News on Climate change, air pollution and allergic trigger factors of asthma*

D'Amato M[1], Cecchi L[2], Annesi-Maesano I[3], D'Amato G[4]

[1]First Division of Pneumology, High Speciality Hospital "V. Monaldi" and University "Federico II" Medical School, Napoli, Italy
[2]Interdepartmental Center of Bioclimatology, University of Florence (Italy).
[3]Epidemiology of Allergic and Respiratory DIseases Department, IPLESP, INSERM & UPMC Paris6, Sorbonnes Universités, Medical School Saint-Antoine, Paris (France).
[4]Division of Respiratory and Allergic Diseases; Department of Respiratory Diseases; High Specialty Hospital A.Cardarelli Napoli Italy; University of Napoli Federico II. School of Specialization in Respiratory Diseases

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Conflicts of interest

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Address for correspondence:

Prof. Gennaro D'Amato

Division of Respiratory and Allergic Diseases; Department of Respiratory Diseases;High Specialty Hospital A.Cardarelli Napoli Italy; University of Napoli Federico II. School of Specialization in Respiratory Diseases

Via Rione Sirignano, 10 - 80121 Napoli Italy

gdamatomail@gmail.com

Summary

The rising frequency of obstructive respiratory diseases,in particular allergic asthma, observed over the last years, can be partially explained by changes occurring in the environment, with increasing presence in atmosphere of chemical (particulate matter and gaseous components such as nitrogen dioxide and ozone) and biologic (aeroallergens) trigger factors. Aeroallergens are able to stimulate, in allergic subjects, the airways' sensitization, inducing symptoms of bronchial asthma.

Over the last 50 years, global earth's temperature has markedly risen likely because of growing emission of anthropogenic greenhouse gas concentrations. Major changes involving the atmosphere and the climate, including global warming induced by human activity, have a major impact on the biosphere and human environment.

Urbanization and high levels of vehicle emissions induce symptoms of bronchial obstruction (in particular bronchial asthma) prevalently in people living in urban areas compared with those who live in rural areas. Measures of mitigation need to be applied for reducing future impacts of climate change and global warming on our planet, but until global emissions continue to rise, adaptation to the impacts of future climate variability are required.

Key words: Air pollution and obstructive respiratory diseases; airways hyperreactivity in asthma; air pollution and asthma; climate change and asthma; climate change and respiratory allergy; thunderstorm asthma.

Resumen

La creciente frecuencia de enfermedades respiratorias obstructivas, en particular del asma alérgica, observada en los últimos años, puede explicarse parcialmente por diversos cambios ocurridos en el medio ambiente, con presencia creciente en la atmósfera de sustancias químicas (material particulado y componentes gaseosos como dióxido de nitrógeno y ozono) y por factores desencadenantes biológicos (aeroalergenos). Los aeroalérgenos son capaces de estimular, en sujetos alérgicos, la reactividad de las vías respiratorias, induciendo síntomas de asma bronquial.

En los últimos 50 años, la temperatura global de la tierra ha aumentado notablemente debido a la creciente emisión de concentraciones de gases de efecto invernadero generados por la actrividad humana. Los principales cambios que afectan a la atmósfera y al clima, incluido el calentamiento global, tienen un gran impacto en la biosfera y en nuestro entorno.

El incremento de las áreas residenciales y los altos niveles de emisiones vehiculares inducen síntomas de enfermedades que cursan con obstrucción bronquial (en particular asma bronquial) con mayor prevalencia en personas que viven en áreas urbanas en comparación con aquellos que viven en áreas rurales. Se deben aplicar medidas que mitiguen estos factores para reducir los impactos futuros del cambio climático y el calentamiento global en nuestro planeta. Mientras que las emisiones globales continúen aumentando, deberemos adaptarnos a los impactos de la variabilidad climática futura.

Palabras clave: Contaminación del aire y enfermedades respiratorias obstructivas; hiperreactividad de las vías respiratorias en el asma; contaminación del aire y asma; cambio climático y asma; cambio climático y alergia respiratoria; asma de las tormentas.

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Introduction

The massive increase in atmosphere of chemical and biologic pollutants in the last century has made air quality an environmental problem of the first order in a large number of regions of the world. The negative impact of poor air quality on human health is now well known and several manuscripts have well focalized the association between air pollutants and human health, both in the short and long term [1-16].

The prevalence of obstructive airway diseases such as asthma has increased dramatically to epidemic proportions worldwide. Besides air pollution from industry derived emissions and motor vehicles, the rising trend can only be explained by profound changes in the environments where we live around the planet, in both developed and developing countries [1-6]. Asthma and COPD are among the top 10 leading chronic conditions, causing activity restriction and consuming substantial health-care resources and can significantly affect patients and pose a substantial economic burden for both patients and managed-care plans. Asthma is a chronic inflammatory disorder, characterized by reversible airflow obstruction and hyperresponsiveness. In a Global Initiative of Asthma (GINA) report on the burden of asthma, it has been estimated that asthma is one of the most common chronic diseases in the world: 300 million people in the world have asthma [7].

The total costs of asthma for the 25 countries of the European Union are estimated at 3 billions of euros [7].

Air pollution significantly affects health, causing up to 7 million premature deaths annually with an even larger number of hospitalizations and days of sick leave. Climate change could alter the dispersion of primary pollutants, particularly particulate matter, and intensify the formation of secondary pollutants, such as ozone [1,12,14,17-26].

The world economy has been transformed over the last fifty years with developing countries being at the core of these changes. Many of these changes are considered to have negative effects on respiratory health and to enhance the frequency and severity of respiratory diseases such as asthma in the general population. Increased concentrations of greenhouse gases, and especially carbon dioxide (CO_2), in the atmosphere have already warmed the planet substantially, causing variability in temperature, increased air pollution, forest fires, droughts, floods, thunderstorms and more severe and prolonged heat waves, all of which can put the respiratory health of the public at risk [1-3].

These changes in climate and air quality, both outdoors and indoors, have a measurable impact not only on the morbidity but also on the mortality of patients with asthma and other obstructive respiratory diseases such as COPD. There is also

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considerable evidence that subjects affected by asthma are at an increased risk of developing chronic obstructive airway exacerbations with continuous exposure to gaseous and particulate components of air pollution.
Global warming is expected to affect the start, duration, and intensity of the allergenic pollen season on the one hand, and the rate of asthma exacerbations due to air pollution, respiratory infections, and/or cold air inhalation, and other conditions on the other hand [1-6,21,22] Control of environment requires attention to exposures that originate from both the outdoor and indoor environments. This attention with consequent reduction of outdoor and indoor air pollution can help the improvement of symptoms of obstructive respiratory diseases such asthma, reducing the burden of this disease.

Components of outdoor air pollution in urban areas

The negative effect of urban air pollution (chemical and biologic) on human health and on respiratory diseases is well known. Epidemiologic studies have demonstrated that urbanization, high levels of vehicle emissions, and westernized lifestyle are correlated to an increase in the frequency of obstructive respiratory diseases prevalent in people who live in urban areas compared with those who live in rural areas [1,6,7,27] (Table 1).. Air pollutants may not only increase the frequency and intensity of symptoms in already allergic patients but may promote airway sensitization to airborne allergens in predisposed subjects. By interaction with pollen grains and plant-derived particles, pollutants can modify the morphology of these antigen-carrying agents and alter their allergenic potential. In addition, by inducing airway inflammation, pollutants may overcome the mucosal barrier and so "prime" allergen-induced responses. In other words airway mucosal damage and impaired mucociliary clearance induced by air pollution may facilitate the access of inhaled allergens to the cells of the immune system.

Shortly, air pollutants show their proinflammatory effects on airways by causing direct cellular injury or by inducing intracellular signaling pathways and transcription factors that are known to be sensitive to the oxidative stress [22-28]. Reduction in exposures to air pollution in order to prevent asthma episodes can be approached at a policy level through changes in indoor and outdoor air pollution and in the correction of lifestyle of asthmatic subjetcs.

The most abundant components of air pollution in urban areas are particulate matter, nitrogen dioxide (NO_2) and ozone O_3 [22-29].

Chemical air pollutants (PM, Nitrogen dioxide (NO2), Ozone (O3))

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Particulate matter (PM) is a mixture of organic and inorganic solid and liquid particles of different origins, size, and composition [22,23,27]. Ultrafine particulate matter (UFPM), with diameters of 0.1mm or less, is a major component of vehicles' emissions. These particles accumulate into larger fine particulate matter with a diameter of 2.5 mm ($PM_{2.5}$, particulate matter with a diameter of 2.5 mm or less), within short distances from the point of release. PM_{10} consists of $PM_{2.5}$ and larger particles of mainly crustal or biological origin including many aeroallergens. On the basis of epidemiological and laboratory studies [24-27] $PM_{2.5}$ appears to be a more potent agent for the development of respiratory and cardiovascular disease compared with PM_{10}. PM_{10} can penetrate the lower airways, and $PM_{2.5}$ is thought to constitute a notable health risk because it can be inhaled more deeply into the lungs at the alveoli level. Although human lung parenchyma retains $PM_{2.5}$, particles larger than 5mm and smaller than 10mm reach the proximal airways only, wherein they are eliminated by mucociliary clearance if the airway mucosa is intact. A large portion of urban particulate matter originates from diesel engines, as diesel exhaust particles (DEPs), which include other components such as polycyclic aromatic hydrocarbons (PAHs). DEPs account for up to 90% of airborne particulate matter in the world's largest cities and are composed of fine (2.5–0.1mm) and ultrafine (0.1mm) particles, which can also coalesce to form aggregates of varying sizes. PM_{10} levels have been associated with early respiratory exacerbations in children with persistent asthma and with higher prevalence rates even after having considered the dispersion of the particles. Although there is compelling evidence that ambient air pollution exacerbates existing asthma, the link with the development of asthma syndrome is still less well established, as few studies provide extensive exposure data. Researches have elucidated the mechanisms whereby fine particles induce adverse effects; they appear to affect the balance between antioxidant pathways and airway inflammation. Gene olymorphisms involved in antioxidant pathways can modify responses to air pollution exposure. Acute exposure to diesel exhaust causes specific effects like irritation of nose and eyes, headache, lung function abnormalities, respiratory changes, fatigue, and nausea, whereas chronic exposure is associated with cough, sputum production, and diminished lung function. Inflammation in the airways of healthy individuals after exposure to diesel exhaust and DEPs has been observed [22,23-27], and elevated expression and concentrations of inflammatory mediators have similarly been observed in the respiratory tract after diesel exhaust and DEP exposure. Recently, Carlstenet al. [27] observed that inhalation of diesel exhaust at environmentally relevant concentrations augments allergen induced allergic inflammation in the lower

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airways of atopic individuals. Particularly, diesel exhaust not only augmented the allergen induced increase in airway eosinophils, interleukin-5 (IL-5), and eosinophil cationic protein (ECP) but also augmented markers of nonallergic inflammation and monocyte chemotactic protein (MCP)-1 and suppressed activity of macrophages and myeloid dendritic cells [27].

In the context of outdoor air pollution we need to consider that open biomass burning plays an important role in atmospheric pollution and in climate change.

Nitrogen dioxide (NO_2) is a precursor of photochemical smog found in urban and industrial regions and is most often generated by cars and trucks exhausts, together with power plants. In conjunction with sunlight and hydrocarbons, NO_2 results in the production of O_3. Like O_3, NO_2 is an oxidizing pollutant, but with a lower chemical reactivity than O_3. NO_2 exposure is associated with increased emergency room visits, wheezing, and medication use among children with asthma. Controlled exposure studies on asthmatic patients have shown that NO_2 can enhance the allergic response to inhaled allergens and NO_2 concentrations in ambient air are also reportedly associated with cough, wheezing, and shortness of breath in atopic patients.

Ozone (O_3) is generated at ground level by photochemical reactions involving NO_2, hydrocarbons, andultraviolet (UV) radiation. Tropospheric ozone (O_3) is formed in the presence of bright sunshine and high temperatures by the reaction between volatile organic compounds (VOC) and nitrogen oxides (NOx), both emitted from natural and anthropogenic sources. An association between tropospheric ozone concentrations and temperature has been demonstrated from measurements in outdoor smog chambers and from measurements in ambient air [29-31].
O_3 inhalation induces epithelial damage and consequent inflammatory responses in the upper and lower airways as shown by increased levels of inflammatory cells and mediators in nasal and bronchoalveolar lavage [29-32]. Exposure to increased atmospheric levels of O_3 induces reduction of lung function, increased airway hyperreactivity to bronchoconstrictor agents, and is related to an increased risk of asthma exacerbations in asthmatic patients. Epidemiologic studies have provided evidence that high ambient concentrations of this air pollutant are associated with an increased rate of asthma exacerbations, increased hospital admissions, and/or emergency department (ED) visits for respiratory diseases, including asthma. Furthermore, several studies suggest that O_3 increases asthma morbidity by enhancing airway inflammation and epithelial permeability. It has been speculated for a long time that O_3 and other pollutants may render allergic-atopic patients more susceptible to the antigen they are sensitized. Beck et al. [29] observed that high environmental O_3 levels enhance allergenicity of birch pollen with clinical relevance

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for susceptible individuals. The acute health effects of exposure to ambient O_3 have been examined in many geographical regions. Potential adverse effects include decrease in lung function, airway inflammation, symptoms of asthma, increases in hospitalization due to respiratory diseases, and excess mortality. O_3 exposure has both a priming effect on allergen-induced responses and an intrinsic proinflammatory action in the airways of allergic-atopic asthmatic patients. In the long term, continuous exposure to high O3 levels impairs respiratory function and causes or exacerbates airway inflammation in healthy patients and in asthma patients. At the population level, long-term exposure to O3 may reduce lung function in schoolchildren and adults and increase the prevalence of asthma and asthmatic symptoms. In addition, studies have shown that asthma can be exacerbated by O3, as measured by increased visits to EDs on days with higher levels of O3 and other pollutants. Recently Malig et al. [30] explored ozone's connection to asthma and total respiratory ED visits. A multisite timestratified case-crossover study of O_3 exposures for approximately 3.7 million respiratory ED visits from 2005 through 2008 was conducted among California residents living within 20 km of an O3 monitor. The result was that short-term O_3 exposures among California residents living near an O_3 monitor were positively associated with ED visits for asthma, acute respiratory infections, pneumonia, chronic obstructive pulmonary disease, and upper respiratory tract inflammation from 2005 through 2008. Those associations were typically larger and more consistent during the warm season. Due to climate change, ozone- and fine particle-related mortalities are expected to increase in most studies; however, results differ by region, assumed climate change scenario and other factors such as population and background emissions.

Biological outdoor triggers of bronchial obstruction in asthma – allergens

Among the outdoor allergens able to induce allergic asthma there are molds and pollens.

- Moulds

There is a very large number of mould species, and very few have been well studied with regard to their effects on asthma. Moulds can be found in both indoor and outdoor environments [1,22]. Aspergillus and Penicillium species are among the most common indoor moulds, and Alternaria can be found in both indoor and outdoor environments.

Sensitisation to moulds has been associated with increased asthma severity and death, hospital admission and intensive care admissions in adults and with increased bronchial reactivity in children [1].

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The pathogenetic mechanisms by which certain mould allergens induce more severe airways disease than other common allergens need to be clarified. A possible explanation is that fungi, compared to other allergens, have the additional ability to actively germinate and infect the host skin or attempt to colonise the respiratory tract. It was suggested that mould allergens acting in concert with other nonallergen proteins or toxins produce an enhanced host response. When outdoors, patients should avoid heavy exposure to moldy vegetation and use a properly fitting particulate mask when working with moldy material. Although there have been no randomized trials of mold abatement in persons with asthma, there is adequate evidence to recommend these basic interventions to reduce exposure for mold-sensitized patients with asthma.

Pollens

Effects of climate change on air pollution and allergenic pollen

Climate change may affect air pollutant levels in several ways: the influence on regional weather (changes of wind patterns and amount and intensity of precipitation, increase of temperature) may have an effect on severity and frequency of air pollution episodes and also on anthropogenic emissions (for example, increase of energy demand for space heating or cooling); the enhancement of the urban heat island effect may increase some secondary pollutants (i.e., ozone), and it can indirectly increase natural sources of air pollutant emissions (e.g., decomposition of vegetation, soil erosion, and wildfires) [1]. Pollen from birch exposed to higher ozone-levels induce larger wheals and flares in skin prick test compared to lower ozone-exposed pollen suggesting an allergenicity increasing effect of ozone [29]. Changes in temperature and precipitation may also increase frequency and severity of forest fires, sometimes with public health consequences. Changes in wind patterns may increase episodes of long distance transport of pollutants as well as of pollen grains, making large-scale circulation patterns as important as regional ones [1].
Climate change appears to induce an increased concentration of all health-related air pollutants. Climate change influences not only the levels and the type of air pollution but also allergenic pollens. Global warming affects the onset, duration, and intensity of the pollen season as well as the allergenicity of the pollen. Studies on plant responses to elevated atmospheric levels of CO_2 indicate that plants exhibit enhanced photosynthesis and reproductive effects and produce more pollen [1]. Moreover, the plants flower earlier in urban areas than in corresponding rural areas with earlier pollination of about 2–4 days. Over the last decades, many studies have shown changes in production, dispersion, and allergen content of pollen and spores and that nature of the changes may be different in different regions and species. Current

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knowledge on the worldwide effects of climate change on respiratory allergic diseases is provided by studies on the relationship between asthma and environmental factors, like meteorological variables, airborne allergens, and air pollution. Published data suggest an increasing effect of aeroallergens on allergic patients, leading to a greater likelihood of development of an allergic respiratory disease in sensitized patients and an aggravation in patients already symptomatic [1].

Thunderstorm asthma and risk of asthma crisis.

According to current climate change scenarios, there will be an increase in intensity and frequency of heavy rainfall episodes, including thunderstorms and thunderstorm asthma is a term used to describe an observed increase in acute bronchospasm cases following the occurrence of thunderstorms during pollen seasons [31-38]. Associations between thunderstorms and asthma morbidity have been identified in multiple locations around the world, predominantly in Europe (Birmingham, London, Naples(Italy)) and in Australia (particularly in Melbourne three times with last event on November 2016 as the most catastrophic epidemic of asthma attack induced by a thunderstorm with 9 deaths and 8.500 subjects in emergency departments in a day [37], during the pollen season and it is now recognized that thunderstorms are a risk factor for asthma attacks in patients suffering from pollen allergy (Table 2) [35-37].
Thunderstorms can concentrate pollen grains at ground level, which may release allergenic particles of respirable size into the atmosphere after their rupture by osmotic shock. During the first 20–30 min of a thunderstorm, patients suffering from pollen allergy may inhale a high concentration of the allergenic material that is dispersed into the atmosphere [35-37].

A Take home message should be that subjects affected by pollen allergy should be alert to the danger of being outdoors without correct treatment of rhinitis and asthma during a thunderstorm in the pollen season

Measures to improve outdoor air quality and to reduce the risk of inhalation of air pollution.

Much remains to be studied by using biologic, genetic, epidemiologic and clinical approaches to air pollution [38-41].
Governments worldwide and international organizations such as the World Health Organization and European Union are facing a growing problem of the respiratory effects induced by gaseous and particulate pollutants arising from motor vehicle emissions. The last release of the Intergovernmental Panel on Climate Change

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(IPCC) [3] stated that climate change is very likely due to human activity, according to an impressive amount of data published in the last years, and policymakers seem now to take into greater consideration preventive measures (such as the Kyoto Protocol) and alternative energy sources. Desirable positive effects of these measures may be achieved in the next decades but, presumably, global temperature will continue to increase in a short term perspective.
Wearing personal protective equipment (N95 mask or equivalent) might be a useful for avoiding detrimental effect of ambient air pollutants. Masks have been proved useful in reducing respiratory virus transmission during a pandemic. These masks can also help people to prevent adverse effects from vehicular pollution but more studies are needed to demonstrate their real utility [1,3].

The farm environment is able to reduce the risk of asthma.

The Amish and Hutterites are U.S. agricultural populations whose lifestyles are remarkably similar in many respects but whose farming practices, in particular, are distinct; the former follow traditional farming practices whereas the latter use industrialized farming practices. The populations also show striking disparities in the prevalence of asthma, and little is known about the immune responses underlying these disparities. Stein et al [42] studied environmental exposures, genetic ancestry, and immune profiles among 60 Amish and Hutterite children, measuring levels of allergens and endotoxins and assessing the microbiome composition of indoor dust samples. Whole blood was collected to measure serum IgE levels, cytokine responses, and gene expression, and peripheral-blood leukocytes were phenotyped with flow cytometry. The effects of dust extracts obtained from Amish and Hutterite homes on immune and airway responses were assessed in a murine model of experimental allergic asthma. Despite the similar genetic ancestries and lifestyles of Amish and Hutterite children, the prevalence of asthma and allergic sensitization was 4 and 6 times as low in the Amish, whereas median endotoxin levels in Amish house dust was 6.8 times as high. Differences in microbial composition were also observed in dust samples from Amish and Hutterite homes. Profound differences in the proportions, phenotypes, and functions of innate immune cells were also found between the two groups of children. In a mouse model of experimental allergic asthma, the intranasal instillation of dust extracts from Amish but not Hutterite homes significantly inhibited airway hyperreactivity and eosinophilia.The results of the study of Stein et al in humans and mice indicate that the Amish environment induces protection against asthma by engaging and shaping the innate immune response.

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While the burning of fossil fuels accounts for roughly 75 percent of humankind's carbon dioxide emissions, deforestation is the second-largest source [43]. Forests play a major role in controlling greenhouse gases by absorbing CO_2 during photosynthesis. When forests are cut down, it reduces the planet's ability to absorb what humans emit [43].

Conclusions

There are observations that climate change is able to induce changes in production and dispersion of chemical and biologic components of atmospheric air pollution. In particular atmospheric allergen content of pollen and spores is increased with proinflammatory effect on airways of allergic patients.In other words a body of evidence suggests that major changes to our world are occurring and involve the atmosphere and its associated climate [1,11,12-14, 35-39]. These changes, including global warming induced by human activity, have an impact on the biosphere and on the human environment. The global changes in terms of population growth and demands, air pollution and increase of earth temperature are unprecedented and are threatening the future of humans. These changes are also impelling a redistribution of life on hearth, posing risks for all aspects of human life, including economic development, livelihoods, food security and global health,. Increase of production and concentration of aeroallergens and air pollutants and of their geographical distribution with changes of climate and weather patterns are among the observed and predicted consequences. Although most of environmental changes have occurred already and are irreversible, there is still time to take action. One of the major challenges is the reduction of greenhouses emissions, some of them are also air pollutants. However, public health approaches to decrease exposure of citizens to air pollution must be implemented considering that it is important to reduce the use of fossil fuels, reducing the private traffic in towns, improving the public transport and favoring pedestrian traffic. Moreover, it is important also to plant non-allergenic trees in cities.In this context it is important to consider that unfortunately each year a lot of hectares of woods are destroyed by fires, frequently setted criminally, and this is a real pity for the life of our Planet [43].

Some KEY POINTS:

- **Asthma is heterogeneous disease that is strongly influenced by environmental factors such as meteorological events and climate change that vary in type and intensity acrossthe world.**

- **Exposure to climate change and air pollution is linked to many signs of obstructive respiratory diseases, such as asthma exacerbation of symptoms and increased medication use, visits to EDs and hospital admissions.**

- **It is in particular the vehicular pollution that degrades the quality of air in urban areas, whereas industrial pollution still constitutes the largest source of air pollution in countries undergoing industrialization.**

- **In the last 50 years, 50% of pluvial forests on the planet have been destroyed, and each year 13 million hectares of forests are being destroyed or deteriorated. These are aggravating factors of climate change.**

- **subjects affected by pollen allergy should be alert to the danger of being outdoors without correct treatment of rhinitis and asthma during a thunderstorm in the pollen season**

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TABLE 1. Air pollutants show their proinflammatory effects on airways by causing direct cellular injury or by inducing intracellular signaling pathways and transcription factors that are known to be sensitive to the oxidative stress.

Chemical air pollutants of urban areas exert their detrimental effects on airways by:
- increasing permeability of airway epithelium;
- reducing the ciliary activity of epithelial cells of airways;
- inducing inflammatory changes in cells of airways;
- modulating cell cycle and death of cells of airways.

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Table 2. Characteristics of described epidemics of thunderstorm-associated asthma (references 29-35).

- The occurrence of epidemics is strictly linked to thunderstorm;
- The thunderstorm-related asthma epidemics are registered during late spring and during summer when there are high atmospheric concentrations of airborne pollen grains;
- In the epidemics aren't involved subjects with pollinosis, who stay indoors with windows closed during thunderstorm;
- There aren't high levels of gaseous and particulate components of air pollution during epidemics;
- There is a major risk for asthma in patients who are not under antiasthma correct treatment;
- Patients with allergic rhinitis and without previous asthma can experience bronchoconstriction, sometimes also severe.