

Effects of climate change on environmental factors in respiratory allergic diseases

G. D'Amato* and L. Cecchi^{†,‡}

*Division of Respiratory and Allergic Diseases, Department of Chest Diseases, High Speciality Hospital 'A.Cardarelli', Napoli, Italy, [†]Interdepartmental Centre of Bioclimatology, University of Florence, Florence, Italy and [‡]Allergy Clinic, Azienda Sanitaria 10 Firenze, Florence, Italy

Clinical and Experimental Allergy

Summary

A body of evidence suggests that major changes involving the atmosphere and the climate, including global warming induced by human activity, have an impact on the biosphere and the human environment. Studies on the effects of climate change on 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. However, there is also considerable evidence that subjects affected by asthma are at an increased risk of developing obstructive airway exacerbations with exposure to gaseous and particulate components of air pollution. 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. Pollen allergy is frequently used to study the interrelationship between air pollution, rhinitis and bronchial asthma.

Epidemiological studies have demonstrated that urbanization, high levels of vehicle emissions and westernized lifestyle are correlated to an increase in the frequency of pollen-induced respiratory allergy, prevalent in people who live in urban areas compared with those who live in rural areas. Meteorological factors (temperature, wind speed, humidity, etc.) along with their climatological regimes (warm or cold anomalies and dry or wet periods, etc.), can affect both biological and chemical components of this interaction. In addition, by inducing airway inflammation, air pollution overcomes the mucosal barrier priming allergen-induced responses. In conclusion, climate change might induce negative effects on respiratory allergic diseases. In particular, 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 suggest that environmental risk factors will have a stronger effect in the following decades.

Correspondence:

Prof. Gennaro D'Amato, Division of Respiratory and Allergic Diseases, Department of Chest Diseases, High Speciality Hospital 'A.Cardarelli', Napoli, Italy.
E-mail: gdamato@qubisoft.it

Introduction

It is now widely accepted that the earth's temperature is increasing, as confirmed by the warming of the oceans, rising sea levels, melting glaciers, retreating sea ice in the Arctic and diminished snow cover in the Northern Hemisphere. Moreover, changes are also occurring in the amount, intensity, frequency and type of precipitation as well as the increase of extreme events, like heat waves, droughts, floods and hurricanes. As stated in the recent Working Group I report of the Intergovernmental Panel on Climate Change (IPCC), 'most of the observed increase in globally averaged temperatures since the mid-20th century is very likely due to the observed increase in anthropogenic greenhouse gas concentrations' [1].

Carbon dioxide (CO₂) is the most important anthropogenic greenhouse gas and its atmospheric concentration has increased from a pre-industrial value of about 280–379 p.p.m. in 2005; about 75% of the anthropogenic CO₂ emissions to the atmosphere during the past 20 years resulted from fossil fuel burning; most of the rest resulted from changes in land use, especially deforestation. The same trend has been observed in the other prevalent anthropogenic greenhouse gases methane (CH₄) and nitrous oxide (N₂O) [2].

Major changes in atmosphere and the climate have a major impact on the biosphere and the human environment. Many prevalent human diseases are linked to climate fluctuations, from cardiovascular mortality and respiratory illnesses due to heat waves, altered

transmission of infectious diseases and malnutrition from crop failures [3].

A number of reports on time trends in allergic respiratory diseases have shown a substantial increase in prevalence since the early 1960s. However, accumulating evidence indicates that rising trends in the prevalence of asthma and atopy among adults and older children may have plateaued or even decreased after increasing for decades, especially in countries with existing high prevalence [4]. Data on prevalence in younger children are less reassuring [5].

The effects of climate change on respiratory allergy are still unclear 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.

Data about the influence of weather on asthma are poor and inconclusive [6]. Weather affects asthma directly, acting on airways, or indirectly, influencing airborne allergens and pollutant levels. The complex composition of aerosol reaching the airways and the several compounds that play a role in this relationship might explain the controversial results of studies conducted so far.

Indoor and outdoor allergen exposure is a well-known aggravating factor for asthmatic patients [7] even if its role in asthma development is not fully understood. Pollen grains are responsible for seasonal exacerbations of allergic asthma and rhinitis and they disperse according to the flowering period of the plant of origin. Knowledge of a plant's geographical distribution and its flowering period [8] and possible variations induced by climate change scenarios is of great importance.

Several studies have shown that air pollution is consistently associated with adverse health effects [9–11] and it has a quantifiable impact on respiratory diseases, on cardiovascular diseases and stroke [12, 13]. Data linking changes in environmental variables and changes in incidence and prevalence of bronchial asthma are still lacking, even if an increasing body of evidence shows the adverse effects of ambient air pollution [14, 15].

The aim of the present review is to briefly discuss current concepts in the field of environmental factors affecting allergic respiratory diseases and hypothesize possible long-term effects of climate change. Possible impacts of climate change on allergy and asthma prevalence are beyond the purpose of this paper, but the role of predictable changes in air pollution and aeroallergen exposure will be considered.

Air pollution

The massive increase in emissions of air pollutants due to economic and industrial growth in the last century has made air quality an environmental problem of the first

order in a large number of European countries and in North America and is now an emerging problem in other regions of the world, in particular in highly populated Asian urban areas (i.e. megacities of China, India, Thailand, etc.). The enormous world-wide increase in the number of motor vehicles has resulted in a tremendous increase in energy consumption and in air-polluting emissions from cars, in particular those with diesel engines. Several air pollutants are on the list of greenhouse gases involved in global warming. In urban areas with high levels of vehicular traffic, the most abundant air pollutants are respirable particulate matter (PM), nitrogen dioxide (NO₂) and ozone (O₃). Other than NO₂ and precursors of O₃, diesel fuel combustion results in the production of diesel exhaust particles (DEPs), which consist of an elemental carbon core with a large surface area to which hundreds of chemicals and transition metals are attached. DEPs include fine (2.5–0.1 µm) or ultrafine (< 0.1 µm) particles, but these primary DEPs can coalesce to form aggregates of varying sizes. In general, the effects of air pollutants on lung function depend on the environmental concentration of the pollutant, the duration of pollutant exposure and the total ventilation of the exposed persons. However, a factor clouding the issue is that laboratory evaluations do not reflect what happens during natural exposure, when atmospheric pollution mixtures in polluted cities are inhaled. As a consequence, even if it is plausible that ambient air pollution plays a role in the onset and in the increasing frequency of respiratory allergy, it is not easy to show how this happens at a public health level. In addition, it is important to recall that an individual's response to pollution exposure depends on the source and components of air pollution, as well as meteorological conditions. Indeed, some air pollution-related incidents with asthma aggravation do not depend only on the increased production of air pollution, but rather on atmospheric regimes that favour the accumulation of air pollutants at ground level.

What are the effects of air pollution on respiratory allergic disease?

In the context of urban air pollution, PM, and especially the fraction of particles smaller than 2.5 µm, is the component more significantly related to health effects [16].

Several human experimental studies [17–19] with dilute diesel exhaust show extensive inflammatory effects in the bronchial wall with adverse functional consequences. The underlying mechanisms have been associated with oxidative stress and activation of several mitogen-activated protein kinases and transcription factors, and disturbances in cell functions by the physical and chemical characteristics of diesel exhaust [20–22]. There is evidence that living near roads with high levels of

car traffic is associated with impaired respiratory health, since road traffic with its gaseous and particulate emissions is currently, and is likely to remain, the main contributor to air pollution in most urban settings. Recently, Gauderman and colleagues provided evidence that living close to motorways in California, USA, leads to reduced lung development in children. In a longitudinal study, more than 3600 children were followed up from ages 10–18 years with measurements of lung function every year. Children living < 500 m from motorways had reduced lung-function growth compared with those living more than 1500 m away. It is important to note that these results were independent of regional air quality [23]. This study confirmed previous findings showing that lung function and asthma in children [24–26] as well as in adults [27–29] is affected by air pollution. However, analysis of emergency department admissions for asthma in Taiwan underlined the increased susceptibility of children compared with adults [30].

Exposure to increased atmospheric levels of O₃ induces a decrement in lung function and increased airway reactivity to bronchoconstrictor agents, and is related to an increased risk of asthma exacerbation in asthmatic subjects [31, 32]. Epidemiological studies have provided evidence that high ambient concentrations of this air pollutant are associated with an increased rate of asthma attacks and increased hospital admissions or emergency department visits for respiratory diseases, including asthma [31, 33–35]. Several studies suggest that O₃ increases asthma morbidity by enhancing airway inflammation and epithelial permeability [33, 34, 36].

O₃ exposure significantly increases levels of inflammatory cells (in particular neutrophils) and mediators, such as IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) and fibronectin, in bronchoalveolar lavage fluid (BALF) of asthmatic subjects [36, 37].

It has long been speculated that O₃ and other pollutants may render allergic subjects more susceptible to the antigen they are sensitized to [37, 38]. It has been observed that the incidence of new diagnoses of asthma is associated with heavy exercise in communities with high concentrations of O₃. Thus, air pollution and outdoor exercise could contribute to the development of asthma in children [39].

Pollen/pollutants interaction

Studies have demonstrated that urbanization, high levels of vehicular emissions and a westernized lifestyle are correlated with the increasing frequency of pollen-induced respiratory allergy and people who live in urban areas tend to be more affected by pollen-induced respiratory allergy than people living in rural areas [40–44].

There is a growing body of evidence that components of air pollution interact with inhalant allergens carried by

pollen grains [45, 46] and may enhance the risk of both atopic sensitization and exacerbation of symptoms in sensitized subjects [45].

Pollen grains or plant-derived paucimicronic components carry allergens that can produce allergic symptoms [14]. They may also interact with air pollution (particulate matter, ozone) in producing these effects. Furthermore, 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 [14, 15, 17, 18]. In addition, vegetation reacts with air pollution and environmental conditions and influences plant allergenicity.

In a recent study in four European cities, allergens from pollens, latex and also β-glucans were shown to be bound to ambient air particles. Thus, combustion particles in ambient air can act as carriers of allergens and as depots of allergens inhaled into the airways [47].

Moreover, in experimental conditions, *Phleum pratense* (timothy grass) pollen releases more allergen-containing granules when treated with increasing concentrations of NO₂ and O₃ than when exposed to air only. The effects of these traffic-related pollutants might lead to an increase of bioavailability in airborne pollen allergens [48].

Weather

Data about the influence of weather conditions on asthma are poor and debated. Weather conditions affect asthma directly, acting on airways, or indirectly, influencing airborne allergens and pollutant levels.

A decrease in air temperature is an aggravating factor for asthmatic symptoms, regardless of the geo-climatic areas under study [49–52]; furthermore, studies based on the synoptic method (categorization of daily weather into air mass types, which are homogeneous bodies of air with distinct thermal and moisture characteristics) supported findings derived from analyses with only air temperature as the meteorological variable [53]. While results of the effects of cold air on asthma are consistent, the role of humidity, wind and rainfall is still unclear and studies including these variables showed inconclusive and inconsistent results, maybe because their impact on the diffusion of pollen and pollutants is higher than that of air temperature [54–57]. Conversely, a prospective study from New Zealand has not showed any statistically significant association between meteorological variables and symptoms of asthma recorded daily in a diary [58].

Humidity indirectly affects respiratory allergic diseases, influencing atmospheric levels of aeroallergens. There is evidence that low humidity allows the release of pollen from anthers favouring dispersion and transport phases, while high humidity is associated with lower airborne pollen concentration. Conversely, spore release is generally favoured by high levels of humidity, even if

mechanisms of release show differences among fungi species [59, 60].

A thunderstorm is an extreme weather event that can induce dramatic consequences on respiratory allergic asthma, as shown in the last 15 years (Table 1). Several asthma outbreaks during thunderstorms were described in the United Kingdom [61], Australia [62, 63] and Italy [64]. Despite some uncertainties, the mechanism underlying asthma epidemics might be pollen grain rupture by osmotic shock and release of part of their content, including respirable, allergen-carrying starch granules (0.5–2.5 μm) into the atmosphere [65].

Upper respiratory infections play a key role in exacerbation of asthma [66], contributing to the typical increase of hospitalizations and medical calls in cold months [67] and during spring. The reasons for the seasonal pattern of infections are predominantly behavioural because people spend a longer time in confined and crowded places, allowing a wider diffusion and transmission of viruses. However, recent findings also suggest an impairment of natural immunity mechanisms of airways induced by breathing cold air [68].

What might the effects of climate change be on environmental risk factors for respiratory allergic diseases?

In the light of current knowledge, air pollution and aeroallergens seem critical in evaluating the possible effects of climate change on allergic respiratory diseases. An increasing body of evidence suggests that climate change might affect both environmental factors.

How does climate change influence air pollution type and levels?

Climate change may affect air pollutant levels in several ways: the influence on regional weather regimes (changes of wind patterns and amount and intensity of precipitation, increase of temperature) may have an effect on the severity and frequency of air pollution episodes and also on anthropogenic emissions (e.g. increased of energy demand for space cooling); the enhancement of urban heat island effect may increase some secondary pollutants

(i.e. ozone); and it can indirectly affect natural sources of air pollutant emissions (e.g. decomposition of vegetation, soil erosion, wildfires) [69, 70].

Tropospheric ozone is formed in the presence of bright sunshine and high temperatures by the reaction between volatile organic compounds (VOC) and nitrogen oxides (NO_x), both of them emitted from natural and anthropogenic sources. An association between tropospheric ozone (O_3) concentrations and temperature has been demonstrated from measurements in outdoor smog chambers and from measurements in ambient air [71, 72] even if it does not occur when the ratio of VOC to NO_x is low. Tropospheric ozone concentrations are increasing in most regions [73] and this trend is expected to continue over the next 50 years [74].

Heterogeneous composition of particulate matter makes projection of the effects of climate change on its concentration very difficult. A study performed in the United Kingdom projected a large decrease in days with high particulate concentrations due to changes in meteorological conditions; in addition, effects of legislation on reduction of fuel and vehicle emissions are expected to further improve PM air concentrations [75]. On the other hand, a more recent study projected an increase in summertime pollution episodes of black carbon and carbon monoxide in the northeastern and midwestern United States by 2050 [76], underlining the importance of local climatic conditions in this type of study. Particulate matter partly originates from natural sources and climate change could affect some of them. Changes in temperature and precipitation may also increase the frequency and severity of forest fires, sometimes with public health consequences [77, 78].

SO_2 and NO_x oxidize in the atmosphere to form sulphuric acid and nitric acid, respectively, and oxidation rate is accelerated by higher temperatures. The negative effect of global warming, which could induce an increasing potential of acid deposition (e.g. acid rain) [69], might be counterbalanced by a decrease of SO_2 emissions because of reduced use, e.g. for public electricity and heat production as shown in Europe [79] and the United States [80].

Changes in circulation patterns may increase episodes of long-distance transport of pollutants [81, 82] as well as

Table 1. Current epidemiological observations supporting the link between thunderstorms and epidemics of rhinitis and asthma exacerbations

Thunderstorm-asthma: epidemiological evidences

The occurrence of epidemics is closely linked to thunderstorms

The thunderstorm-related epidemics are limited to late spring and summer when there are high levels of airborne pollen grains

There is a close temporal association between the arrival of the thunderstorm, a major rise in the concentration of pollen grains and the onset of epidemics

Subjects with pollen allergy who stay indoors with windows closed during thunderstorms are not involved

During epidemics there are not high levels of gaseous and particulate components of air pollution

There is a major risk for subjects who are not under anti-asthma correct treatment

Subjects with allergic rhinitis and without previous asthma can experience severe bronchoconstriction

of pollen grains, making large-scale circulation patterns as important as regional ones.

In summary, climate change appears to induce an increased concentration of all health-related air pollutants, except SO₂. Of particular concern are potential changes in tropospheric ozone and particulate matter. However, the consequence of higher temperature on ozone concentration might be partially counterbalanced by a decrease in demand for heating systems during mild winter due to the global warming. Moreover, the mitigating effects of measures to reduce air pollutant emissions have to be considered [69].

Projection about the effects of climate change on health-related air pollution is hampered by several limits: future emissions depend on numerous factors, such as population growth, economic development, energy use and production; current knowledge about the effects of weather on air pollution is still unsatisfactory; there is still a need for better emission inventories and observational datasets; long-term effects and actual enforcement of international agreements to reduce air pollution and greenhouse gases emissions (e.g. the Kyoto protocol) are unpredictable.

How does climate change influence allergenic pollen?

Plant species require a certain amount of heat to complete their development; then air temperature plays a key role, together with other factors, such as day-length, water and nutrients availability, and soil type. An increasing amount of evidence from all over the world shows that the timing of life cycle events of a large number of species have responded to the observed increase in the earth's temperature. Changes also involve plants producing allergenic pollen, with expected consequences on atopic population [70]. Data provided by 30 years of observations within the International Phenological Gardens network showed that spring events advanced by 6 days, the highest rate of phenological change being observed in western Europe and the Baltic regions [83]. Conversely, phenological trends appear to be different along the eastern border of Europe, sometimes showing a 1–2-week later start of the phases [84]. An earlier start of the season was confirmed in studies focused on allergenic plants, such as birch, [85, 86] mugwort [87], Urticaceae [88] grass [89, 90] and Japanese cedar [91], even if different methods and different lengths of datasets have been used. Because of the earlier onset, the pollen seasons are more often interrupted by adverse weather conditions in late winter/early spring.

Duration of the pollen season is also extended, especially in summer and in late-flowering species [92]. There is evidence of significantly stronger allergenicity in pollen from trees grown at increased temperatures [93, 94].

Increasing CO₂ and temperature seem to induce substantial increases in pollen production from ragweed in experimental conditions [95–98]. The same results were obtained in a study of ragweed plants growing in urban and rural areas, providing an elegant 'natural' model for evaluating the possible effects of global warming [99].

More recently, Singer *et al.* [100] showed that Amb 1 concentration in ragweed pollen increased as a function of CO₂ concentration even if the well-demonstrated differences in allergenic content among and within ragweed populations have to be taken into account [101].

The observed long-term changes in the large-scale atmospheric circulation have an impact on wind patterns [2]. These changes might contribute to increase the occurrence of episodes of long-distance transport of new allergenic pollen, as shown in the case of ragweed in central Italy [102, 103].

Although updated and exhaustive maps are still lacking, the distribution of allergenic plants in Europe seems, in part, changed in recent years. The cases of grass and ragweed are explanatory. Grass pollen is responsible for a high percentage of pollinosis world-wide and variations in total pollen count have been observed in the last decades [88, 104]. The analysis of the UK time series of aerobiological data, the longest in the world, showed a decreasing trend in terms of yearly grass pollen counts and a severity of pollen season and an earlier start of the season. However, there are remarkable differences between the three study sites (Cardiff, London and Derby), underlining the role of local determinants (such as climate), plants adaptation (i.e. tolerance to environmental factors), changes in land use, changes in species and effects of air pollutants [88]. Since allergenic pollen counts are usually provided by urban traps, it can be argued that the observed reduction in grass pollen levels in some European regions can be induced by the rapid growth of urban areas.

From a wider point of view, the trend at an urban level could be counterbalanced by the effects of global warming and increased CO₂ concentration, which are thought to favour, for example, a northward expansion of some species of grasses [105].

Since the last decades of the 19th century, ragweed has become increasingly important from an allergological point of view, covering large areas of Central and Eastern Europe [8]. In the eastern countries the expansion of ragweed seems to be associated with major socio-economic transitions rather than with climate change. This observation could be explained by the increase in areas of disturbed land (suitable for ragweed proliferation) that occurred during the inception and collapse of communism [106].

Even if an increasing number of observations show that global warming is affecting all phases of plant development, there are still uncertainties about the effects on the

start, length and end of the pollen season of allergenic plants. The numerous papers published on this topic showed the effects to be different for each plant and geographical area under study. Also biological and socio-economic factors play a role. Moreover, only a few experimental studies reported an increase in pollen allergenicity in a CO₂-enriched environment [107], representing this as a key topic to be developed in the next decade. In addition, the lack of complete European maps of allergenic plant distribution makes a thorough projection of changes very challenging.

Possible changes in airborne allergenic pollen levels in Europe in the next decades are shown in Table 2, including the effects that they may have on the allergic population.

What might the effects of climate change be on respiratory allergic diseases?

Several factors make the projection very challenging in this field. Firstly, climate change scenarios are based on models, which try to represent the evolution of the atmospheric behaviour according to some defined socio-economic global projections. However, such models are not able to represent small-scale dynamics, limiting these applications. Since slight increases in the earth's temperature seem to have a dramatic effect on living organisms, slight differences in the magnitude of global warming might substantially change our pre-visions on the effects on human health [2]. Secondly, changes in health-related pollen and pollutants are difficult to predict, as discussed above. Finally, trends of world-wide asthma prevalence are still unclear, being different in developing and in industrialized countries. The so-called 'hygiene hypothesis' seems nowadays a reasonable explanation for the increase in allergic diseases [108, 109] even if evidence supporting the link between 'higher hygiene' and increase of atopy and asthma prevalence is still inconclusive [110]. One of the cornerstones of this hypothesis is the inverse relationship between asthma prevalence and clinical or

sub-clinical occurrence of viral and bacterial infections, especially involving the gastrointestinal tract; according to the current view, gastrointestinal infections might represent a marker of microbial exposure [111–113]. Given the expected increase in the burden of diarrhoeal diseases [70], one might speculate that climate change will indirectly contribute to increase the protective effect of microbial exposure. However, there is no conflict between the role of hygiene hypothesis and air pollution in explaining increased asthma.

Recent epidemiological studies showed the negative role of urban air pollution on lung development [23, 24, 26–28], shedding light on a possible additional explanation for the increase of asthma prevalence. In this view, studies on the effects of climate change on urban air pollution episodes are of particular interest.

The influence of climate change on symptoms of respiratory allergy is still unpredictable. Two opposite effects could be relevant. On the one hand, global warming could increase the length and severity of the pollen season and, as a consequence, of pollen allergy. Moreover, the increase in the occurrence of heavy precipitation events, as predicted by recent climate change scenarios [1], could make episodes of asthma epidemics more frequent. Finally, the overall effects on health-related air pollutants seem favourable to an increase in urban air pollution episodes. On the other hand, increases in the earth's temperature could reduce the effects of cold air on asthma and rhinitis, also making patients less susceptible to upper respiratory infections (Fig. 1).

Conclusions and future directions

Among the factors implicated in the recent 'epidemic' of bronchial asthma are indoor and outdoor air pollution in most industrialized countries.

It is not easy to evaluate the effects of single air pollutants because there are limitations for each type of study (laboratory exposure study, time-series analysis of changes in asthma mortality or morbidity, cross-sectional

Table 2. Expected changes in airborne allergenic pollen levels and allergenic plants distribution in Europe

Effects of climate change	Pollen involved	Expected impact on atopic patients
Earlier start of pollen season (western and Baltic Europe)	Mugworth [87], pellitory [88], grass [89, 90], birch [85, 86]	Negative
Extended duration of pollen season	Summer and late flowering species [92]	Negative
Increase of long-distance episodes	Ragweed [102, 103]	Negative
Increased pollen allergenicity	Ragweed [100]	Negative
Increased pollen production	Ragweed [95–98]	Negative
Effects of socio-economic factors		
Changes in land use	Grass [89, 105]	Unchanged*
Socio-economic transitions	Ragweed [106]	Negative

*See text.

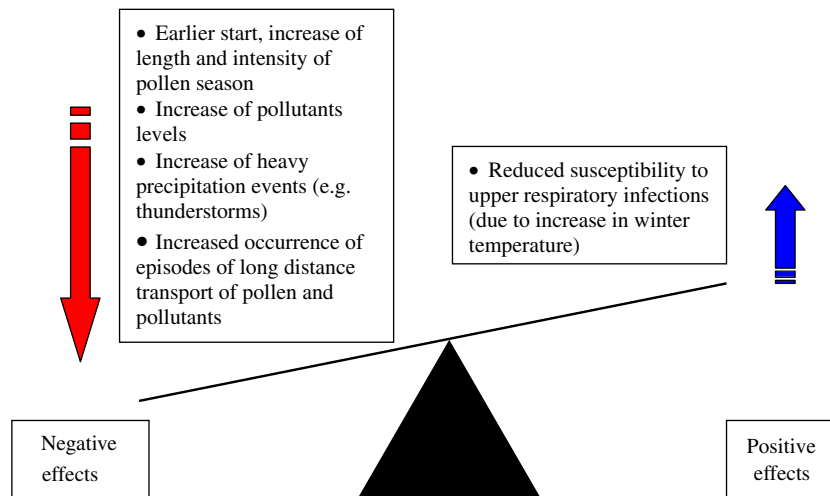


Fig. 1. Possible effects of climate change on patients affected by respiratory allergy (see text).

Table 3. Public preventive measures to decrease the effects of environmental factors affecting respiratory allergic diseases

Measures to decrease population exposure

- Encouraging policies to promote access to non-polluting and sustainable sources of energy, reducing use of fossil fuels
- Controlling vehicle emissions
- Reducing the private traffic in towns, improving public transport and favouring pedestrian traffic
- Planting non-allergenic trees in cities

study of comparison of different geographical areas). For example, laboratory exposure frequently uses a single pollutant: this is different from real-life urban exposure. However, urbanization with its high levels of vehicular emissions and westernized lifestyles parallels the increase in respiratory allergy in most industrialized countries, and people who live in urban areas tend to be more affected by the disease than those in rural areas. In atopic subjects, exposure to air pollution increases airway responsiveness to aeroallergens and pollinosis seems to be a good model with which to study the interrelationship between air pollution and respiratory allergic diseases.

Pollen grains and plant-derived paucimicronic components carrying antigens can produce allergic respiratory symptoms. By adhering to the surface of these airborne allergenic agents, air pollutants could modify their antigenic properties. Several factors influence this interaction, i.e., type of air pollutant, plant species, nutrient balance, climatic factors, degree of airway sensitization and hyperresponsiveness of exposed subjects. However, the damage of airway mucous membranes and the impaired mucociliary clearance induced by air pollution may facilitate the penetration and the access of inhaled allergens to the cells of the immune system, and so promote airway sensitization. Consequently, an increased IgE-mediated response to aeroallergens and enhanced airway inflammation favoured by air pollution could account for the increasing prevalence of allergic respiratory diseases in urban-polluted areas.

It is not easy to evaluate the impact of air pollution on the timing of asthma exacerbations and on the prevalence of asthma in general, because concentrations of airborne allergens and air pollutants are frequently increased contemporaneously. However, an enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of respiratory allergy.

Pollen allergy is frequently used to study the interrelationship between air pollution and respiratory allergy. Climatic factors (temperature, wind speed, humidity, thunderstorms, etc.) can affect both components (biological and chemical) of this interaction. By attaching to the surface of pollen grains and of plant-derived particles of paucimicronic size, components of air pollution could modify not only the morphology of these antigen-carrying agents but also their allergenic potential. In addition, by inducing airway inflammation, which increases airway permeability, pollutants overcome the mucosal barrier and could be able to 'prime' allergen-induced responses.

Much remains to be studied by using biological, genetic, epidemiological and clinical approaches to air pollution [15, 114–117]. However, public health approaches to decrease the exposure of citizens to air pollution must be implemented (Table 3).

As for the last point, it is important to consider that, unfortunately each year several hectares of woods are destroyed by fires, predominantly in the Mediterranean area and frequently in a voluntary way: a crime against

the nature. Of course, these fires and the reduced woods are responsible for an increased greenhouse effect.

Moreover, although there is no general agreement, increasing the antioxidant defences of the human airways by eating antioxidant food should be implemented [118–121].

Governments world-wide and international organizations such as the World Health Organization and the European Union are facing the growing problem of respiratory effects induced by gaseous and particulate pollutants arising from motor vehicle emissions.

It is hoped that a greater awareness of the health effects of DEP will encourage a reduction of diesel engine use and/or scientists to find technologies that are able to substantially decrease the release of exhaust particles. Unfortunately, a sudden change in fossil fuel emission is extremely unlikely and we will have to face the unhealthy effects of particulate matter for a long time. Fortunately, the issue of greenhouse gases seems to be at a turning point. The last release of the IPCC stated that climate change is very likely due to human activity, according to an impressive amount of data published in the last few years [1] and policy makers now seem to take into greater consideration preventive measures (like the Kyoto protocol) and alternative energy sources. Desirable positive effects of these measures may be achieved in the following decades, but global temperature will continue to increase in the short term.

Acknowledgements

We thank Massimiliano Pasqui, climatologist at the Institute of Biometeorology, National Research Council, CNR (Italy), for manuscript revision and Meaghan Hill for checking English. Lorenzo Cecchi was supported by the 'MeteoSalute' project, Regional Health System of Tuscany, Italy.

References

- Solomon S, Qin D, Manning M *et al.* Summary for policy makers. In: Solomon S, Qin D, Manning M, Chen Z, Marquis M, Averyt KB, Tignor M, Miller HL, eds. *Climate change 2007: the physical science basis. Contribution of working group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*. Cambridge, UK: Cambridge University Press, 2007;1–21.
- Solomon S, Qin D, Manning M *et al.* Technical summary. In: Solomon S, Qin D, Manning M, Chen Z, Marquis M, Averyt KB, Tignor M, Miller HL, eds. *Climate change 2007: The physical science basis. Contribution of working group I to the fourth assessment report of the intergovernmental panel on climate change*. Cambridge, UK: Cambridge University Press, 2007.
- Epstein PR. Climate change and human health. *New Engl J Med* 2005; 353:1433–6.
- von Hertzen L, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy* 2005; 60:283–92.
- Asher MI, Montefort S and the ISAAC Phase Three Study Group *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368:733–43.
- Atkinson RW, Strachan DP. Role of outdoor aeroallergens in asthma exacerbations: epidemiological evidence. *Thorax* 2004; 59:277–8.
- GINA Report, Global Strategy for Asthma Management and Prevention. 2006. <http://www.ginasthma.org/Guidelineitem.asp?i1=2&i2=1&intId=60>
- D'Amato G, Cecchi L, Bonini S *et al.* Allergenic pollen and pollen allergy in Europe. *Allergy* 2007; 62:976–90.
- Bell ML, McDermott A, Zeger SL *et al.* Ozone and short-term mortality in 95 US urbane communities, 1987–2000. *JAMA* 2004; 292:2372–8.
- Dominici F, Peng RD, Bell ML *et al.* Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006; 295:1127–34.
- Samet JM, Dominici F, Currier FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *N Engl J Med* 2000; 343:1742–9.
- Miller KA, Siscovick DS, Sheppard L *et al.* Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; 356:447–58.
- Dockery DW, Stone PH. Cardiovascular risks from fine particulate air pollution. *N Engl J Med* 2007; 356:511–3.
- D'Amato G, Holgate ST. The impact of air pollution on respiratory health. European Respiratory Monograph no. 21, Sheffield, UK, 2002.
- D'Amato G, Liccardi G, D'Amato M, Holgate S. Environmental risk factors and allergic bronchial asthma. *Clin Exp Allergy* 2005; 35:1113–24.
- Annesi-Maesano I, Forastiere F, Kunzli N, Brunekreef B. Environment and Health Committee of the European Respiratory Society. Particulate matter, science and EU policy. *Eur Respir J* 2007; 29:428–31.
- Salvi S, Blomberg A, Rudell B *et al.* Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999; 159:702–9.
- Nordenhall C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur Respir J* 2001; 17:909–15.
- McCreanor J, Cullinan P, Nieuwenhuijsen MJ *et al.* Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007; 357:2348–58.
- Kelly FJ. Dietary antioxidants and environmental stress. *Proc Nutr Soc* 2004; 63:579–85.
- Pourazar J, Mudway IS, Samet JM *et al.* Diesel exhaust activates redox-sensitive transcription factors and kinases in human airways. *Am J Physiol Lung Cell Mol Physiol* 2005; 289:L724–30.
- Xia T, Korge P, Weiss JN *et al.* Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. *Environ Health Perspect* 2004; 112:1347–58.

- 23 Gauderman WJ, Vora H, McConnell R *et al.* Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; **369**:571–7.
- 24 Gauderman W, Avol E, Gilliland F *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; **351**:1057–67.
- 25 Gauderman W, Avol E, Lurmann F *et al.* Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology* 2005; **16**:737–43.
- 26 Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. *Clin Exp Allergy* 2006; **36**:1138–46.
- 27 Tager IB, Balmes J, Lurmann F, Ngo L, Alcorn S, Kunzli N. Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* 2005; **16**:751–9.
- 28 Peel JL, Tolbert PE, Klein M *et al.* Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005; **16**:164–74.
- 29 Annesi-Maesano I, Moreau D, Caillaud D *et al.* Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. *Respir Med* 2007; **101**:1721–9.
- 30 Sun HL, Chou MC, Lue KH. The relationship of air pollution to ED visits for asthma differ between children and adults. *Am J Emerg Med* 2006; **24**:709–13.
- 31 Balmes JR. The role of ozone exposure in the epidemiology of asthma. *Environ Health Perspect* 1993; **101** (Suppl. 4): 219–24.
- 32 Peden DB, Setzer RW, Devlin RB. Ozone exposure has both a priming effect on allergen induced responses as well as an intrinsic inflammatory action in the nasal airways of perennial allergic asthmatics. *Am J Respir Crit Care Med* 1995; **151**:1336–45.
- 33 Kreit JW, Gross KB, Moore TB *et al.* Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. *J Appl Physiol* 1989; **66**:217–22.
- 34 Scannell C, Chen LL, Aris RM *et al.* Greater ozone-induced inflammatory responses in subjects with asthma. *Am J Respir Crit Care Med* 1996; **154**:24–9.
- 35 Sandstrom T, Helleday R, Blomberg A. Air pollution and asthma: experimental studies. In: D'Amato G, Holgate ST, eds. *The impact of air pollution on respiratory health. European respiratory Monograph n.21*, Sheffield, UK: European Respiratory Society Journals Ltd., 2002; 52–65.
- 36 Bayram H, Sapsford RJ, Abdelaziz MM, Khair OA. Effect of ozone and nitrogen dioxide on the release of proinflammatory mediators from bronchial epithelial cells on nonatopic, non-asthmatic subjects and atopic asthmatic patients in vitro. *J Allergy Clin Immunol* 2001; **107**:287–94.
- 37 Jorres R, Nowak D, Magnussen H. Effect of ozone exposure on allergen responsiveness in subjects with asthma or rhinitis. *Am J Respir Crit Care Med* 1996; **153**:56–64.
- 38 Molino NA, Wright SC, Katz I *et al.* Effect of low concentration of ozone on inhaled allergen responses in asthmatic subjects. *Lancet* 1991; **338**:199–203.
- 39 McConnell R, Berhane K, Gilliland F *et al.* Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002; **359**:386–91.
- 40 D'Amato G. Urban air pollution and plant-derived respiratory allergy. *Clin Exp Allergy* 2000; **30**:628–36.
- 41 Ishizaki T, Koizumi K, Ikemori R, Ishiyama Y, Kushibiki E. Studies of prevalence of Japanese cedar pollinosis among residents in a densely cultivated area. *Ann Allergy* 1987; **58**:265–70.
- 42 Braun-Fahrlander C, Gassner M, Grize L *et al.* Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community: SCARPOL team: Swiss study on childhood allergy and respiratory symptoms with respect to air pollution. *Clin Exp Allergy* 1999; **29**:28–34.
- 43 von Ehrenstein OS, von Mutius E, Illi S, Baumann L, Böhm O, von Kries R. Reduced risk of hay fever and asthma among children and farmers. *Clin Exp Allergy* 2000; **30**:187–93.
- 44 Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000; **30**:194–200.
- 45 Knox RB, Suphioglu C, Taylor P *et al.* Major grass pollen allergen Lol p1 binds to diesel exhaust particles: implications of asthma and air pollution. *Clin Exp Allergy* 1997; **27**:246–51.
- 46 D'Amato G, Liccardi G, D'Amato M, Cazzola M. The role of outdoor air pollution, and climatic changes on the rising trends of respiratory allergy. *Respir Med* 2001; **95**:606–11.
- 47 Namork E, Johansen BV, Løvik M. Detection of allergens adsorbed to ambient air particles collected in four European cities. *Toxicol Lett* 2006; **165**:71–8.
- 48 Motta AC, Marliere M, Peltre G, Sterenberg PA, Lacroix G. Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen. *Int Arch Allergy Immunol* 2006; **139**:294–8.
- 49 Carey MJ, Cordon I. Asthma and climatic conditions: experience from Bermuda, an isolated island community. *BMJ* 1986; **293**:843–4.
- 50 Rossi OV, Kinnula VL, Tienari J, Huhti E. Association of severe asthma attacks with weather, pollen, and air pollution. *Thorax* 1993; **48**:244–8.
- 51 Kljakovic M, Salmond C. A model of the relationship between consultation behaviour for asthma in a general practice and the weather. *Climate Res* 1998; **10**:109–13.
- 52 Suzuki S, Kamakura T, Takadoro K, Takeuchi F, Yukiya Y, Miyamoto T. Correlation between the atmospheric conditions and the asthmatic symptom. *Int J Biometeorol* 1988; **32**:129–33.
- 53 Jamason PF, Kalkstein LS, Gergen PJ. A synoptic evaluation of asthma hospital admissions in New York city. *Am J Respir Crit Care Med* 1997; **156**:1781–8.
- 54 Chavarria JF. Asthma admissions and weather conditions in Costa Rica. *Arch Dis Child* 2001; **84**:514–5.
- 55 Khot A, Burn R, Evans N, Lenney W, Storr J. Biometeorological triggers in childhood asthma. *Clin Allergy* 1988; **18**:351–8.
- 56 Ehara A, Takasaki H, Takeda Y *et al.* Are high barometric pressure, low humidity and diurnal change of temperature related to the onset of asthmatic symptoms? *Pediatr Int* 2000; **42**:272–4.
- 57 Hashimoto M, Fukuda T, Shimizu T *et al.* Influence of climate factors on emergency visits for childhood asthma attack. *Pediatr Int* 2004; **46**:48–52.
- 58 Epton MJ, Martin IR, Graham P. Climate and aeroallergen levels in asthma: a 12 month prospective study. *Thorax* 1997; **52**:528–34.

- 59 Jones AM, Harrison RM. The effects of meteorological factors on atmospheric bioaerosol concentrations – a review. *Sci Total Environ* 2004; **326**:151–80.
- 60 Burge HA. An update on pollen and fungal spore aerobiology. *J Allergy Clin Immunol* 2002; **110**:544–52.
- 61 Davidson AC, Emberlin J, Cook AD, Venables KM. A major outbreak of asthma associated with a thunderstorm: experience of accident and emergency departments and patients characteristics. Thames Regions Accident and Emergency Trainer Association. *BMJ* 1996; **312**:601–4.
- 62 Bellomo R, Gigliotti P, Treloar A, Holmes P, Suphioglu C, Singh MB. Two consecutive thunderstorm associated epidemic of asthma in Melbourne. *Med J Aust* 1992; **156**:834–7.
- 63 Girgis ST, Marks GB, Downs SH, Kolbe A, Car GN, Paton R. Thunderstorm-associated asthma in an inland town in south-eastern Australia. Who is at risk? *Eur Resp J* 2000; **16**:3–8.
- 64 D'Amato G, Liccardi G, Viegi G, Baldacci S. Thunderstorm-associated asthma in pollinosis patients. *BMJ* 2005, website January 2005 <http://bmj.bmjournals.com/cgi/eletters/309/6947/131/c>.
- 65 D'Amato G, Liccardi G, Frenguelli G. Thunderstorm-asthma and pollen allergy. *Allergy* 2007; **62**:11–6.
- 66 Papadopoulou NG, Xepapadaki P, Mallia P *et al*. Mechanisms of virus-induced asthma exacerbations. A GA2LEN interairways document: state-of-the-art. *Allergy* 2007; **62**:457–70.
- 67 Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. *J Allergy Clin Immunol* 2006; **117**:557–62.
- 68 Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. *Acta Otolaryngol* 2002; **122**:183–91.
- 69 Bernard SM, Samet JM, Grambsch A, Ebi KL, Romieu I. The potential impacts of climate variability and change on air pollution-related health effects in the United States. *Environ Health Perspect* 2001; **109** (Suppl. 2):199–209.
- 70 Confalonieri U, Menne B, Akhtar R *et al*. Human health Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, eds. *Climate change 2007: impacts, adaptation and vulnerability. Contribution of Working Group II to the fourth assessment report of the intergovernmental panel on climate change*. Cambridge, UK: Cambridge University Press, 2007; 391–431.
- 71 USEPA. 1994. Motor Vehicles and the 1990 Clean Air Act. Fact Sheet OMS-11. EPA 400-F-92-013 (<http://www.epa.gov/otaq/11-vehs.htm>).
- 72 USEPA. *Air Quality Criteria for Ozone and Related Photochemical Oxidants*. (EPA/600/P-93/004a-cF). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, 1996.
- 73 Chen K, Ho Y, Lai C, Tsai Y, Chen S. Trends in concentration of ground-level ozone and meteorological conditions during high ozone episodes in the Kao-Ping Airshed, Taiwan. *J Air Waste Manage* 2004; **54**:36–48.
- 74 Prather M, Gauss M, Bernsten T *et al*. Fresh air in the 21st century? *Geophys Res Lett* 2003; **30**:1100.
- 75 Department of Health. *Department of Health and Expert Group on Climate Change and Health in the UK: Health effects of climate change in the UK*. London: Department of Health, 2001; 199–214.
- 76 Mickley LJ, Jacob DJ, Field BD. Effects of future climate change on regional air pollution episodes in the United States. *Geophys Res Lett* 2004; **31**:L24103.
- 77 Hoyt KS, Gerhart AE. The San Diego county wildfires: perspectives of health care. *Disaster Manage Response* 2004; **2**:46–52.
- 78 Moore D, Copes R, Fisk R, Joy R, Chan K, Brauer M. Population health effects of air quality changes due to forest fires in British Columbia in 2003: estimates from physician-visit billing data. *Can J Public Health* 2006; **97**:105–8.
- 79 European Environment Agency (EEA). EN09 emissions (CO₂, SO₂ and NO_x) from public electricity and heat production – explanatory indicators. April 2007, http://themes.eea.europa.eu/Sectors_and_activities/energy/indicators/EN09%2C2007.04/EN09_EU25_Policy_effectiveness_2006.pdf.
- 80 Energy Information Administration (EIA). Annual Energy Outlook 2007 with projections to 2030. Emissions from Energy Use Report #:DOE/EIA-0383, February 2007.
- 81 Gangoiiti G, Millan MM, Salvador R, Mantilla E. Long-range transport and re-circulation of pollutants in the western Mediterranean during the project Regional Cycles of Air Pollution in the west-central Mediterranean area. *Atmos Environ* 2001; **35**:6267–76.
- 82 Buchanan CM, Ryall IJ, Derwent RG *et al*. The origin of high particulate concentrations over the United Kingdom, March 2000. *Atmos Environ* 2002; **36**:1363–78.
- 83 Menzel A, Fabian P. Growing season extended in Europe. *Nature* 1999; **397**:659.
- 84 Ahas R, Aasa A, Menzel A, Fedotovac G, Scheifinger H. Changes in European spring phenology. *Int J Climatol* 2002; **22**:1727–38.
- 85 Emberlin J, Detandt M, Gehrig R, Jaeger S, Nolard N, Rantio-Lehtimäki A. Responses in the start of Betula (birch) pollen seasons to recent changes in spring temperatures across Europe. *Int J Biometeorol* 2002; **46**:159–70.
- 86 Van Vliet AJH, Overeem A, De Groot RS, Jacobs AF, Spiekma FTM. The influence of temperature and climate change on the timing of pollen release in the Netherlands. *Int J Climatol* 2002; **22**:1757–67.
- 87 Stach A, García-Mozo H, Prieto-Baena JC *et al*. Prevalence of artemisia species pollinosis in Western Poland: impact of climate change on aerobiological trends, 1995–2004. *J Investig Allergol Clin Immunol* 2007; **17**:39–47.
- 88 Frenguelli G. interactions between climate changes and allergenic plants. *Monaldi Arch Chest Dis* 2002; **57**:141–3.
- 89 Emberlin J, Mullins J, Corden J *et al*. Regional variations in grass pollen seasons in the UK, long-term trends and forecast models. *Clin Exp Allergy* 1999; **29**:347–56.
- 90 Burr ML. Grass pollen: trends and predictions. *Clin Exp Allergy* 1999; **29**:735–8.
- 91 Teranishi H, Katoh T, Kenda K, Hayashi S. Global warming and the earlier start of the Japanese-cedar (*Cryptomeria japonica*) pollen season in Toyama, Japan. *Aerobiologia* 2006; **22**:90–4.
- 92 Beggs PJ. Impacts of climate change on aeroallergens: past and future. *Clin Exp Allergy* 2004; **34**:1507–13.
- 93 Ahlholm JU, Helander ML, Savolainen J. Genetic and environmental factors affecting the allergenicity of birch (*Betula pubescens* ssp. *czerepanovii* [Orl.] Hämet-Ahti) pollen. *Clin Exp Allergy* 1998; **28**:1384–8.

- 94 Hjelmroos M, Schumacher MJ, Van Hage-Hamsten M. Heterogeneity of pollen proteins within individual *Betula pendula* trees. *Int Arch Allergy Immunol* 1995; **108**:368–76.
- 95 Wayne P, Foster S, Connolly J, Bazzaz F, Epstein P. Production of allergenic pollen by ragweed (*Ambrosia artemisiifolia* L.) is increased in CO₂-enriched atmospheres. *Ann Allergy Asthma Immunol* 2002; **88**:279–82.
- 96 Ziska LH, Caulfield FA. Rising CO₂ and pollen production of common ragweed (*Ambrosia artemisiifolia*), a known allergy-inducing species: implications for public health. *Aust J Plant Physiol* 2000; **27**:893–8.
- 97 Rogers CA, Wayne PM, Macklin EA *et al.* Interaction of the onset of spring and elevated atmospheric CO₂ on ragweed (*Ambrosia artemisiifolia* L.) pollen production. *Environ Health Perspect* 2006; **114**:865–9.
- 98 Wan SQ, Yuan T, Bowdish S, Wallace L, Russell SD, Luo YQ. Response of an allergenic species *Ambrosia psilostachya* (Asteraceae), to experimental warming and clipping: implications for public health. *Am J Bot* 2002; **89**:1843–6.
- 99 Ziska LH, Gebhard DE, Frenz DA, Faulkner S, Singer BD, Straka JG. Cities as harbingers of climate change: common ragweed, urbanization, and public health. *J Allergy Clin Immunol* 2003; **111**:290–5.
- 100 Singer BD, Ziska LH, Frenz DA, Gebhard DE, Straka JG. Increasing Amb a 1 content in common ragweed (*Ambrosia artemisiifolia*) pollen as a function of rising atmospheric CO₂ concentration. *Funct Plant Biol* 2005; **32**:667–70.
- 101 Lee YS, Dickinson DB, Schlager D, Velu JG. Antigen E content of pollen from individual plants of short ragweed (*Ambrosia artemisiifolia*). *J Allergy Clin Immunol* 1979; **63**:336–9.
- 102 Cecchi L, Morabito M, Domeneghetti MP, Crisci A, Onorari M, Orlandini S. Long-distance transport of ragweed pollen as a potential cause of allergy in central Italy. *Ann Allergy Asthma Immunol* 2006; **96**:86–91.
- 103 Cecchi L, Torrigiani Malaspina T, Albertini R *et al.* The contribution of long-distance transport to the presence of *Ambrosia* pollen in central northern Italy. *Aerobiologia* 2007; **23**:145–51.
- 104 Ridolo E, Albertini R, Giordano D, Soliani L, Usberti I, Dall'Aglio PP. Airborne pollen concentrations and the incidence of allergic asthma and rhinoconjunctivitis in northern Italy from 1992 to 2003. *Int Arch Allergy Immunol* 2006; **142**:151–7.
- 105 Olesen JE, Bindi M. Consequences of climate change for European agricultural productivity, land use and policy. *Eur J Agron* 2002; **16**:239–62.
- 106 Kiss L, Béres I. Anthropogenic factors behind the recent population expansion of common ragweed (*Ambrosia artemisiifolia* L.) in Eastern Europe: is there a correlation with political transitions? *J Biogeogr* 2007; **33**:2156–7.
- 107 Beggs PJ, Bambrick HJ. Is the global rise of asthma an early impact of anthropogenic climate change? *Environ Health Perspect* 2005; **113**:915–9.
- 108 Liu AH, Leung DY. Renaissance of the hygiene hypothesis. *J Allergy Clin Immunol* 2006; **117**:1063–6.
- 109 Schaub B, Lauener R, von Mutius E. The many faces of hygiene hypothesis. *J Allergy Clin Immunol* 2006; **117**:969–77.
- 110 Bloomfield SF, Stanwell-Smith R, Crevell RW, Pickup J. Too clean, or not too clean: the Hygiene Hypothesis and home hygiene. *Clin Exp Allergy* 2006; **36**:402–25.
- 111 Jarvis D, Luczynska C, Chinn S, Burney P. The association of hepatitis A and *Helicobacter pylori* with sensitization to common allergens, asthma and hay fever in a population of young British adults. *Allergy* 2004; **59**:1063–7.
- 112 Matricardi PM, Rosmini F, Riondino S *et al.* Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; **320**:412–7.
- 113 Pelosi U, Porcedda G, Tiddia F *et al.* The inverse association of salmonellosis in infancy with allergic rhinoconjunctivitis and asthma at school-age: a longitudinal study. *Allergy* 2005; **60**:626–30.
- 114 Delfino RJ. Who are the children with asthma most susceptible to air pollution? *Am J Respir Crit Care Med* 2006; **173**:1054–5.
- 115 McCunney RJ. Asthma, genes, and air pollution. *J Occup Environ Med* 2005; **47**:1285–91.
- 116 Englert N. Fine particles and human health – a review of epidemiological studies. *Toxicol Lett* 2004; **149**:235–42.
- 117 Schwartz J. Air pollution and children's health. *Pediatrics* 2004; **113** (Suppl. 4):1037–43.
- 118 Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. *Thorax* 2004; **59**:652–6.
- 119 Fogarty A, Lewis SA, Scrivener SL *et al.* Oral magnesium and vitamin C supplements in asthma: a parallel group randomised placebo-controlled trial. *Clin Exp Allergy* 2003; **33**:1355–9.
- 120 Allam MF, Lucane RA. Selenium supplementation for asthma. *Cochrane Database Syst Rev* 2004; **(2)**:003538.
- 121 D'Amato G. Air pollution, reactive oxygen species, and allergic bronchial asthma: the therapeutic role of antioxidants. In: Hughes DA, Darlington LG, Bendich A, eds. *Diet and Human Immune Function*. Humana Press, Totowa, NJ, USA, 2004; 397–409.