory tract varies with the size of PM. Combustion and secondary particles are usually very small (<1 mm in diameter) remaining in the atmosphere for days or weeks and are present in children because of their frequent mouth breathing. PM\textsubscript{10} and PM\textsubscript{2.5} include inhalable particles, which contain more toxic compounds and they can penetrate into the thoracic region of the respiratory system and especially PM\textsubscript{2.5} are small enough to penetrate deeper into the lung than the larger PM . Particles larger than 10 mm in diameter do not typically pass beyond the larynx, but because of their frequent mouth-breathing behavior, these particles can more often deposit in the respiratory tract of children. PM\textsubscript{10} is composed of both fine and
coarse particles; coarse particles in the PM$_{10}$ are 2.5 to 10 mm in diameter and can include dust generated from the breakdown of rocks, soil, and dust includes sulfates, nitrates, ammonium and others inorganic ions (ions of sodium, potassium, calcium, metals etc). Fine particles (PM$_{2.5}$), including those that are formed in the atmosphere from gaseous pollutants, are less than 2.5 mm in diameter and result from the combustion of fuels used in motor vehicle, power plant, and industrial activities (building, mining, ceramic, bricks etc), as well as the combustion of wood (e.g., in wood-burning stoves) and other organic material such as allergens and microbial compounds (39).

In Seattle, three studies have been conducted that found associations between the exacerbation of lung diseases and airborne particulate matter (PM) in children and in elderly people. The first one found that there is a significant association between wood smoke and decrease lung function in elementary school children with asthma and dry light scattering ($\sigma$$_{dp}$), a measure of fine PM (72). Another study carried out in Seattle from 1989 to 1990 found significant associations between both PM < 10 pm in aerodynamic diameter (PM$_{10}$) and light-scattering values (particles approximately < 1.0 pm) and Emergency Department visits for asthma for patients aged 65 years and younger (73) and population under the age of 18 (Norris et al., 1999). Most recently, a study of hospital admissions for asthma found an estimated 4-5% increase in admission rate associated with several measures of PM air pollution (PM10, particulate matter < 2.5 pm in aerodynamic diameter (PM$_{2.5}$), and the coarse fraction PM$_{10}$-PM$_{2.5}$ (74).

Air pollution can affect healthy people and especially risk group, such as elderly and children, persons with chronic diseases and preexisting respiratory conditions. Hoek and Brunekreef (1995) (75) studied the effect of SO2, PM10 and NO$_2$ to respiratory symptoms in 300 children aged 7-11 years in Netherlands. The analyses of this study gave an estimated odds ratio of 0.93 for a 50μg/m$^3$ increase in PM$_{10}$ on lag 0 causing cough, phlegm and other respiratory symptoms. PM$_{10}$ reveals to be an important pollutant to study particularly (76). An important study in Mexico showed that children with mild asthma are affected by high levels of PM (77).

There was consistent associations between childhood emergency department (ED) asthma presentations and regional concentration of PM$_{10}$ with a strongest association of RR=1.1.7 (95% CI 1.0.5 to 1.3.1) in the central district of Melbourne, specially increased NO$_2$ and O$_3$ cause increase in respiratory diseases and mainly in childhood asthma in the Western districts. This study suggests that regional concentrations of PM$_{10}$ may have a significant effect on childhood asthma morbidity. In addition, O$_3$ may play a role however; its effect may vary by geographical region (78).

A Finland study revealed that high concentrations of PM$_{10}$ affect in the respiratory health of children 7 to 12 yr of age living in urban area. The correlations in daily air pollution concentrations were high between the urban and suburban areas. A negative association between morning peak expiratory flow (DPEF) and PM$_{10}$ was observed among children with asthmatic symptoms in both areas. Statistically significant associations were observed at lagged PM$_{10}$ concentrations. Children who suffer from asthmatic symptoms are influenced from particulate air pollution, but on the other hand there is no association between children with cough only. Only SO$_2$ from air pollutants was significantly associated with mornig DPEF in urban area (79) (Table 2).

5. WEATHER CONDITIONS AND AIR POLLUTION ON WHEEZING ILLNESS

Many studies are focusing on effects of air pollutants combined with meteorological parameters on respiratory diseases. In Philadelphia, for 2 years study period, were gathered weather, air pollution and admissions of children with acute bronchial asthma. The findings of that study show that the incidence of bronchial asthma increase during days with high barometric pressure (p<0.0.01) as well as during days of increased air pollution (p<0.0.01). However, when the above conditions coincided, the increase in attacks of bronchial asthma is higher (80).

Ho et al (2007) (33) have studied in Taiwan the relationship of air pollution and weather conditions with the prevalence adolescent asthma and attack rate from October 1995 to March 1996. Correlations between fluctuations in emergency room (ER) visits of asthmatic children (10 to 17 years old) and various environmental parameters were more relevant for weekly than for daily values. Hospital admission rates for asthma correlated positively with concentrations of NO$_x$, SO$_2$ and with high barometric pressure; and negatively with O$_3$ concentration and minimal and maximal temperature. There were no significant correlations with concentrations of particulates, humidity, or airborne pollen and spores. Only during September, when the school year begins and Jewish holidays, that create an emotional stress, the respiratory admissions are higher. The correlations between ER visits and the environmental factors increased significantly when the September peak was excluded, revealing that 61% of the variance in ER visits was explained by NO$_x$, SO$_2$, and O$_3$ concentrations, 46% by weather parameters, 86% by NO$_x$, SO$_2$ and barometric pressure, and 69% by the combination of air pollutants and weather parameters. The major factors found to be associated with ER visits of asthmatic children were high NOx, high SO$_2$, and high barometric pressure. Negative correlation was found between ER visits of asthmatic children and O$_3$ concentrations (81). Lowest temperatures showed an important role in emergency admissions due to respiratory
diseases. For relative humidity, a positive correlation was observed. Regarding the daily distribution, some pollutants showed concentration peaks in hot periods ($O_3$ and $SO_2$) and others in cold periods (CO and $NO_2$) (76).

Another study in Australia showed the relationship between air pollution and respiratory symptoms in children with a history of wheezing in Sydney. The performed analysis revealed significant associations between doctor visits for asthma and PM$_{10}$ levels, while the prevalence of wet cough is associated with NO$_2$ levels. Finally, there was a negative correlation between ozone and humidity and positive correlation between ozone and temperature (82). Finally one recent research, focused on weather types and the levels of chemical and biological pollutants in Carpathian Basin, revealed a relationship between patient numbers (including young people -0 to 20 yr old-) and summer and early autumn period. This period is characterized by high temperature parameters, low relative humidity and high chemical and biological pollutant levels (83).

Nastos and Zerefos (2009) (84) studying consecutive dry and wet days in Greece, they showed that increasing consecutive dry and decreasing consecutive wet days appear in the greater Athens area, but these trends were not significant (95% CL). The mean consecutive dry day’s value is 78 days/year while the mean consecutive wet day’s value is 4 days/year. This finding indicates that the increased dry days in Athens contribute to longer life cycle of particulate matter in the lower boundary layer exacerbating respiratory diseases. Furthermore, desertification-related scenarios reveal a tendency towards drier climatic conditions in the eastern Mediterranean (85). In addition another study in Athens revealed that during dry weather PM$_{10}$ are increased causing asthma exacerbations in older asthmatic children (5-14 year old) and even in younger asthmatic children (0-4 year old) (45).

In addition Samoli et al (2011) (86) found that a 10 mg/m$^3$ increase in PM$_{10}$ was associated with a 2.5% increase (95% confidence interval (CI): 0.0.6%, 5.0.8%) in the number of pediatric asthma hospital admissions, while the same increase in $SO_2$ was associated with a 5.9% 95% CI: 0.8%, 11.3%) increase of childhood asthma admissions. In the summer, $O_3$ was associated with a statistically significant increase in asthma admissions among older children (5-14 years old); in contrast NO$_2$ has limited association with asthma admissions. Statistically significant PM$_{10}$ effects were higher during cold season and during desert dust days at lag 1 causing respiratory problems, while SO$_2$ effects occurred mainly during spring season.

6. AEROALLERGENS AND WHEEZING ILLNESS

6.1. Increase of pollen production and time of pollination

Pollen allergenicity is linked to allergen concentrations and is a major determinant of the health effects in sensitized patients. In fact, environmental change is likely to influence vegetation, with consequent changes in growth and reproductive cycles and in the production of allergenic pollen (seasonal period and intensity) (87). It has been demonstrated recently that pollen grain, under physiological exposure conditions, releases not only allergens but also bioactive lipids that activate human neutrophils and eosinophils in vitro (88,89). Moreover, intact grains of pollen induce activation and maturation of dendritic cells in vitro, suggesting that pollen can act not only as allergen carrier but also as an adjuvant in the induction phase of the allergic immune response (90).

A higher dependency on temperature has been observed in plants that flower in spring and early summer, whereas species that flower in late summer and fall generally are more correlated with photoperiod. Consequently, the former species are more affected by warmer winters and springs, showing an earlier flowering in recent years (91).

Nearly all species and regions analyzed have shown significant changes in seasonal onset of pollination that are consistent with warming trends (92-96). In general, an earlier start of the pollen season has been shown in most studies focused on allergenic plants such as birch (93,97), mugwort (98), Urticaceae (99), grass (100,101) and Quercus (102), even when employing different methods and different length datasets. An

![Table 2. Outdoor pollutants and respiratory health in children](image-url)
earlier start of the season have been found also for other allergenic plants at local level, such as Quercus, Juniperus in the Netherlands (96), and Platanus in Italy and Spain (103).

On average, the length of the growing season in Europe increased by 10–11 days during the last 30 years. Conversely, phenological trends appear to be different in eastern part of Europe, sometimes showing a 1–2-week delay in start of the spring phases (104). Recent findings show that experimental warming aimed at inducing flowering also depends on blooming season: in a North American prairie setting, an advanced flowering phenology was observed for species that began to flower before the summer temperature peak with a delay in those species that started flowering after the summer peak, particularly for ragweed (105) There is some evidence of significantly stronger allergenicity in pollen from trees grown at increased temperatures (106,107). An earlier start and peak of the pollen season is more pronounced in species that start flowering earlier in the year. Due to the earlier onset of pollen seasons, the seasons are more often interrupted by adverse weather conditions in late winter/early spring. In addition, flower intensity increased by 19% in both crop and wild species with similar results being obtained in studies on woody plants (108). Furthermore the linear trend of phenological phases of some forest and fruit trees as well as olive-trees in Croatia show a negative trend of 2–6 days/decade towards an earlier flowering, which is the consequence of a positive significant linear trend in spring temperature (109,110). In general, the literature to date suggests that preseason temperature and precipitation are predictors of floral intensity for both woody plants and for weeds and grasses.

Additionally, the association between changes in temperature is likely to vary across plant species (annual, more than perennial species and insect pollinators advancing more than wind pollinators). Similar trends have already been demonstrated, linking weather change with longer pollen seasons, greater exposure, and increased disease burden for late summer weeds such as Artemisia (mugwort) and Ambrosia (ragweed) (98,111).

6.2. Change of pollen distribution
Changes in climate appear to have altered the spatial distribution of pollens. Knowledge of a plant’s geographical distribution and its flowering period and possible variations induced by climate change is of great importance (87). New patterns of atmospheric circulation over Europe might contribute to episodes of long distance transport of allergenic pollen, increasing the risk of new sensitzations among the allergic population (112). There is growing evidence to show that climate change might also facilitate the geographical spread of particular plant species to new areas, which become climatically suitable (113).

Global warming is related to altitudinal and latitudinal plant migrations, changing plant species’ diversity and density, and consequently, provoking habitat alteration or fragmentation (114). Equally, either habitat alteration or fragmentation may contribute to local extinctions by altering biodiversity. All these different events alter the local airborne allergenic pollen count and diversity. These findings are potentially biased by the occurrence of long and medium distance transport episodes of allergenic pollen as shown in several European countries (112,115-117). The climate changes projected during the next century will influence plant and fungal reproductive systems and alter the timing, production, and distribution of aeroallergens. Hence, spores from allergenic fungi have been shown to travel even longer distances, such as from Africa or Asia to America (118,119). The projected alteration of wind patterns associated with climate change might induce an increase in such episodes, although this has to remain conjunctural. Such trends can be reflected in clinical outcomes.

7. WEATHER CONDITIONS AND AEROALLERGENS

Different meteorological factors affect pollen emission, notably temperature, sunlight and humidity. On the other hand, weather patterns influence the movement and dispersion of all aeroallergens in the atmosphere through the action of wind and rainfall but depend in addition on atmospheric stability. Pollen season dates, duration and intensity, and a possible advance in the start of the allergy season because of weather change are under investigation but current data suggest that such changes are possible, although will likely be different between different taxa and species (114).

7.1. Humidity and aeroallergens

As aeroallergens are sensitive to meteorological conditions like temperature and humidity, a better understanding of the relationship of these aeroallergens to allergic disease is relevant due to expected changes in outdoor climatic conditions globally in coming years (120). Probably the most important process that takes place during the pollen transport is the release of allergen from the grains. In a dry atmosphere, pollen is very stable and can keep its content over years (121). However, under the specific conditions of a high relative air humidity the allergen release can take place within minutes (122). Assessment of the effects of meteorological factors on pollen loads revealed that the highest pollen concentration is recorded when relative air humidity is falling and maximal air temperature is rising. However, in a recent analysis, data indicated that ragweed pollen concentration in the air generally increased at a relative air humidity of around 70%, and minimal air temperature not less than 12°C (123). Furthermore, several studies have found that increased atmospheric concentrations
of some mold spore types are associated with increased temperature and humidity (124,125).

In an investigation, where the authors qualitatively estimated the conditions favouring or precluding the released pollen to be transported regionally, pollen release was not correlated to temperature or light either, but it was to low relative humidity. More pollen was released if the relative humidity fell below 50% (126). There was no clear periodicity, and pollen could be released just at any time, depending on when the sufficient minimum humidity was reached.

### 7.2. Wind and aeroallergens

Appearance of pollen in the air is determined by the plants releasing it and by the meteorological processes, which influence pollen release, dispersal, transport or deposition on surfaces (127).

Many studies of the dispersal distance of the anemophilous pollen have focused on the deposition of pollen within relatively short distances. Suspended particles are usually transported by the wind, and dispersed by the existing turbulence within the lowest atmospheric layer (boundary layer) where deep convection can bring up particles to free atmosphere and be suspended in an air mass moved by synoptic systems. Depending on the altitude reached, they could be transported and deposited at great distances (122). Emerging evidence showed that long distance transport might represent a cause of sensitization and of symptoms among the allergic population, in areas far from the source of pollen.

Ragweed seems to be frequently involved in the trans boundary transport in Europe (128, 129). In central Italy, several episodes of detection of ragweed pollen appeared to be linked to air mass coming from the Balkans (possibly Hungary) and pollen count often reached the clinical threshold suggesting a possible increase in the sensitization rate and clinical impact on allergic population (112). This hypothesis was supported by a preliminary observation of the increasing trend of ragweed allergy in a neighbouring region where plants are not present, as well (130). Furthermore, there is convincing evidence to prove that the long-range transport of pollen from distant regions can significantly modify pollinating seasons (i.e. the start time and duration of high atmospheric pollen concentrations) in many European areas. This is particularly important for northern Europe, where flowering takes place later in the spring regions (131). In Finland, birch pollen are shown to come from Baltic States, Russia, Germany, Poland and Sweden, depending on the particular meteorological situation. Since the pollen count can reach high levels during these episodes, large-scale forecasting might be useful for the allergic population (122).

### 7.3. Thunderstorm and aeroallergens

According to current climate change scenarios, there will be an increase in intensity and frequency of heavy rainfall episodes, including thunderstorms, over the next few decades (132), which can be expected to be associated with an increase in the number and severity of asthma attacks both in adults and in children (8). Evidence exists that thunderstorms during the pollen season are associated with allergic asthma epidemics in patients with pollinosis (113, 133). These thunderstorm-related epidemics are limited to late spring and summer, when pollen counts are high (1).

The most prominent hypothesis for the thunderstorm-related allergic respiratory diseases is that weather conditions such as rain or humidity may induce hydration and fragmentation of pollen grains, which releases allergenic biological aerosols into the atmosphere. Thunderstorms concentrate at ground level pollen grains that release allergenic particles of respirable size into the atmosphere after their rupture by osmotic shock (113). Consequently, during the first phase of a thunderstorm, pollen-allergic individuals may inhale a high concentration of dispersed allergenic material that release allergenic particles of respirable size into the atmosphere after their rupture by osmotic shock (134). It has been hypothesized that an increase in fungal spores during a thunderstorm could contribute to asthma epidemics (135,136). Individuals with allergic rhinitis only and no previous asthma can experience severe bronchoconstriction during thunderstorms (87).

### 8. CLIMATE CHANGE

Anthropogenic global warming, which includes both higher temperatures and higher ambient CO₂ levels, speeds flower development, resulting in earlier blooming. Substantial increases in pollen production resulted from exposure to increased CO₂ concentration, in experimental conditions (137-139) and in urban vs rural areas; the latter study provides a reliable model for evaluating the effects of global warming (140). Other attributes of allergenic plants are also responsive to CO₂ concentration and/or temperature increases (141,142).

There is now a wealth of evidence that climate change has had and will have further impact on a variety of allergenic plants (143). Increased CO₂ increases plant biomass and pollen production. Increased temperature stimulates earlier flowering and longer pollen seasons for some plants. Increased ambient CO₂ may cause some plant products to become more allergenic. It is conceivable that increases in airborne pollen numbers will increase the efficiency of wind-borne pollination, thereby increasing propagation of such plants (144). The extent to which these climate-related ecological changes are coupled with worsening air pollution will further add to the burden of allergic disease in exposed
populations (16). The expectation then is that there will be increasing amounts of robust allergenic plants and an increasing aeroallergen burden for sensitized patients with inhalant allergy (fig 1). The possible mechanisms of the interaction between pollutants (particulate matter, ozone, sulphur dioxide, nitrogen dioxide) and pollens include airway mucosal damage, impaired mucociliary clearance, increased permeability, easier penetration of pollen allergens in the mucus membranes, and easier interaction with cells of the immune system (113). There is also evidence that predisposed subjects have increased airway reactivity induced by air pollution and increased bronchial responsiveness to inhaled pollen allergens. Some components of air pollution seem to have an adjuvant immunologic effect on IgE synthesis in atopic subjects (145). It has long been speculated that \( \text{O}_3 \) and other pollutants may render allergic subjects more susceptible to the antigen they are sensitised to. It has been observed that the incidence of new diagnoses of asthma are associated with heavy exercise in communities with high concentrations of \( \text{O}_3 \), thus, air pollution and outdoor exercise could contribute to the development of asthma in children (50).

Furthermore, some studies report an increase in the allergen content of pollen produced by plants growing at higher temperatures and in \( \text{CO}_2 \)-enriched atmosphere. Concentrations of the ragweed (\( \text{Ambrosia artemisiifolia} \)) major allergen (\( \text{Amb a 1} \)) increases in a \( \text{CO}_2 \)-enriched atmosphere, concentrations being selected according to future climate change scenarios. This suggests that increased \( \text{CO}_2 \) could potentiate the sensitization rate and/or severity of symptoms in ragweed allergy (146). The expected consequence would be an increase in pollen production, which has been confirmed in several experimental studies on \( \text{A. artemisiifolia} \) (ragweed) in which, under heightened \( \text{CO}_2 \) levels, both pollen production (137,139) and floral spikes per plant were increased (140).

Additionally, studies on plant responses to elevated \( \text{CO}_2 \) concentrations indicate that plants exhibit enhanced photosynthesis and reproductive effects and produce more pollen (147-149). An earlier start and peak of the pollen season is more pronounced in species that start flowering early in the year. Moreover, plants flower earlier in urban areas than in the corresponding rural areas with earlier pollination of approximately 2 to 4 days. Meteorological factors (temperature, wind speed, humidity, thunderstorms, etc) along with their climatic regimens (warm or cold anomalies and dry or wet periods, etc) can affect both biological and chemical components of this interaction (150). In addition, by inducing airway inflammation, air pollution overcomes the mucosal barrier, leading to the priming of allergen-induced responses. Climate changes might induce negative

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**Figure 1.** Ambient air pollution and aeroallergen burden.
effects on respiratory allergic diseases, favouring the increased length and severity of the pollen season, the higher occurrence of heavy precipitation events, and the increasing frequency of urban air pollution episodes (150).

It is of particular interest that while the prevalence of allergic rhinitis and allergic asthma is increasing in some European cities, the atmospheric concentration of grass pollen is falling (113,148,151). This decrease has been attributed to substantial reductions in grassland over large areas of Europe. In fact, during the last 30 years, grassland in Western Europe has decreased by more than 20% (87). As a consequence, the increase in the number of cases of allergic rhinitis and asthma induced by grass pollen is probably related, among other factors, to increased air pollution. People who live in urban areas tend to be more affected by pollen-induced allergic respiratory allergy than those living in rural areas, where individuals who are exposed to traffic usually experience a higher frequency of allergic respiratory diseases than those who are less exposed. Moreover, UV radiation in a polluted urban atmosphere favours the formation of ozone, which is affected mostly by elevated daytime temperatures, low wind speeds, and clear skies (conditions observed in regions such as the Mediterranean, California, and Central and South America, all of which have high levels of traffic) (87). An urban lifestyle has been found to be associated with a greater risk of allergic sensitization, including pollen allergy (143,152).

9. CONCLUDING REMARKS

The effects of climate change alters local weather patterns, including minimum and maximum temperature, rain precipitation, and storms, which affect on the rate of asthma exacerbations due to respiratory infections and/or cold air inhalation on the other (6).

Furthermore, global warming is expected to affect the start, duration, and intensity of the pollen season. Knowledge of a plant’s geographical distribution and its flowering period and possible variations induced by weather variations is of great importance. The climate changes projected during the next century will influence plant and fungal reproductive systems and alter the timing, production, and distribution of aeroallergens (87). Increased exposure to allergens combined with exposure to pollutants, mainly ground-level ozone, that act synergistically to intensify the allergic response, could point to increased respiratory problems in the future.

The dominant air pollutants triggering childhood wheezing illness are ozone and particulate matter and especially PM$_{2.5}$ – PM$_{10}$, while temperature and humidity are the two main weather parameters which influenced on childhood pulmonary diseases. The knowledge of adverse health effects of ambient air pollution and in cold weather exposures would be useful to avoid the increasing of lung diseases in sensitive group of population. Climate change is unequivocal, accelerating, and largely anthropogenic, and will continue through at least the 21st century. Both individuals with allergy and asthma are at risk of worsening disease, more symptomatic days, and reduced quality of life as a result of these environmental changes.

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**Abbreviations:** O<sub>3</sub>: ozone; NO<sub>x</sub>: nitrogen oxides; NO<sub>2</sub>: nitrogen dioxide; SO<sub>x</sub>: sulphur oxide; SO<sub>2</sub>: particulate matter; PM<sub>2.5</sub>: particulate matter < 2.5 μm in aerodynamic diameter; PM<sub>10</sub>: particulate matter < 10 μm in aerodynamic diameter

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