

Invited Review to European Respiratory Journal

Climate change, extreme weather events, air pollution and respiratory health in Europe

De Sario M¹, Katsouyanni K², Michelozzi P¹

¹ Department of Epidemiology, Lazio Regional Health Service, Roma, Italy

² National and Kapodistrian University of Athens, Athens, Greece

Corresponding Author

Manuela De Sario

Department of Epidemiology, Lazio Regional Health Service, Italy

Via di Santa Costanza, 53

00198 Roma, Italy

e-mail: m.desario@deplazio.it

Phone: +39-06-83060457

Fax: +39-06-83060374

Abstract

Due to climate change, air pollution patterns are changing in several urbanized areas of the world, with a significant effect on respiratory health both independently and synergistically with weather conditions; climate scenarios show Europe as one of the most vulnerable regions. European studies on heat wave episodes have consistently shown a synergistic effect of air pollution and high temperatures, while the potential weather-air pollution interaction during wildfires and dust storms is unknown. Allergens patterns are also changing in response to climate change and air pollution can modify the allergenic potential of pollens especially in presence of specific weather conditions. The underlying mechanisms of all these interactions are not well known; the health consequences vary from decreases in lung function to allergic diseases, new onset of diseases, exacerbation of chronic respiratory diseases, and premature death. These multidimensional climate-pollution-allergen effects need to be taken into account in estimating both climate and air pollution-related respiratory effects in order to set up adequate policy and public health actions to face both the current and future climate and pollution challenges.

Keywords: air pollution; allergens; climate change; extreme weather events; respiratory diseases; susceptibility

Introduction

The continuous increment in anthropogenic emissions of carbon dioxide (CO₂) and other greenhouse gases following the Industrial Revolution is dramatically changing the climate overall and at regional level. As other parts of the world, Europe has experienced a progressive warming (+0.90°C for 1901 to 2005) and an increase in mean precipitation except in some regions (i.e. the Mediterranean Region) that are becoming arid [1, 2]. Climate scenarios for the next century predict that the warming will be associated with more frequent, more intense and longer lasting heat waves especially in Southern and Eastern Europe but also in areas not currently susceptible to such events [2, 3]. This will be paralleled by an increase in the intensity of short duration precipitation events (1 to 2 days) in regions such as the Mediterranean where also a decrease in mean precipitation is expected [2]. The higher intensity of rainfall events will increase the likelihood of floods, especially flash floods, throughout Europe, while the occurrence of heatwaves and droughts will increase the risk of wildfires and desertification notably around the Mediterranean basin [2].

In urban areas, climate change is likely to influence outdoor air pollution levels because the generation and dispersion of air pollutants, such as ozone and particulate, depend in part by local patterns of temperature, wind, solar radiation and precipitation [4]. In some regions, air quality is projected to further worsen due to the increased frequency of wildfires that cause the release into the atmosphere of gaseous and particulate pollutants. In addition, changes in wind patterns and desertification will modify the long-range transport of pollutants emitted by human activities and biomass burning [4].

Changing patterns of disease is occurring in response to changing environmental conditions. As widely recognized, air pollution has a significant impact on human health, with a great burden on respiratory diseases, particularly on asthma, rhinosinusitis, chronic obstructive pulmonary disease (COPD) and respiratory tract infections [5]. Changes in climate are expected to additionally aggravate the effect of air pollution on these diseases. Prompted by these scenarios, the American Thoracic Society and the European Respiratory Society have recently expressed their concern on the threat posed by air pollution and climate change on respiratory disease [6, 7]. Current and future impacts on respiratory mortality and morbidity deriving from

changes in climate as well as from trends in air pollutants are therefore a priority for the researchers, respiratory clinicians and policy-makers agenda.

This review summarizes the scientific evidence on the effects of climate-related hazards on respiratory health from epidemiological studies. Specifically, we considered those climate events which may be influenced most by climate change and for which climate conditions are interlinked with air quality: temperature extremes, wildfires and dust storms. The conceptual framework for these interactions is summarized in Figure 1. Pathogenetic mechanisms, vulnerable population subgroups and policy implications are discussed and research needs are identified.

Climate change and air quality

Climate change and air pollution are intrinsically connected since greenhouse gases and air pollutants originate from the same source, fossil fuel combustion [8-10]. Combustion processes in fact emit both greenhouse gases, like carbon dioxide, methane (CH₄) and nitrous oxide (N₂O), and air pollutants like particulate matter (PM), sulphur dioxide (SO₂), nitrogen dioxide (NO₂) and carbon monoxide (CO).

From both a global and a regional level, now and in the future climate change and air pollution trends counterbalance in determining air quality: on the one hand, a reduction in anthropogenic emissions resulting from the implementation of the already adopted emission control legislation in each country and energetic sector improvements, on the other hand climate change effects in most cases leading to an increase in pollution levels [11].

The correlation between climate and air quality is noteworthy for ozone. Ozone levels are directly driven by weather since ozone-generating photochemical reactions of air pollutants (nitrogen oxides, NO_x; methane; volatile organic compounds, VOCs) need high temperatures and bright sunshine, conditions typical of summer months [11]. High temperatures are often associated with dry weather conditions which significantly contribute to high ozone levels during heat waves through a drought stress on vegetation that inhibits stomatal uptake of ozone [8, 12]. Anthropogenic emissions of ozone precursors will decline in industrialized countries but not in the emerging economies; hemispheric background ozone concentrations will increase due to higher frequency in forest fires [11]. Considering climate change scenarios, a large climate

change-related ozone increase is expected in Southern European regions that will overcome the beneficial reduction in ozone precursor anthropogenic emissions in these countries [11].

Climatic factors affect particulate matter concentrations to a different extent depending on the PM chemical components [8]. On the one hand high temperature results in an increase in sulfate aerosols due to faster SO₂ oxidation, and on the other, it brings a reduction in nitrate PM concentrations due to increased gas phase transition [8]. However, under climate change the nitrate burden is predicted to increase as well as all the other aerosol species except sulphates [13]. Over Europe, the predicted increase in overall aerosols concentrations will be by 20–40 µg/m³, relative to the present-day values [13]. Changes will be driven by precipitation changes conditions since wet deposition represents the primary PM sink but also by increments in water vapor that increase oxidation of SO₂ and sulfate concentrations. Another important factor is represented by air stagnation conditions that will increase PM concentrations in polluted regions [4, 8]. Climate change-related increase in wildfires will also influence particulates levels [14, 15]; an increase in fire risk in Mediterranean countries is expected especially in areas with high forest cover [4, 16]. The 2003 heat wave in Europe is emblematic since it was associated also with both record wildfires and high PM levels [8]. During wildfires the main concern is on fine particles (particles with diameter lower than 2.5 µm, PM_{2.5}) since they have a longer lifetime (on the order of days) and may be carried for long distances from their source regions [17]. Future PM concentrations are also driven by long-range transport of dust aerosols. The long-range transport of pollutants emitted by human activities, burning biomass and dust will also be influenced by future climate changes due to changes in wind patterns and desertification [4].

Another important linkage between climate and air quality is that primary products of combustion processes (i.e. carbon monoxide, non-methane volatile organic compounds, nitrogen oxides, sulphur dioxide, black carbon, organic carbon aerosol) and some secondary pollutants (i.e. ozone) have the potential to increase global warming directly or indirectly [18]. Carbon monoxide, non-methane VOCs and nitrogen oxides cause a reduction in the oxidant power of the atmosphere increasing the lifetime of methane, one of the most important warming agents and a precursor to ozone [18]. Nitrate particles as well as organic carbon aerosol have instead a

cooling effect on the climate. Sulphur dioxide partly converts to sulphate particles which also have a cooling potential and partly reacts with black carbon which has a strong warming effect [18]. Also wildfire may directly contribute to global warming since they emit large quantities of greenhouse gases (i.e. CO, carbon dioxide, methane) [19].

Respiratory health effects

Since the 1990s, an extensive European collaboration has been set up through the EU-funded research programmes in the field of air pollution (APHEA, APHEIS, AIRNET, APHEKOM) and climate change (cCASHh, PHEWE, EuroHEAT, CIRCE) [20]. These studies have substantially contributed to the current epidemiological knowledge on the short-term health effects of air pollution and high temperatures/heat waves in Europe and to set up WHO guidelines [21] and EU air pollution standards. Several of these projects also specifically investigated the synergy between air pollution and high temperature exposure and heat wave events (PHEWE, EuroHEAT, CIRCE) [22]. The ongoing EU project PHASE (Public Health Adaptation Strategies to Extreme weather events) will provide further insights into the synergy between air pollution and extreme weather events (e.g. heat waves, cold spells) and an innovative aspect will be to investigate also their environmental consequences (floods, wildfires) that are projected to increase with predicted climate change.

Air pollution effects.

Respiratory diseases are on the rise worldwide, especially allergic diseases such as asthma and rhinitis [23, 24]. This trend has been documented both in industrialized and developing countries but was greater in regions where prevalence was previously low [23, 24]. However, geographical differences have emerged from studies comparing areas at different urbanization level or Eastern and Western European countries, providing evidence of higher frequency of respiratory allergic diseases in westernised and more urbanised areas [25, 26]. The causes of such large heterogeneity both on the temporal and geographical scales should be searched in environmental exposures since genetic factors cannot change so rapidly to such an extent; outdoor air pollution is one possible explanation of the observed trends [27]. Primary (i.e. oxides of nitrogen, VOC) and secondary pollutants (i.e. ozone) have been associated with a wide range of respiratory health effects, including exacerbations of

diseases in subjects already affected by chronic respiratory illnesses such as asthma and COPD, that account for repeated hospitalizations and emergency department visits for the underlying disease, declines in lung function, asthma attacks, emergency room visits, hospital admissions, premature mortality and, possibly, the occurrence of new respiratory problems, i.e. new-onset asthma [5, 6, 21, 28, 29]. Despite the decreasing current trends in anthropogenic air pollution levels in the US and Europe (although not uniformly) [30], there is strong evidence that air pollutants have an effect on respiratory health even at the low levels actually measured [28]. In Europe since the '90s, the APHEA multicentre project identified and quantified the short-term health effects of these air pollution levels (see Table in online depository). Immediate effects (lag 0-1) associated with 10 $\mu\text{g}/\text{m}^3$ increase in pollutant were 0.4% for NO_2 [31], 0.6% for PM_{10} [32], 0.8% for black smoke and 1.1% for ozone [33]. The delayed effects are even greater, 4.2% for PM_{10} (lag 0-40) [34], and 3.4% for ozone (lag 0-20) [35]; these pollutants had the most prolonged lagged effects on respiratory mortality compared to total or cardiovascular mortality [34, 35]. Air pollutants have also an effect on hospital admissions for specific causes i.e. PM_{10} and sulphur dioxide is associated with 0.5-1.5% increase in admissions for asthma and COPD in specific age groups [36-38].

Outdoor temperature effects.

European projects have documented that respiratory health is largely affected not only by air pollution but also by weather conditions, especially in 75+ yrs population (Table 1). During summer, each degree increase in maximum apparent temperature (a combined indicator of temperature and humidity) above a city specific threshold level (ranging from 23 to 29°C) is related to circa 7% increase in daily respiratory deaths [39]. A smaller but still significant effect has been observed on respiratory hospital admissions, around 3-5% [40]. The effect of extreme events, i.e. heat waves, is much larger accounting for an increase in respiratory mortality during each heat-wave day ranging from 12.1% to 61.3% [41]. Effects of high temperature and heat waves are greatest in Mediterranean than North-Continental European cities [39-41]. Also cold temperatures are of concern for respiratory health, with a 3-4% increase in daily mortality and hospitalizations for respiratory causes in 75+ population for each degree Celsius decrease in minimum temperature or minimum apparent temperature. In this case, northern populations seem to be at greater risk than southern ones [42, 43]. Results from the available studies suggest an effect of heat and heat waves and

cold temperature on mortality, hospital admissions, admissions in geriatric units and emergency visits for specific respiratory diseases such as asthma and COPD and pneumonia although results are limited and somewhat contrasting and more evidence is needed [44].

Other weather conditions, i.e. specific variables such as humidity and rainfall, but also combinations of several meteorological variables (i.e. temperature, humidity, visibility, cloud cover, air pressure, wind speed) defined as "air masses" have been associated to increases in mortality and morbidity but specific evidence for respiratory causes is scanty and there is no clear evidence that these variables may have an independent effect apart from temperature [45-51].

Synergy (effect modification) of air pollution and temperature effects

Several European time-series and case-crossover studies have provided indirect evidence (i.e. that effects are stronger in the warm season or in warmer cities) suggestive of interactions between air pollution and heat, although other explanations are consistent with these results [52-55]. The multicentre APHEA study, found ozone effects on respiratory mortality only during summer [33], while single-city studies provided contrasting results, with a significant effect on respiratory deaths all year round [56], and a positive association on physician consultations for asthma and on pediatric asthma hospital admissions only in the summer months [57, 58]. A study in Cyprus showed a ozone effect on respiratory admissions stronger in warm season [59].

The APHEA project provided also evidence of seasonal differences in the effect of pollutants other than ozone, i.e. black smoke and SO₂, whose effects on respiratory mortality were also found higher in summer [52]. Other studies found similar [54, 60], or contrasting findings [56, 58, 61]. The APHEA study provided evidence of effect modification not only by season but also according to typical temperatures for the area; the greatest PM₁₀ effects were in the warmest cities but no result for respiratory causes was available [62]. On the other side of the relationship, a study from Greece found a greater effect of heat waves in Athens were pollution levels were higher than in all other urban areas [63].

Several studies provided consistent evidence of a synergy between the two exposures [63-76], with only one study showed no evidence of interaction [77]. In all these studies the potential interaction between air pollution health effects and high/low temperature was tested through interaction terms or by means of a stratified analysis in time series and case-crossover analyses. Among studies carried out in a European country (Table 2), three studies [54, 75, 78] analysed the synergistic effect on mortality for respiratory causes. In the study in UK, the ozone effect on respiratory mortality during hot days corresponded to a rate ratio of 1.009 while the pollutant had no effect on ordinary days (rate ratio=1.000), but the ozone-heat interaction was significant only in London and ozone-heat interactions were greatest in those aged <75 years [75]. In Italy, an effect of PM10 on respiratory mortality was found only for temperatures above the 50th percentile compared to no effect in days with temperature below the 50th percentile [54]. The study of Carder et al. [78] carried out in Scotland found instead a positive interaction between cold temperatures and black smoke concentrations on respiratory mortality. Other European studies analysed total mortality; they were focused on specific heat wave episodes [63-67] or on both warm and cold periods [68] and provided evidence of significant interaction between high temperature and pollutants, mainly ozone. Two multicentre studies suggest that the synergistic effect may vary among cities according to local climate characteristics, activity patterns and physical adaptation [67, 75].

The synergy between temperature and air pollution has been also evaluated in multicentre European studies analysing the other side of effect modification: air pollution levels modifying the health effect of temperature or heat waves (Table 3) [22, 79]. For ozone, there is consistent evidence of interaction with heat/heat wave effects on mortality for natural causes in the elderly but no evidence of interaction on respiratory mortality [22, 79]. Concerning PM10, the study before year 2000 did not find any interaction with temperature while the more recent time series studies showed a significant effect modification. In particular, PM10 significantly modified heat wave effect on mortality for respiratory causes in Mediterranean cities (65-74 yrs) [79] and there is a suggestion of interaction with effect of high temperature on this group of diseases. For PM10 there is also evidence of effect modification of temperature effect during cold season, with lower cold effect on respiratory mortality in high pollution days [22].

Overall, results about temperature-air pollution interactions suggest that this topic cannot be disregarded when studying temperature or air pollution effects regarding respiratory causes, since the true magnitude of the associations may be underestimated. Results differ by pollutant considered and study area, suggesting that the underlying mechanisms are driven by local conditions. Moreover, the evaluation of effect modification presents specific methodological challenges. In many studies stratification can provide quantitative estimates, but results are dependent on the selection of cut-offs for strata. On the other hand, the use of more flexible models, i.e. joint pollutant-temperature response surface on health outcomes, has the disadvantage to not provide parametric estimates [73].

Other weather conditions such as humidity have been suggested to interact with air pollutants effects. Low absolute humidity may increase the effect of total suspended particles (TSP) on hospitalizations for COPD [80]. Humidity was also found to be a significant effect modifiers of the effect of air pollutants on mortality, as found in the 29 EU cities included in the APHEA2 project [62]; the observed effect of PM10 increased as humidity levels decreased. Another remarkable type of interaction is that from air masses and air pollutants. In a study in Birmingham, UK, two winter air masses associated with increased admission rates for respiratory causes (continental anticyclonic gloom and continental anticyclonic fine and cold) were also favourably associated with high PM10 levels [81].

Air pollution and wildfires effects.

Wildfire smoke is a complex mixture of particles, liquids and gaseous compounds. The effect of fires is usually measured respect to fine PM (PM_{2.5}) levels since it predominates in the smoke [82-84], and is thought to be responsible of greater part of the observed health effects. Fine particles are created directly during the combustion process and also formed later from emitted gases through condensation and atmospheric chemical reactions [17]. During wildfires, levels of PM are usually well above the background pollution level for the area usually beyond air quality standard (24-h mean PM₁₀: 50 µg/m³; 24-h mean PM_{2.5}: 25 µg/m³), over 500 µg/m³ in some cases [17, 82-84]. The extreme event is identified according to a certain threshold, i.e. the 99th percentile of particulate distribution. This allows to distinguish extreme events from situations in which background pollution sources predominate.

Since wildfires are usually episodes of short duration, the length of the exposure may be too short to detect the health effects as well as to evaluate their impact on air quality [82-84]. As in the case of urban air pollution, during wildfire episodes the respiratory system is particularly affected: increases in mortality, hospitalizations, emergency visits for all respiratory causes and for specific diseases (mainly asthma, COPD, lower and upper respiratory diseases), asthma and COPD exacerbations, respiratory symptoms and decreases in lung function both in healthy subjects and in asthmatic and COPD patients [82-84]. Most evidence on short-term effects of wildfires comes from the US, Asia and Australia while only few studies have been carried out in the European context [85-88], despite wildfires are common in the Mediterranean forests of Greece, Spain, Italy and Portugal [16]. In the study carried out in Athens, Greece, the occurrence of a large forest fire (one which burnt more than 30 000 000 m²), lead to significant short-term effect on mortality for respiratory causes in the elderly [85]; this effect could be explained only in part by an increase in ambient particle concentrations. A survey carried out in Barcelona, Spain during 2003 wildfires on healthy 6- to 19-year-old documented increased respiratory and eye symptoms with increasing frequency of wildfire smoke exposure; associations were stronger in subjects with lowest lung function [87]. Increases in hospital attendances for respiratory conditions and asthma have been documented during the fires which surrounded Vilnius in Lithuania in 2002 [88].

Studies on wildfire health effects commonly adjust for meteorological variables. Since during wildfire events ambient temperature is usually high, there is also a potential for interaction as demonstrated by the concomitance of heat wave and wildfire conditions in summer 2010 in Russia and the huge impact on population in terms of adverse effects on respiratory health [89]. This interaction could be explained, at the point of emissions, by changes in smoke constituents driven by temperature, sunlight, water vapour and interaction with other pollutants [17]. Furthermore, meteorological conditions influence smoke dispersion and transportation [19]. The long range transport of smoke plumes for thousands kilometres is a public health concern also in European countries as, for example, in Finland where long-range transported PM episodes originated from wildfires in Russia, Belarus, Ukraine and the Baltic countries are common [86]. However, no study to date has evaluated the possible effect modification of weather on PM related effects during wildfire. Other wildfire

consequences include visibility impairment and ozone (O₃) generation [90]; also these factors may interact with PM levels in determining health effects [88].

Overall, the available evidence suggests an effect of wildfire on respiratory health. The greatest methodological challenge in these studies regards the estimate of exposure; in most cases PM measurements from air quality monitoring station are used but these are limited to specific points and therefore not well representative of actual exposure. The more recent approach of burnt areas from satellite data seems to be more effective in identifying areas at risk. Moreover, wildfires are rare events and effect depends also on the local context; therefore results are not easily generalizable and to date there is no consensus to estimate the exposure taking into account dispersion process of smoke [91].

Air pollution and desert dust storms effects.

Desertic regions throughout the world are known to be the source of dust storms that are driven by weather conditions and transported over long distance, with North Africa (Sahara) the main contributing area (over 50%) [92-94]. Dust particles derive from earth's crust and affect air quality in particular PM₁₀ and coarse particulates (PM_{2.5-10}) levels [92-94]. For example, during Saharan events PM₁₀ concentrations exceed EU daily limit value overcoming 100 µg/m³ or 150 µg/m³ at rural stations [59, 92, 94]. As wildfire smoke, also dust storms may be transported over thousands kilometers, changing composition and concentration of pollutants on the way and following specific trajectories that can be back-derived by mathematical models. These episodes can cause PM concentration peaks in areas with low local emissions also very far from the emission sources, including rural background areas [95].

The Mediterranean and Europe are particularly affected by dust storms from North Africa with significant impact on air quality and human health [92, 94]. The growing evidence in these regions suggests a greater effect of PM on dust days than in non dust days [59, 96-105], in particular on mortality or hospital admissions for respiratory causes [97, 98, 100-105] (Table 4). On the contrary, no effect was found in a study in Cyprus [59], while a greater effect on non dust days was found in Athens [99]. Overall, associations are more coherent regards coarse particles (PM_{2.5-10}) than for PM_{2.5} and PM₁₀. Only studies outside Europe, mainly from Asia and

Australia, evaluated dust storms effects on specific respiratory diseases, such as pneumonia, rhinitis, COPD and asthma; however, evidence is still limited and rather contrasting especially regards hospital admissions for these diseases [92, 94].

As in the case of wildfires, the meteorological context is important also in the case of dust storms; cyclone and anticyclone systems may favour the long-range transport of dust and convective activity and rainfalls cause the abatement of dust air masses [95]; in addition, dust storms tend to occur in contemporary with high ambient temperatures and high ozone levels [94]. Despite these important links, the interaction between weather variables and dust storms has not been analysed yet. However, the effect modification of particulates by Saharan dust days was robust both to ozone adjustment and to the exclusion of extremely warm days [98]. To the best of our knowledge, only one study have quantified the direct health effect of dust storms on health providing evidence for an increase in asthma and respiratory admissions especially in younger population [106].

The study of the effect of dust storms presents specific methodological challenges [92, 94]. First, the low frequency of dust days restricts analysis of cause-specific mortality or morbidity. Moreover, for their nature the occurrence and intensity of dust intrusions is strongly linked to the specific local context. For example, Saharan dust storms mostly affect the Eastern Mediterranean Basin regions and their frequency, intensity, seasonality, as well as years considered and local climate conditions affect the dust composition and consequently health effects. Similarly to wildfires, the definition of dust event is critical. Usually dust days are defined based on overcome of a specific threshold of PM, or on the basis of back-trajectory analysis, considered to be a marker of dust transport from the source regions. In urban areas dust events may be underestimated due the presence of other sources of dust mainly anthropogenic [94].

Mechanisms and vulnerable subgroups

The respiratory system is the main target of gases, aerosols and particles present in air pollution. A wide range of effects on the respiratory system are triggered by environmental toxicants, from reversible local responses to long-term chronic effects: local irritation, direct cellular damage on epithelium of respiratory airways, allergic responses (i.e. asthma), cancer. The underlying mechanisms are different for the

different pollutants. Ozone provokes an oxidative damage to the respiratory epithelium resulting in lung inflammation, decrements in lung function, worsening of respiratory tract symptoms and increased airway reactivity [107]. Particulate matter, via enhanced oxidative stress, may disrupt lung endothelial cell barrier integrity, thereby inducing lung dysfunction and adverse cardiopulmonary outcomes [108].

Not only air pollution but also high and low temperatures have a strong effect on respiratory health as seen above (see paragraph "Outdoor temperature"). Underlying mechanisms are better known for cold than for heat. Cold temperature may affect respiratory health in different ways and seem to affect not only susceptible but also healthy subjects. Breathing cold air causes the cooling of nasal and bronchial mucosa seriously impairing ciliar motility and consequently reducing immune system's resistance to respiratory infections [109, 110]. Exposure to cold air may also increase the number of granulocytes and macrophages in the lower airways in healthy subjects [111] and induce bronchoconstriction [112, 113] suggesting that cold exposure could be involved in the pathogenesis of the asthma-like condition. Part of the increase in respiratory outcomes during cold periods may also be attributed to cross-infections from increased indoor crowding during winter [114].

Differently from what observed for cold, the health consequences deriving from exposure to heat seem to be greater in patients affected by chronic respiratory diseases. In these patients, it may be hypothesized that thermoregulatory responses to heat stress, particularly those involving the respiratory system, may be ineffective to dissipate excess heat thus increasing their risk to developing heat stress conditions such as dehydration and heatstroke. However this hypothesis is still not supported by experimental studies [115]. A different pathway linking heat exposure to respiratory health outcomes involves the clinical course of heat-related illnesses such as heatstroke. In patients with heat stroke, an acute lung inflammation and damage might occur [116] and heat may trigger a series of physiological changes in the lung leading to a severe respiratory distress syndrome [117, 118]. Recent experimental evidence suggests that chronic heat stress exposure could increase the susceptibility of animals to the highly pathogenic respiratory viruses by reducing local immunity in the respiratory tract, i.e. the number of pulmonary alveolar macrophages [119]. Other weather conditions, particularly humidity, may adversely affect respiratory health but their role is still unclear. Some studies showed that in both healthy and asthmatic subjects humidity may decrease lung capacity and increasing airways

resistance [120, 121] while in others humidity did not influence non-specific airway hyperresponsiveness [122]. Humidity may also indirectly affect respiratory allergic diseases by influencing atmospheric levels of aeroallergens, with low humidity favouring release, dispersion and transport of pollen [123, 124]. Extreme weather events such as thunderstorms may trigger asthma epidemics by inducing pollen grain rupture by osmotic shock that releases respirable allergens into the atmosphere [123, 124].

The above mentioned evidence of a synergistic effect between air pollution and temperature can have different explanations. Since the respiratory surfaces are the primary route by which air pollutants enter the body, the activation of thermoregulatory responses at pulmonary level during prolonged heat exposure may augment the total intake of airborne pollutants due to the increase in ventilation rate and lung volumes [125, 126]. It has also been suggested that variations in the sources of air pollution and meteorological factors can result in changes in characteristics of the air pollution mixture across seasons [68, 127, 128]. However, in an experimental study modifications in PM components were not able to explain the seasonal difference in PM effects that could instead be related with the highest prevalence of allergens in spring and summer influencing the onset and severity of allergic diseases [129]. The higher effects of pollutants observed in summer than in winter might also be due to the lower exposure measurement error during summer as a consequence of more time spent outdoors or, especially for particles, due to a more similar composition between indoor and outdoor pollutants [54, 68, 127, 130, 131]. Another hypothesis is that the lower winter mortality for infectious diseases resulting in a lower mortality among the elderly, i.e. among those most susceptible, has the consequence of a larger pool of susceptible people at risk of air pollution effect in the following summer [68, 127, 130]. To explain the interaction between pollutant and low temperature [78], a hypothesized mechanism is that the cold-related impairment of respiratory mucociliary function may inhibit the clearance of pollutants [109, 110]. Meteorological factors such as temperature may also influence the interaction between allergens and air pollution in producing respiratory adverse effects since air pollution-related damage on respiratory epithelium increases airway permeability stimulating allergen-induced responses and absorption of pollutants to the surface of pollen grains may modify their allergenic potential [123, 124]. Also humidity may modify air pollution effect on respiratory health. Airways of individual suffering from respiratory

diseases seem to be protected against the effect of particles by high humidity probably due to the reduced number of particles [80].

Mechanisms explaining the respiratory effects of wildfires and dust storms are mainly linked with air pollution associated to these events. Particulate matter is the predominant air pollutant in fire smoke that contains also gases including carbon monoxide, nitrous oxides, polycyclic aromatic hydrocarbons, VOCs, ozone and nitrous dioxide [82-84]. Wood smoke particles have been shown to activate systemic and pulmonary inflammation in healthy human subjects [92, 94]. There is still insufficient evidence to establish whether wildfire PM10 may have a greater effect than urban background PM10 [17, 82-84].

However, smoke particulate is probably different in composition respect to urban PM, having a greater concentration of PM10 that can accumulate in the lungs. An in vivo experiment found that responses to wood smoke consist in higher inflammatory and cytotoxic responses than those triggered by urban particulate matter [82]. Apportionment techniques are expected to provide important insights to whether fire components are less or more toxic than the same constituents from fossil fuel burning and to clarify the underlying mechanisms.

In the case of dust storms, not only the chemical composition of particles but also its biological content is the probable causative agent of respiratory health effects [92-94]. In particular, coarse particles may have a greater allergenic and inflammatory property, absorbing to their surface pollens and microorganisms such as bacteria and fungi, as well as endotoxins, which are components of the bacterial wall that can cause respiratory and systemic inflammatory responses, and exacerbate lung disease [92-94]. This hypothesis is coherent with recent evidence of an increase in infectious diseases (i.e. meningitis) in dust days [94]. Moreover, in their long-range travel dust particles may absorb metals, pesticides and industrial products mixing with anthropogenic emissions of industrial regions (e.g.: North African); Inhaling these compounds can cause lungs irritation, reducing lung capacity through activating oxidative stress pathways [92, 94]. As in the case of wildfires, chemical speciation and toxicity studies may clarify whether dust particles are more or less toxic than urban PM, considering also that dust may be one of the component of PM itself other than interact with it.

Vulnerable subgroups

The links between climate and air pollution on human health are complicated by the presence in a population of specific subgroups at greater risk of adverse health effects (i.e. vulnerable subgroups) owing to a series of environmental, individual and population characteristics. According to the Intergovernmental Panel on Climate Change, vulnerability is defined as a function of the level of exposure (character, magnitude and rate of weather event), of the level of the susceptibility and the adaptive capacity of populations [132]. Several climate-sensitive subgroups have been identified: heat and heat waves have a stronger impact on people with impaired physiological and behavioural responses to heat due to age, gender, socio-economic factors, pre-existing chronic diseases, use of certain medications and environmental conditions (i.e. lack of air conditioning) but the pattern of susceptibility factors is population-specific and may vary over time [115, 133]. Regarding cold exposure, indoor climatic conditions seem to confer a greater vulnerability especially in the elderly [134, 135], while there is contrasting evidence of socioeconomic gradient of risk [136, 137]. Less known are the susceptibility factors to other extreme events like wildfires and dust storms. Subjects with asthma and COPD, women and children are more likely to be affected by wildfires [17, 82-84]; children, elderly, people of low income and persons with cardiovascular and respiratory disease may be more susceptible to dust storms [92-94].

On the other hand, individual characteristics to identify subgroups at greater risk due to air pollution are pollutant-specific. Susceptible subjects to particulate matter comprise elderly, people of low socioeconomic status and COPD and cardiovascular disease patients [138, 139], while regarding ozone there is contrasting evidence on whether some subgroups have a greater risk of adverse effects than the general population [140, 141].

Research needs in the context of respiratory health

Considering climate change scenarios, to quantify the effect estimates on respiratory health and to identify vulnerable population subgroups are crucial research areas to carry out health impact assessments to understand future impacts and to support decision-makers and health care community in the fight against this global environmental threat [6].

Table 5 summarizes for each climate hazard the main respiratory outcomes and the population subgroups for which there is evidence of association from epidemiological studies; research gaps and future expected impacts under climate change are also pointed out. Overall, every climate hazard appear to have a significant impact on the respiratory system, although evidence on specific respiratory diseases and specific age groups is still limited. At European level, there is scarce epidemiological evidence about cold extremes and wildfires effects. Multicentre studies are lacking in the analysis of rare and local-extent episodes such as dust storms and wildfires. The ongoing PHASE (www.hpa.org.uk/Topics/EmergencyResponse/ExtremeWeatherEventsAndNaturalDisasters/PHASE/) and MEDPARTICLES (www.epidemiologia.lazio.it/medparticles/index.php/en/) multicenter projects will provide further insights on both these hazardous exposures. Pre-existing respiratory diseases are important vulnerability factors to both temperature and air pollution effects. Since vulnerability factors are specific for each climate hazard and may vary across populations and over time, more research is needed, in particular on younger age groups and children, but also on other population segments as low socioeconomic groups.

Considering future impacts on respiratory diseases, population aging, increased prevalence of chronic diseases and the socioeconomic transitions which are currently ongoing in several countries the portion of population at risk will probably increase [142, 143]. Almost all climate hazards will worsen under climate change, and as much the related disease burden. The only beneficial effect will consist in the reduction of cold-related effect (i.e. respiratory infections) due to warmer winters [143]. However, due to the complexity of the above mentioned climate-air quality interactions, a great deal of uncertainty remains regarding future trends of climate and pollutants and research is needed to increase modelling capability to better understand the interplay between human activities, air pollution and regulatory requirements, climate policy, economic factors, and to predict future trends of air pollutants, accounting for uncertainty and variability in projections of global change. Advances in modelling capability can derive from disease surveillance integrated with air pollution, weather and climate data and from combining ecological approaches (time series studies) with spatial methods to produce a more complete evaluation of health effects taking into account both geographical and temporal variations. From a public health point of

view, since health professionals have joined late the climate change debate [144], they are urged to develop modelling skills in relation to climate change, particularly by combining climate models with ecological and health outcome models for projecting disease dynamics under various climate scenarios.

Policy implications

Due to the close climate and air pollution inter-linkages, climate change policies need to be integrated with air quality policies to be effective. Moreover, mutual benefits can be achieved: actions to mitigate climate change by reducing greenhouse gases emissions may help in reducing air pollution since they involve main changes in transport and energy sectors which are also driving pollutant sinks and, at the same time, clean air measures can reduce anthropogenic emissions that are important contributors to global warming. Cobenefits of climate policies on air pollution have been evaluated for Europe [145]. Although limitations in data availability, especially in relation to the scenario datasets and modelling uncertainties, cobenefits resulted for all investigated emission scenarios, with the scenarios based on energy efficiency strategies leading to larger cobenefits [145].

At the European level, although stringent emission targets have been made (i.e. to reduce the domestic GHG emissions by 80 percent by 2050 compared to 1990 levels), the greatest reductions in GHG emissions have been achieved only as an indirect effect of the current economic crisis [146]. To accomplish GHG reductions targets, countries need to reach the convergence between resource productivity and efficiency. However, energy efficiency improvements, i.e. switching to fuel with a low-carbon content but higher price, lead to increases in environmental inequality posing the major risks to disadvantage groups, for example due to inadequate housing and heating systems. To cope with economic and climate changes, European countries need to develop a more comprehensive policy framework that integrates climate policy, industrial policy, employment and social policy [146].

Conclusions

Climate and climate change are affecting air pollution effects on respiratory health in several ways: climate variations are predicted to influence the start, duration and intensity of the pollen season, to increase the frequency and intensity of heat waves,

heavy precipitation events (i.e. thunderstorms) and wildfires and to raise long-range transport of air pollutants and allergens [4].

To face both the current and future climate and pollution challenges, adequate policy and public health actions are needed, taking into account the interrelations between the two hazardous exposures. Since climate change is a global problem with the worst consequences occurring not in developed but in developing countries, global actions are needed. Policies to reduce greenhouse emissions need to be established especially in countries which hold the greatest emission burden. In parallel, developing countries are increasingly affected by urban air pollution due to the rapid economic and population growth [147, 148]. The way forward to face both these challenges needs the multisectorial collaboration of epidemiologist, climatologist, respiratory and allergy specialists, policy makers, public health professionals that share the heavy responsibility to guide world through the climate crisis and make the environment sustainable for future generations.

Acknowledgments

This work was funded within the EU project PHASE project (EAHC contract number: 20101103).

References

1. Gualdi S, Navarra A. Scenari climatici nel bacino mediterraneo. *Forest@* 2006; 2: 19-30.
2. Alcamo, J., J.M. Moreno, B. Nováky, M. Bindi, R. Corobov, R.J.N. Devoy, C. Giannakopoulos, E. Martin, J.E. Olesen, A. Shvidenko, 2007: Europe. *In: Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*, M.L. Parry, O.F. Canziani, J.P. Palutikof, P.J. van der Linden and C.E. Hanson, Eds., Cambridge University Press, Cambridge, UK, 541-580.
3. Meehl GA, Tebaldi C. More intense, more frequent, and longer lasting heat waves in the 21st century. *Science* 2004; 305: 994-7.
4. Denman, K.L., G. Brasseur, A. Chidthaisong, P. Ciais, P.M. Cox, R.E. Dickinson, D. Hauglustaine, C. Heinze, E. Holland, D. Jacob, U. Lohmann, S Ramachandran, P.L. da Silva Dias, S.C. Wofsy and X. Zhang, 2007: Couplings Between Changes in the Climate System and Biogeochemistry. *In: Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change* [Solomon, S., D. Qin, M. Manning, Z. Chen, M. Marquis, K.B. Averyt, M.Tignor and H.L. Miller (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA.
5. American Thoracic Society. What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 2000; 161(2 Pt 1): 665-73.
6. Ayres JG, Forsberg B, Annesi-Maesano I, Dey R, Ebi KL, Helms PJ, Medina-Ramón M, Windt M, Forastiere F; Environment and Health Committee of the European Respiratory Society. Climate change and respiratory disease: European Respiratory Society position statement. *Eur Respir J* 2009; 34: 295-302.
7. Pinkerton KE, Rom WN, Akpınar-Elci M, Balmes JR, Bayram H, Brandli O, Hollingsworth JW, Kinney PL, Margolis HG, Martin WJ, Sasser EN, Smith KR, Takaro TK; American Thoracic Society Environmental Health Policy Committee. An official American Thoracic Society workshop report: Climate change and human health. *Proc Am Thorac Soc*. 2012 Mar;9(1):3-8.
8. Jacob DJ, Winner DA. Effect of climate change on air quality. *Atmospheric Environment* 2009; 43: 51-63.
9. Noyes PD, McElwee MK, Miller HD, Clark BW, Van Tiem LA, Walcott KC, Erwin KN, Levin ED. The toxicology of climate change: environmental contaminants in a warming world. *Environ Int* 2009; 35: 971-86.
10. Dennekamp M, Carey M. Air quality and chronic disease: why action on climate change is also good for health. *N S W Public Health Bull* 2010; 21: 115-21

11. Engardt M, Bergström R, Andersson C. Climate and emission changes contributing to changes in near-surface ozone in Europe over the coming decades: Results from model studies. *Ambio* 2009; 38: 452-458.
12. Ordonez C, Mathis H, Furger M, Henne S, Huglin C, Staehelin J, Prevot ASH. Changes of daily surface ozone maxima in Switzerland in all seasons from 1992 to 2002 and discussion of summer 2003. *Atmos Chem Phys* 2005; 5: 1187-1203.
13. Liao H, Chen W-T, Seinfeld JH. Role of climate change in global predictions of future tropospheric ozone and aerosols. *J Geophys Res* 2006; 111: D12304. doi:10.1029/2005JD006852
14. Krawchuk MA, Moritz MA, Parisien MA, Van Dorn J, Hayhoe K. Global pyrogeography: the current and future distribution of wildfire. *PLoS One* 2009; 4: e5102.
15. Spickett JT, Brown HL, Rumchev K. Climate change and air quality: the potential impact on health. *Asia Pac J Public Health* 2011; 23(2 Suppl): 37S-45S.
16. Moriondo M, Good P, Durao R, Bindi M, Giannakopoulos C, Corte-Real J. Potential impact of climate change on fire risk in the Mediterranean area. *Climate Research* 2006; 31: 85-95.
17. Naeher LP, Brauer M, Lipsett M, Zelikoff JT, Simpson CD, Koenig JQ, Smith KR. Woodsmoke health effects: a review. *Inhal Toxicol* 2007; 19: 67-106.
18. Smith KR, Jerrett M, Anderson HR, Burnett RT, Stone V, Derwent R, Atkinson RW, Cohen A, Shonkoff SB, Krewski D, Pope CA 3rd, Thun MJ, Thurston G. Public health benefits of strategies to reduce greenhouse-gas emissions: health implications of short-lived greenhouse pollutants. *Lancet* 2009; 374: 2091-2103.
19. Viswanathan S, Eria L, Diunugala N, Johnson J, McClean C. An analysis of effects of San Diego wildfire on ambient air quality. *J Air Waste Manag Assoc* 2006; 56: 56-67.
20. Forastiere F, De Sario M, Michelozzi P. The Italian contribution to EU research programs on health effects of air pollution and climate in a changing environment. *Epidemiol Prev* 2010; 34: 39-46.
21. WHO. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005 Summary of risk assessment. World Health Organization, 2006.
22. Katsouyanni K, Analitis A. Investigating the Synergistic Effects Between Meteorological Variables and Air Pollutants: Results from the European PHEWE, EUROHEAT and CIRCE Projects. *Epidemiology* 2009; 20: S264. doi: 10.1097/01.ede.0000362883.27030.8f
23. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C; and the ISAAC Phase Three Study Group. Worldwide trends in the prevalence of

- asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; 62: 758-66.
24. Björkstén B, Clayton T, Ellwood P, Stewart A, Strachan D; ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008; 19: 110-24.
 25. von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998; 28(Suppl 5): 45-9.
 26. Douwes J, Pearce N. Asthma and the westernization 'package'. *Int J Epidemiol* 2002; 31: 1098-102.
 27. Anderson HR. Air pollution and trends in asthma. *Ciba Found Symp* 1997; 206: 190-202.
 28. Ren C, Tong S. Health effects of ambient air pollution--recent research development and contemporary methodological challenges. *Environ Health* 2008; 7: 56.
 29. Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Künzli N, Avol E, Gilliland F, Lurmann F, Molitor JN, Molitor JT, Thomas DC, Peters J, McConnell R. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008; 116: 1433-8.
 30. Granier, C, Bessagnet, B, Bond, T, D'Angiola, A, van der Gon, HD, Frost, GJ, Heil, A, Kaiser, JW, Kinne, S, Klimont, Z, Kloster, S, Lamarque, JF, Liousse, C, Masui, T, Meleux, F, Mieville, A, Ohara, T, Raut, JC, Riahi, K, Schultz, MG, Smith, SJ, Thompson, A, van Aardenne, J, van der Werf, GR, van Vuuren, DP: Evolution of anthropogenic and biomass burning emissions of air pollutants at global and regional scales during the 1980-2010 period, *Climatic Change* 2011; 109, doi:10.1007/s10584-011-0154-1, 2011
 31. Samoli E, Aga E, Touloumi G, Nisiotis K, Forsberg B, Lefranc A, Pekkanen J, Wojtyniak B, Schindler C, Niciu E, Brunstein R, Dodic Fikfak M, Schwartz J, Katsouyanni K. Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. *Eur Respir J* 2006; 27: 1129-38.
 32. Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, Touloumi G, Schwartz J, Anderson HR, Cambra K, Forastiere F, Zmirou D, Vonk JM, Clancy L, Kriz B, Bobvos J, Pekkanen J. Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology* 2006; 17: 230-3.
 33. Gryparis A, Forsberg B, Katsouyanni K, Analitis A, Touloumi G, Schwartz J, Samoli E, Medina S, Anderson H, Niciu E, Wichmann H, Kriz B, Kosnik M, Skorkovsky J, Vonk J, Dortbudak Z. Acute effects of ozone on mortality from the air pollution and health: A European approach project. *Am J Resp Crit Care* 2004; 170: 1080-1087.

34. Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Peacock J, Anderson RH, Le Tertre A, Bobros J, Celko M, Goren A, Forsberg B, Michelozzi P, Rabczenko D, Hoyos SP, Wichmann HE, Katsouyanni K. The temporal pattern of respiratory and heart disease mortality in response to air pollution. *Environ Health Perspect* 2003; 111: 1188-93.
35. Samoli E, Zanobetti A, Schwartz J, Atkinson R, Le Tertre A, Schindler C, Pérez L, Cadum E, Pekkanen J, Paldy A, Touloumi G, Katsouyanni K. The temporal pattern of mortality responses to ambient ozone in the APHEA project. *J Epidemiol Community Health* 2009; 63: 960-6.
36. Sunyer J, Atkinson R, Ballester F, Le Tertre A, Ayres JG, Forastiere F, Forsberg B, Vonk JM, Bisanti L, Anderson RH, Schwartz J, Katsouyanni K; APHEA 2 study. Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. *Occup Environ Med* 2003; 60: e2.
37. Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. *Air Pollution and Health: a European Approach. Am J Respir Crit Care Med* 2001; 164(10 Pt 1): 1860-6.
38. Atkinson RW; APHEA 2 Project. Acute effects of air pollution on admissions: reanalysis of APHEA 2. *Am J Respir Crit Care Med* 2004; 169: 1257-8.
39. Baccini M, Biggeri A, Accetta G, Kosatsky T, Katsouyanni K, Analitis A, Anderson HR, Bisanti L, D'Ippoliti D, Danova J, Forsberg B, Medina S, Paldy A, Rabczenko D, Schindler C, Michelozzi P. Heat effects on mortality in 15 European cities. *Epidemiology* 2008; 19: 711-9.
40. Michelozzi P, Accetta G, De Sario M, D'Ippoliti D, Marino C, Baccini M, Biggeri A, Anderson HR, Katsouyanni K, Ballester F, Bisanti L, Cadum E, Forsberg B, Forastiere F, Goodman PG, Hojs A, Kirchmayer U, Medina S, Paldy A, Schindler C, Sunyer J, Perucci CA; PHEWE Collaborative Group. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. *Am J Respir Crit Care Med* 2009; 179: 383-9.
41. D'Ippoliti D, Michelozzi P, Marino C, de'Donato F, Menne B, Katsouyanni K, Kirchmayer U, Analitis A, Medina-Ramón M, Paldy A, Atkinson R, Kovats S, Bisanti L, Schneider A, Lefranc A, Iñiguez C, Perucci CA. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. *Environ Health* 2010; 9: 37.
42. Analitis A, Katsouyanni K, Biggeri A, Baccini M, Forsberg B, Bisanti L, Kirchmayer U, Ballester F, Cadum E, Goodman PG, Hojs A, Sunyer J, Tiittanen P, Michelozzi P. Effects of cold weather on mortality: results from 15 European cities within the PHEWE project. *Am J Epidemiol* 2008; 168: 1397-408.
43. Marino C, de'Donato F, Michelozzi P, D'Ippoliti D, Katsouyanni K, Analitis A, Biggeri A, Baccini M, Accetta G, Perucci CA, The PHEWE Collaborative Group. Effects of Cold Weather on Hospital Admissions: Results from 12 European Cities Within the PHEWE Project. *Epidemiology* 2009; 20: S67-S68. doi: 10.1097/01.ede.0000362910.23459.81

44. Turner LR, Barnett AG, Connell D, Tong S. Ambient temperature and cardiorespiratory morbidity: a systematic review and meta-analysis. *Epidemiology*. 2012 Jul;23(4):594-606.
45. 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: 1781-1788.
46. McGregor GR, Walters S, Wordley J. Daily hospital respiratory admissions and winter air mass types, Birmingham, UK. *Int J Biometeorol* 1999; 43: 21-30.
47. Braga A, Zanobetti A, Schwartz J. The Time Course of Weather Related Deaths. *Epidemiology* 2001; 12: 662-667.
48. Keatinge WR, Donaldson GC. Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. *Environ Res* 2001; 86: 209-16.
49. Schwartz J, Samet J, Patz J. Hospital Admissions for Heart Disease: The Effects of Temperature and Humidity. *Epidemiology* 2004; 15: 755-61.
50. Abe T, Tokuda Y, Ohde S, Ishimatsu S, Nakamura T, Birrer RB. The relationship of short-term air pollution and weather to ED visits for asthma in Japan. *Am J Emerg Med* 2009; 27: 153-9.
51. Mireku N, Wang Y, Ager J, Reddy RC, Baptist AP. Changes in weather and the effects on pediatric asthma exacerbations. *Ann Allergy Asthma Immunol* 2009; 103: 220-4.
52. Zmirou D, Schwartz J, Saez M, Zanobetti A, Wojtyniak B, Touloumi G, Spix C, Ponce de León A, Le Moullec Y, Bacharova L, Schouten J, Pönkä A, Katsouyanni K. Time-series analysis of air pollution and cause-specific mortality. *Epidemiology* 1998; 9: 495-503.
53. Anderson HR, Bremner SA, Atkinson RW, Harrison RM, Walters S. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occup Environ Med* 2001; 58: 504-10.
54. Stafoggia M, Schwartz J, Forastiere F, Perucci CA; SISTI Group. Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. *Am J Epidemiol* 2008; 167: 1476-85.
55. Stieb DM, Szyszkowicz M, Rowe BH, Leech JA. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environ Health* 2009; 8: 25.
56. Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Strachan DP. Air pollution and daily mortality in London: 1987-92. *BMJ* 1996; 312: 665-9.

57. Hajat S, Haines A, Goubet SA, Atkinson RW, Anderson HR. Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. *Thorax* 1999; 54: 597-605.
58. Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environ Res* 2011a; 111: 418-24.
59. Middleton N, Yiallourous P, Kleanthous S, Kolokotroni O, Schwartz J, Dockery DW, Demokritou P, Koutrakis P. A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. *Environ Health* 2008; 7: 39.
60. Tramuto F, Cusimano R, Cerame G, Vultaggio M, Calamusa G, Maida CM, Vitale F. Urban air pollution and emergency room admissions for respiratory symptoms: a case-crossover study in Palermo, Italy. *Environ Health* 2011; 10: 31.
61. Touloumi G, Samoli E, Katsouyanni K. Daily mortality and "winter type" air pollution in Athens, Greece - a time series analysis within the APHEA project. *J Epidemiol Community Health* 1996; 50(Suppl 1): S47-S51.
62. Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, Rossi G, Zmirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, Paldy A, Braunstein R, Pekkanen J, Schindler C, Schwartz J. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology* 2001; 12: 521-31.
63. Katsouyanni K, Pantazopoulou A, Touloumi G, Tselepidaki I, Moustiris K, Asimakopoulos D, Pouloupoulou G, Trichopoulos D. Evidence for interaction between air pollution and high temperature in the causation of excess mortality. *Arch Environ Health* 1993; 48: 235-42.
64. Sartor F, Snacken R, Demuth C, Walckiers D. Temperature, ambient ozone levels, and mortality during summer 1994, in Belgium. *Environ Res* 1995; 70: 105-13.
65. Sartor F, Demuth C, Snacken R, Walckiers D. Mortality in the elderly and ambient ozone concentration during the hot summer, 1994, in Belgium. *Environ Res* 1997; 72: 109-17.
66. Dear K, Ranmuthugala G, Kjellström T, Skinner C, Hanigan I. Effects of temperature and ozone on daily mortality during the August 2003 heat wave in France. *Arch Environ Occup Health* 2005; 60: 205-12.
67. Filleul L, Cassadou S, Médina S, Fabres P, Lefranc A, Eilstein D, Le Tertre A, Pascal L, Chardon B, Blanchard M, Declercq C, Jusot JF, Prouvost H, Ledrans M. The relation between temperature, ozone, and mortality in nine French cities during the heat wave of 2003. *Environ Health Perspect* 2006; 114: 1344-7.
68. Nawrot TS, Torfs R, Fierens F, De Henauw S, Hoet PH, Van Kersschaever G, De Backer G, Nemery B. Stronger associations between daily mortality and fine

- particulate air pollution in summer than in winter: evidence from a heavily polluted region in western Europe. *J Epidemiol Community Health* 2007; 61: 146-9.
69. Ren C, Tong S. Health effects of ambient air pollution--recent research development and contemporary methodological challenges. *Environ Health* 2008; 7: 56.
 70. Qian Z, He Q, Lin HM, Kong L, Bentley CM, Liu W, Zhou D. High temperatures enhanced acute mortality effects of ambient particle pollution in the "oven" city of Wuhan, China. *Environ Health Perspect* 2008; 116: 1172-8.
 71. Hu W, Mengersen K, McMichael A, Tong S. Temperature, air pollution and total mortality during summers in Sydney, 1994-2004. *Int J Biometeorol* 2008; 52: 689-96.
 72. Mohr LB, Luo S, Mathias E, Tobing R, Homan S, Sterling D. Influence of season and temperature on the relationship of elemental carbon air pollution to pediatric asthma emergency room visits. *J Asthma* 2008; 45: 936-43.
 73. Ren C, Williams GM, Mengersen K, Morawska L, Tong S. Temperature enhanced effects of ozone on cardiovascular mortality in 95 large US communities, 1987-2000: Assessment using the NMMAPS data. *Arch Environ Occup Health* 2009; 64: 177-84.
 74. Lin CM, Liao CM. Temperature-dependent association between mortality rate and carbon monoxide level in a subtropical city: Kaohsiung, Taiwan. *Int J Environ Health Res* 2009; 19: 163-74.
 75. Pattenden S, Armstrong B, Milojevic A, Heal MR, Chalabi Z, Doherty R, Barratt B, Kovats RS, Wilkinson P. Ozone, heat and mortality: acute effects in 15 British conurbations. *Occup Environ Med* 2010; 67: 699-707.
 76. Li G, Zhou M, Cai Y, Zhang Y, Pan X. Does temperature enhance acute mortality effects of ambient particle pollution in Tianjin City, China. *Sci Total Environ* 2011; 409: 1811-7.
 77. Hales S, Salmond C, Town GI, Kjellstrom T, Woodward A. Daily mortality in relation to weather and air pollution in Christchurch, New Zealand. *Aust N Z J Public Health* 2000; 24: 89-91.
 78. Carder M, McNamee R, Beverland I, Elton R, Van Tongeren M, Cohen GR, Boyd J, Macnee W, Agius RM. Interacting effects of particulate pollution and cold temperature on cardiorespiratory mortality in Scotland. *Occup Environ Med* 2008; 65: 197-204.
 79. Analitis A, Michelozzi P, D' Ippoliti D, de'Donato F, Menne B, Matthies F, Atkinson RW, Iñiguez C, Basagaña X, Schneider A, Lefranc A, Paldy A, Bisanti L, Katsouyanni K. Heat waves effect on mortality: an investigation of the effect modification and confounding by air pollutants within the EuroHEAT project. *Epidemiology* (in press)

80. Leitte AM, Petrescu C, Franck U, Richter M, Suci O, Ionovici R, Herbarth O, Schlink U. Respiratory health, effects of ambient air pollution and its modification by air humidity in Drobeta-Turnu Severin, Romania. *Sci Total Environ* 2009; 407: 4004-11.
81. McGregor GR, Walters S, Wordley J. Daily hospital respiratory admissions and winter air mass types, Birmingham, UK. *Int J Biometeorol* 1999; 43: 21-30.
82. Finlay SE, Moffat A, Gazzard R, Baker D, Murray V. Health impacts of wildfires. *PLoS Curr.* 2012 Nov 2;4:e4f959951cce2c. doi: 10.1371/4f959951cce2c.
83. Boman BC, Forsberg AB, Järholm BG. Adverse health effects from ambient air pollution in relation to residential wood combustion in modern society. *Scand J Work Environ Health* 2003; 29: 251-60.
84. Dennekamp M, Abramson MJ. The effects of bushfire smoke on respiratory health. *Respirology* 2011; 16: 198-209.
85. Analitis A, Georgiadis I, Katsouyanni K. Forest fires are associated with elevated mortality in a dense urban setting. *Occup Environ Med* 2012; 69: 158-162.
86. Hanninen O, Salonen RO, Koistinen K, Lanki T, Barregard L and Jantunen M. Population exposure to fine particles and estimated excess mortality in Finland from an East European wildfire episode. *J Expo Sci Environ Epidemiol* 2009; 19: 414-22
87. Mirabelli MC, Kunzli N, Avol E, Gilliland FD, Gauderman WJ, McConnell R, et al. Respiratory Symptoms Following Wildfire Smoke Exposure: Airway Size as a Susceptibility Factor. *Epidemiology* 2009 May;20(3):451-9.
88. Ovadnevaite J, Kvietkus K, Marsalka A. 2002 summer fires in Lithuania: Impact on the Vilnius city air quality and the inhabitants health. *Science of The Total Environment* 2006 Mar 1;356(1-3):11-21.
89. Grumm RH. The Central European and Russian Heat Event of July-August 2010. *BAMS* 2010; 92: 1285-1296.
90. Azevedo JM, Gonçalves FL, de Fátima Andrade M. Long-range ozone transport and its impact on respiratory and cardiovascular health in the north of Portugal. *Int J Biometeorol* 2011; 55: 187-202.
91. Henderson SB, Brauer M, Macnab YC, Kennedy SM. Three measures of forest fire smoke exposure and their associations with respiratory and cardiovascular health outcomes in a population-based cohort. *Environ Health Perspect.* 2011 Sep;119(9):1266-71. Epub 2011 Jun 9.
92. de Longueville F, Ozer P, Doumbia S, Henry S. Desert dust impacts on human health: an alarming worldwide reality and a need for studies in West Africa. *Int J Biometeorol.* 2012 May.

93. Schwartz J, Norris G, Larson T, Sheppard L, Claiborne C, Koenig J. Episodes of high coarse particle concentrations are not associated with increased mortality. *Environ Health Perspect* 1999; 107: 339-42.
94. Karanasiou A, Moreno N, Moreno T, Viana M, de Leeuw F, Querol X. Health effects from Sahara dust episodes in Europe: literature review and research gaps. *Environ Int.* 2012 Oct 15;47:107-14. Epub 2012 Jul 15.
95. Niemi JV, Saarikoski S, Aurela M, Tervahattu H, Hillamo R, Westphal DL, Aarnio P, Koskentalo T, Makkonen U, Vehkamäki H, Kulmala M. Long-range transport episodes of fine particles in southern Finland during 1999–2007. *Atmospheric Environment* 2009; 43: 1255–1264.
96. Perez L, Tobias A, Querol X, Künzli N, Pey J, Alastuey A, Viana M, Valero N, González-Cabré M, Sunyer J. Coarse particles from Saharan dust and daily mortality. *Epidemiology* 2008; 19: 800-7.
97. Jiménez E, Linares C, Martínez D, Díaz J. Role of Saharan dust in the relationship between particulate matter and short-term daily mortality among the elderly in Madrid (Spain). *Sci Total Environ* 2010; 408: 5729-36.
98. Mallone S, Stafoggia M, Faustini A, Gobbi GP, Marconi A, Forastiere F. Saharan dust and associations between particulate matter and daily mortality in Rome, Italy. *Environ Health Perspect* 2011; 119: 1409-14.
99. Samoli E, Kougea E, Kassomenos P, Analitis A, Katsouyanni K. Does the presence of desert dust modify the effect of PM10 on mortality in Athens, Greece? *Sci Total Environ* 2011a; 409: 2049-54.
100. Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environ Res* 2011b;111:418–24.
101. Tobias A, Pérez L, Díaz J, Linares C, Pey J, Alastruey A, et al. Short-term effects of particulate matter on total mortality during Saharan dust outbreaks: a case-crossover analysis in Madrid (Spain). *Sci Total Environ* 2011b;412:386–9.
102. Zauli Sajani S, Miglio R, Bonasoni P, Cristofanelli P, Marinoni A, Sartini C, Goldoni CA, De Girolamo G, Lauriola P. Saharan dust and daily mortality in Emilia-Romagna (Italy). *Occup Environ Med* 2011; 68: 446-51.
103. Alessandrini E, Stafoggia M, Faustini A, Gobbi GP, Forastiere F. The role of Saharan dust in the association between fine particles and hospital admissions in Rome. *Epid Prev* 2012; 36 (5):30.

104. Díaz J, Tobías A, Linares C. Saharan dust and association between particulate matter and case-specific mortality: a case-crossover analysis in Madrid (Spain). *Environ Health*. 2012 Mar 8;11:11.
105. Perez L, Tobías A, Querol X, Pey J, Alastuey A, Díaz J, Sunyer J. Saharan dust, particulate matter and cause-specific mortality: a case-crossover study in Barcelona (Spain). *Environ Int*. 2012 Nov 1;48:150-5. doi: 10.1016/j.envint.2012.07.001
106. Thalib L, Al-Taiar A. Dust storms and the risk of asthma admissions to hospitals in Kuwait. *Sci Total Environ*. 2012 Sep 1;433:347-51. Epub 2012 Jul 20.
107. 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.
108. Wang T, Chiang ET, Moreno-Vinasco L, Lang GD, Pendyala S, Samet JM, Geyh AS, Breyse PN, Chillrud SN, Natarajan V, Garcia JG. Particulate matter disrupts human lung endothelial barrier integrity via ROS- and p38 MAPK-dependent pathways. *Am J Respir Cell Mol Biol* 2010; 42: 442-9.
109. Clary-Meinesz CF, Cosson J, Huitorel P, Blaive B. Temperature effect on the ciliary beat frequency of human nasal and tracheal ciliated cells. *Biol Cell* 1992; 76: 335-8.
110. Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. *Acta Otolaryngol* 2002; 122: 183-91.
111. Larsson K, Tornling G, Gavhed D, Müller-Suur C, Palmberg L. Inhalation of cold air increases the number of inflammatory cells in the lungs in healthy subjects. *Eur Respir J* 1998; 12: 825-30.
112. Amirav I, Plit M. Temperature and humidity modify airway response to inhaled histamine in normal subjects. *Am Rev Respir Dis* 1989; 140: 1416-20.
113. Koskela H, Tukiainen H. Facial cooling, but not nasal breathing of cold air, induces bronchoconstriction: a study in asthmatic and healthy subjects. *Eur Respir J* 1995; 8: 2088-93.
114. Keatinge WR. Winter mortality and its causes. *Int J Circumpolar Health* 2002; 61: 292-9.
115. Kenny GP, Yardley J, Brown C, Sigal RJ, Jay O. Heat stress in older individuals and patients with common chronic diseases. *CMAJ* 2010; 182: 1053-60.

116. Hsi-Hsing Y, Ching-Ping C, Juei-Tang C, Lin MT. Inhibition of acute lung inflammation and injury is a target of brain cooling after heatstroke injury. *J Trauma* 2010; 69: 805-12.
117. el-Kassimi FA, Al-Mashhadani S, Abdullah AK, Akhtar J. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. *Chest* 1986; 90: 571-4.
118. Michelozzi P, Accetta G, De Sario M, D'Ippoliti D, Marino C, Baccini M, Biggeri A, Anderson HR, Katsouyanni K, Ballester F, Bisanti L, Cadum E, Forsberg B, Forastiere F, Goodman PG, Hojs A, Kirchmayer U, Medina S, Paldy A, Schindler C, Sunyer J, Perucci CA; PHEWE Collaborative Group. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. *Am J Respir Crit Care Med* 2009; 179: 383-9.
119. Jin Y, Hu Y, Han D, Wang M. Chronic heat stress weakened the innate immunity and increased the virulence of highly pathogenic avian influenza virus H5N1 in mice. *J Biomed Biotechnol* 2011; 2011: 367846.
120. Aitken ML, Marini JJ, Culver BH. Humid air increases airway resistance in asthmatic subjects. *West J Med* 1988; 149: 289-93.
121. Eschenbacher WL, Moore TB, Lorenzen TJ, Weg JG, Gross KB. Pulmonary responses of asthmatic and normal subjects to different temperature and humidity conditions in an environmental chamber. *Lung* 1992; 170: 51-62.
122. Arantes-Costa FM, Zoriki S, Santos MH, Kobata CH, Vieira JE, Martins MA. Effects of ventilation, humidity and temperature on airway responsiveness to methacholine in rats. *Eur Respir J* 2002; 19: 1008-14.
123. D'Amato G, Liccardi G, D'Amato M, Cazzola M. Outdoor air pollution, climatic changes and allergic bronchial asthma. *Eur Respir J* 2002; 20: 763-776.
124. D'Amato G, Cecchi L. Effects of climate change on environmental factors in respiratory allergic diseases. *Clin Exp Allergy* 2008; 38: 1264-74.
125. Gordon CJ. Role of environmental stress in the physiological response to chemical toxicants. *Environ Res* 2003; 92: 1-7.
126. Leon LR. Thermoregulatory responses to environmental toxicants: the interaction of thermal stress and toxicant exposure. *Toxicol Appl Pharmacol* 2008; 233: 146-61.
127. Peng RD, Dominici F, Pastor-Barriuso R, et al. Seasonal analyses of air pollution and mortality in 100 US cities. *Am J Epidemiol* 2005; 161: 585-94.
128. Ito K, Thurston GD, Silverman RA. Characterization of PM_{2.5}, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. *J Expo Sci Environ Epidemiol* 2007; 17(Suppl 2): S45-S60.
129. Hetland RB, Cassee FR, Låg M, Refsnes M, Dybing E, Schwarze PE. Cytokine release from alveolar macrophages exposed to ambient particulate

- matter: heterogeneity in relation to size, city and season. *Part Fibre Toxicol* 2005; 2: 4.
130. Stafoggia M, Forastiere F, Michelozzi P, Perucci CA. Summer temperature-related mortality: effect modification by previous winter mortality. *Epidemiology* 2009; 20: 575-83.
131. Keeler GJ, Dvonch T, Yip FY, Parker EA, Isreal BA, Marsik FJ, Morishita M, Barres JA, Robins TG, Brakefield-Caldwell W, Sam M. Assessment of personal and community-level exposures to particulate matter among children with asthma in Detroit, Michigan, as part of Community Action Against Asthma (CAAA). *Environ Health Perspect* 2002; 110(Suppl 2): 173-81.
132. IPCC 2007. Summary for Policymakers. *In: Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*, M.L. Parry, O.F. Canziani, J.P. Palutikof, P.J. van der Linden and C.E. Hanson, Eds., Cambridge University Press, Cambridge, UK, 7-22.
133. Kovats RS, Hajat S. Heat stress and public health: a critical review. *Annu Rev Public Health* 2008; 29: 41-55.
134. Healy JD. Excess winter mortality in Europe: a cross country analysis identifying key risk factors. *J Epidemiol Community Health* 2003; 57: 784-9.
135. Rudge J, Gilchrist R. Excess winter morbidity among older people at risk of cold homes: a population-based study in a London borough. *J Public Health* 2005; 27: 353-8.
136. Wilkinson P, Pattenden S, Armstrong B, Fletcher A, Kovats RS, Mangtani P, McMichael AJ. Vulnerability to winter mortality in elderly people in Britain: population based study. *BMJ* 2004; 329: 647.
137. Donaldson GC, Keatinge WR. Cold related mortality in England and Wales; influence of social class in working and retired age groups. *J Epidemiol Community Health* 2003; 57: 790-1.
138. Zeka A, Zanobetti A, Schwartz J. Individual-level modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol* 2006; 163: 849-59.
139. Forastiere F, Stafoggia M, Berti G, Bisanti L, Cernigliaro A, Chiusolo M, Mallone S, Miglio R, Pandolfi P, Rognoni M, Serinelli M, Tessari R, Vigotti M, Perucci CA; Particulate matter and daily mortality: a case-crossover analysis of individual effect modifiers. *Epidemiology* 2008; 19: 571-80.
140. Ren C, Melly S, Schwartz J. Modifiers of short-term effects of ozone on mortality in eastern Massachusetts--a case-crossover analysis at individual level. *Environ Health* 2010; 9: 3.
141. Medina-Ramón M, Schwartz J. Who is more vulnerable to die from ozone air pollution? *Epidemiology* 2008; 19: 672-9.

142. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007; 370: 765-73.
143. McMichael AJ, Woodruff RE, Hales S. Climate change and human health: present and future risks. *Lancet* 2006; 367: 859-69.
144. Haines A, McMichael AJ, Smith KR, Roberts I, Woodcock J, Markandya A, Armstrong BG, Campbell-Lendrum D, Dangour AD, Davies M, Bruce N, Tonne C, Barrett M, Wilkinson P. Public health benefits of strategies to reduce greenhouse-gas emissions: overview and implications for policy makers. *Lancet*. 2009 Dec 19;374(9707):2104-14. Epub 2009 Nov 26. Review
145. Colette A, Koelemeijer R, Mellios G, Schucht S, Péré J-C, Kouridis C, Bessagnet B, Eerens H, Van Velze K, Rouil L.. Cobenefits of climate and air pollution regulations The context of the European Commission Roadmap for moving to a low carbon economy in 2050. ETC/ACM Technical Paper 2011/20March 2012
146. Benchmarking Working Europe 2012. European Trade Union Institute Brussels, 2012
147. McMichael AJ. The urban environment and health in a world of increasing globalization: issues for developing countries. *Bull World Health Organ* 2000; 78: 1117-26.
148. Forastiere F. Climate change and health: a challenge for epidemiology and public health. *Int J Public Health* 2010; 55: 83-4.

Figure 1. Climate change, its influence on extreme weather events, air pollution and aeroallergens, and effects on respiratory health.

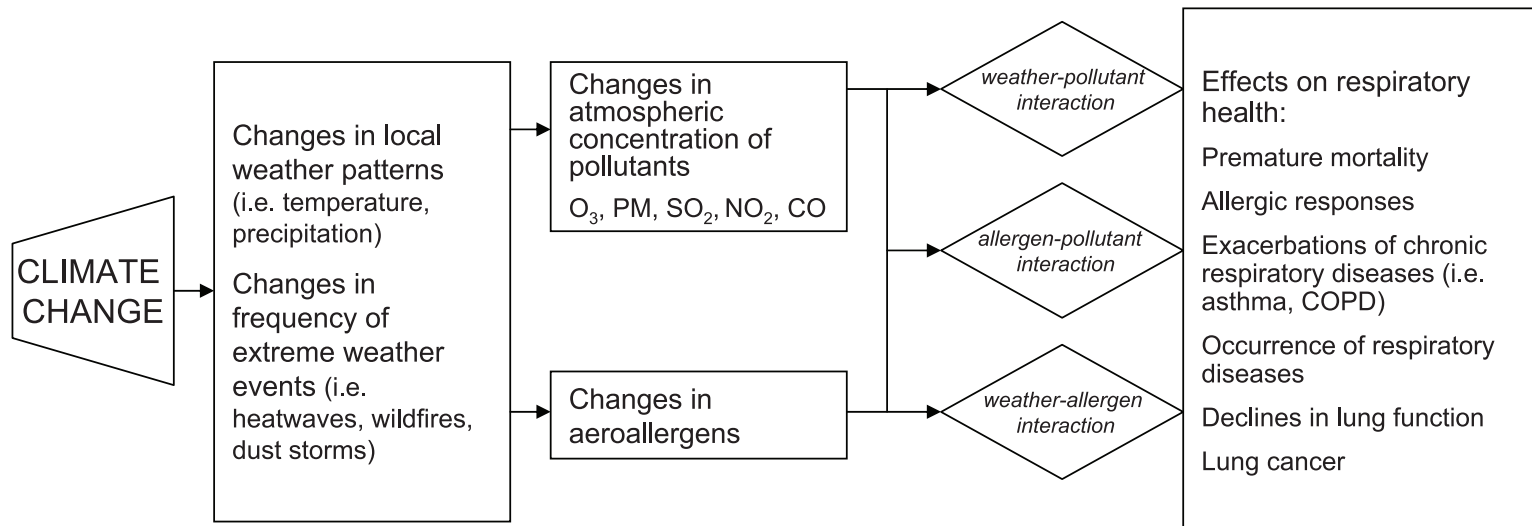


Table 1. Multicentre time-series studies of short-term effects of heat, cold and heat waves on respiratory health in Europe.

Exposure	EU Project	Reference	Number of cities	Population	Temperature indicator (°C)	Health indicator	% change per 1°C increase in Temperature indicator or during heat wave days (95% CI)*	Lag
Heat	PHEWE	Baccini 2008 [39]	15	all ages	Tappmax threshold: 29.4 Mediterranean cities 23.3 North-Continental cities	Respiratory deaths	6.7% (2.4, 11.3%) Mediterranean cities	Lag 0-3
				75+ yr			6.1% (2.5, 11.1%) North-Continental cities	
		Michelozzi 2009 [40]	12	all ages	Tappmax 90 th ptile (range): 19.7, 36.4	Respiratory admissions	2.1% (0.6, 3.6%) Mediterranean cities	Lag 0-3
				75+ yr			1.2% (0.1, 2.2%) North-Continental cities 4.5% (1.9, 7.3%) Mediterranean cities 3.1% (0.8, 5.5%) North-Continental cities	
Heat wave	EuroHEAT	D'Ippoliti 2010 [41]	7	65-74 yr	Tappmax 90 th ptile (range): 27.1, 39.9 [^]	Respiratory deaths	32.4% (14.3, 53.3%) males; 45.8% (22.3, 73.7%) females - Mediterranean cities	no lag
				75-84 yr			16.8% (6.3, 28.1%) males; 12.6% (-0.1, -27.0%) females - North-Continental cities	
				85+ yr			44.8% (30.9, 60.0%) males; 61.3% (44.3, 80.4%) females - Mediterranean cities	
							19.0% (11.0, 27.6%) males; 21.4% (12.9, 30.6%) females - North-Continental cities	
Cold	PHEWE	Analitis 2008 [42]	15	all ages	Tappmin median (range): -5.3, 11.1	Respiratory deaths	2.8% (1.6, 4.0%) Mediterranean cities [°]	Lag 0-15
				15-64 yr			3.7% (2.9, 4.5%) North-Continental cities [°]	
				65-74 yr			3.1% (2.1, 4.1%) [°]	
				75+ yr			3.5% (2.8, 4.3%) [°]	
		Marino 2009 [43]	12	all ages	Tmin mean (range): -0.9, 13.7	Respiratory admissions	-1.6% (-2.5, -0.6%) Mediterranean cities	Lag 0-15
				75+ yr			-2.5% (-3.6, -1.3%) North-Continental cities -2.7% (-3.3, -2.1%) Mediterranean cities -4.1% (-5.7, -2.5%) North-Continental cities	

Mediterranean cities (PHEWE: Athens, Rome, Barcelona, Valencia, Turin, Milan, and Ljubljana; EuroHEAT: Athens, Barcelona, Milan, Rome, and Valencia)

North-Continental cities (PHEWE: Prague, Budapest, Zurich, Paris, Helsinki, Stockholm, London, and Dublin; EuroHEAT: Budapest, London, Munich and Paris)

* 90%CI in D'Ippoliti et al. 2010 [41]

[°] % increase per 1°C decrease in Temperature indicator

[^] study period except summer 2003

Table 2. Interaction of weather variables on air pollution effects: epidemiological studies in European cities published since '90s.

Reference	Country <i>period</i>	Study design	Population	Health indicator	Method to detect interaction	Results
Pattenden 2010 [75]	15 conurbations (UK) <i>Summer 1993-2003</i>	Time-series	All ages	Mortality (total and specific causes)	Interaction terms	Positive interaction of ozone and high temperature, significant only in London
Carder 2008 [78]	Scotland (3 cities) <i>1981-2001</i>	Time-series	All ages	Mortality (total and specific causes)	Interaction terms	No evidence of effect modification by season. Significant positive interaction of black smoke and low temperature on RESP causes
Stafoggia 2008 [54]	Italy (9 cities) <i>1997-2004</i>	Case-crossover	35+ yrs	Mortality (total and specific causes)	Interaction terms; stratification by temperature	Significant positive interaction of PM10 and summer/high temperatures for natural/CVD; heterogeneity for RESP causes
Nawrot 2007 [68]	Flanders (Belgium) <i>1997-2003</i>	Time-series	All ages	Mortality (total and specific causes)	Stratification by season/temperature	Significant positive interaction of PM10 and summer for natural, CVD and RESP causes. Interaction between PM10 and high temperature on effect on total mortality
Filleul 2006 [67]	France (9 cities) <i>Summer 2003</i>	Time-series	All ages	Mortality (total)	Joint response surfaces	Positive interaction of ozone and high temperature heterogeneous among cities
Dear 2005 [66]	France (12 cities) <i>Summer 2003</i>	Episode analysis	All ages	Mortality (total)	Interaction terms	Significant positive interaction of ozone and high temperature
Sartor 1995, 1997 [64, 65]	Belgium, <i>Summer 1994</i>	Episode analysis	65+ yrs	Mortality (total)	Stratification by temperature	Significant positive interaction of ozone and high temperature at levels >20°C
Katsouyanni 1993 [63]	Athens (Greece) <i>Summer 1987</i>	Episode analysis	All ages	Mortality (total)	Interaction terms	Significant positive interaction of SO ₂ and high temperature; suggestive interaction for ozone and smoke

RESP: respiratory

IHD: ischemic heart disease

CVD: cardiovascular

CP: cardiopulmonary (total cardiovascular and respiratory causes)

ED: Emergency Department

EC: Elemental carbon

* Time-series classification and regression tree model

CHF: congestive heart failure

Table 3. Interaction of air pollution on heat/heat waves-related effects: evidence from European studies.

Reference	Country <i>period</i>	Study design	Population	Health indicator	Method to detect interaction	Results
Katsouyanni 2009 [22]	15 EU cities <i>summer 1990-2000</i>	Time-series of temperature	All ages	Mortality (total and specific causes)	stratification by air pollution	Ozone: significant positive interaction with temperature on total mortality: 1.66% vs 2.10% (all ages) (fixed effects model) Black smoke: significant positive interaction with temperature on CVD mortality
Analitis 2012 [79]	9 EU cities <i>summer 1990-2004</i>	Time-series of heat wave days	All ages	Mortality (total and specific causes)	stratification by air pollution	Ozone: significant positive interaction with heat waves in North-Continental cities for natural causes (all ages) and CVD (all ages, 75-84 yrs); no significant interaction for RESP. PM10: significant positive interaction with heat waves for natural causes and CVD (all ages, 75-84, 85+) and for RESP in Mediterranean cities (65-74 yrs)
Katsouyanni 2009 [22]	10 EU cities <i>summer 1990-2004</i>	Time-series of temperature and heat wave days	All ages	Mortality (total and specific causes)	stratification by air pollution	PM10: significant positive interaction with high temperature on all causes and CVD (0-64 yrs, 65+ yrs); suggestion of positive interaction for RESP mortality. Ozone: significant positive interaction with high temperature on all causes. No significant interaction with CVD and RESP. NO ₂ : no significant interaction No evidence of interaction between pollutant and heat wave effect

RESP: respiratory
CVD: cardiovascular

Table 4. Interaction of dust storms on air pollution effects: evidence from European studies.

Reference	Country <i>period</i>	Study design	Population	Health indicator	Method to detect interaction	Results
Middleton 2008 [59]	Nicosia (Cyprus) <i>1995-2004</i>	Time-series	All ages	Hospital admissions (total and specific causes)	Stratification by dust days and PM quartiles	The effects of PM10 on dust-storm days on all-cause and cardiovascular admissions was comparable to the effects seen on non-storm days with the highest PM10 levels. No significant effect on respiratory admissions.
Perez 2008 [96]	Barcelona (Spain) <i>2003-2004</i>	Case-crossover	All ages	Mortality (total causes)	Stratification by dust days; interaction terms	Effect of PM10-2.5 greater during dust days compared with non dust days. No evidence of interaction for PM2.5.
Jimenez 2010 [97]	Madrid (Spain) <i>2003-2005</i>	Time-series	All ages	Mortality (total and specific causes)	Stratification by dust days; interaction terms	Effects of PM10 only on dust days, on all-cause, cardiovascular and respiratory mortality; no effect of PM2.5 or PM10-2.5 on dust days.
Mallone 2011 [98]	Rome (Italy) <i>2001-2004</i>	Case-crossover	All ages	Mortality (total and specific causes)	Stratification by dust days; interaction terms	Effect of PM10-2.5 greater during dust days compared with non dust days for all causes and cardiac causes and diseases of circulatory system; suggestion of positive interaction on respiratory causes. Positive interaction of PM10 with dust days on cardiac mortality. No evidence of interaction for PM2.5.
Samoli 2011a [99]	Athens (Greece) <i>2001-2006</i>	Time-series	All ages	Mortality (total and specific causes)	Stratification by dust days; interaction terms	Effect of PM10 higher in non dust days and essentially null effects during dust days; significant interactions except for respiratory and cardiovascular causes among those <75 years
Samoli 2011b [100]	Athens (Greece) <i>2001-2006</i>	Time-series	All ages	Pediatric asthma emergency admissions	Stratification by dust days; interaction terms	Effects of PM10 greater on dust days compared with non dust days
Tobias 2011 [101]	Madrid (Spain) <i>2003-2005</i>	Case-crossover	All ages	Morbidity (total causes)	Stratification by dust days; interaction terms	Effect of PM10-2.5 greater during dust days compared with non dust days for all causes. No evidence of interaction for PM2.5.
Zauli Sajani 2011 [102]	Emilia-Romagna region (Italy) <i>2002-2006</i>	Case-crossover	All ages	Mortality (total and specific causes)	Stratification by dust days; interaction terms	Evidence of increased respiratory mortality on dust days in hot season in 75+ yrs old, although interaction was not significant. No evidence of effect modification for any season for natural and cardiovascular mortality.
Alessandrini 2012 [103]	Rome (Italy) <i>2001-2004</i>	Case-crossover	All ages	Morbidity (total and specific causes)	Stratification by dust days; interaction terms	Effect of PM10-2.5 greater during dust days compared with non dust days for respiratory causes; suggestion of positive interaction of PM10 on cerebrovascular causes.
Diaz 2012 [104]	Madrid (Spain) <i>2003-2005</i>	Case-crossover	All ages	Morbidity (total and specific causes)	Stratification by dust days; interaction terms	Effect of PM10 greater during dust days compared with non dust days for respiratory causes during cold season,

						for cardiovascular causes during warm season
Perez 2012 [105]	Barcelona (Spain) <i>2003-2007</i>	Case-crossover	All ages	Mortality (total and specific causes)	Stratification by dust days; interaction terms	Effect of PM10-2.5 greater during dust days compared with non dust days for cardiovascular causes; suggestion of positive interaction of PM2.5 during dust days for cardiovascular and respiratory mortality
Thalib 2012 [106]	Kuwait 1996-2000	Time-series	All ages	Respiratory and asthma hospital admissions	Stratification by dust days	Evidence of greater risk for asthma admission in <15 yrs and all ages during the dust days compared with non dust days (lag 0); not significant for older age groups. Effect on respiratory admissions in <15yrs, 15-64 yrs, all ages. No effect on 65+ yrs old.

Table 5. Synthesis of evidence on respiratory outcomes by climate hazard: vulnerable subgroups, research gaps and future impacts

Climate hazard	Study outcomes	Study population groups	Research gaps	21th century impacts under climate change scenarios
High temperature/ heat waves	All respiratory diseases (mortality, HA)	Children, adult, elderly	<ul style="list-style-type: none"> Effect on specific diseases/morbidity outcomes 	<ul style="list-style-type: none"> Increase in effects due to the higher frequency of hot extremes and heat waves Reduced effects due to change in adaptive capacity of populations Increasing in vulnerable population due to aging, also in developing countries Increasing in vulnerable population due to increasing prevalence of chronic respiratory diseases in industrialized countries Change in heat-related effects in different socio-economic scenarios Increase in infectious diseases in children under 5 in developing countries
	Pneumonia (mortality, HA, geriatric admissions)	Adult, elderly	<ul style="list-style-type: none"> Effect on children and young age groups Effect on low socio economic subgroups 	
	COPD (mortality, HA)	Elderly	<ul style="list-style-type: none"> Short and long-term harvesting effect 	
	Asthma (mortality, HA, prevalence)	Children, adult	<ul style="list-style-type: none"> Population health impacts Pathogenetic mechanisms 	
Cold temperature/ cold spells	All respiratory diseases (mortality, HA, GPs visits)	Children, adult, elderly	<ul style="list-style-type: none"> Effect on specific diseases/morbidity outcomes 	<ul style="list-style-type: none"> Reduced cold-related effects due to warmer winters in industrialized countries Increasing in vulnerable population due to aging, also in developing countries Increasing in vulnerable population due to prevalence of chronic respiratory diseases in industrialized countries
	Lower respiratory tract disease (mortality, GPs visits)	Elderly	<ul style="list-style-type: none"> Effect on younger age groups Effect on low socio economic subgroups 	
	Asthma (ED visits, GPs visits)	Children, adult	<ul style="list-style-type: none"> To identify vulnerability factors (i.e. indoor) 	
	Upper respiratory tract disease (GPs visits)	Elderly	<ul style="list-style-type: none"> Effect on populations where cold spells are rare Population health impacts 	
Wildfires	All respiratory diseases (mortality, HA/rehospitalization, GPs visits, ED visits)	Children, elderly	<ul style="list-style-type: none"> To identify vulnerability factors Evidence from European studies Evidence from multicentre studies 	<ul style="list-style-type: none"> Increase in effects due to the higher frequency of wildfires Increase in long-range transport of air pollutants due to changes in wind patterns and to increases in desertification Increasing in vulnerable population due to aging, also in developing countries Increasing in vulnerable population due to prevalence of chronic respiratory diseases in industrialized countries
	Asthma (ED visits, outpatient attendance, decreases lung function, asthma symptoms)	Children, adults, asthmatics	<ul style="list-style-type: none"> Interaction with urban air pollution Interaction with heat waves Population health impacts 	
	Upper respiratory tract disease (outpatient attendance, respiratory symptoms)	Children	<ul style="list-style-type: none"> Pathogenetic mechanism 	
	COPD (ED visits, HA, exacerbation of symptoms)	Adult, elderly, COPD patients		
	Lower respiratory tract disease (hospital admissions, emergency room visits)	Children, elderly		
Dust storms	All respiratory diseases (mortality, HA, ED visits)	Children, adult, elderly	<ul style="list-style-type: none"> Effect on specific diseases/morbidity outcomes 	<ul style="list-style-type: none"> Increase in long-range transport of air pollutants due to changes in wind patterns and to increases in desertification Increasing in vulnerable population due to aging, also in developing countries Increasing in vulnerable population due to prevalence of chronic respiratory diseases in industrialized countries Increase in infectious diseases in children under 5 in developing countries
	COPD (ED visits, HA)	Elderly	<ul style="list-style-type: none"> Evidence from multicentre studies 	
	Asthma (mortality, pediatric admissions, HA, ED visits, decreases lung function, asthma exacerbations)	Children, adults, asthmatics	<ul style="list-style-type: none"> Evidence from studies in areas most exposed To identify vulnerability factors 	
	Pneumonia (HA)	Children, adult, elderly	<ul style="list-style-type: none"> Interaction with weather conditions Effect of consecutive days of dust storms 	
	Rhinitis (HA, clinical visits)	Children	<ul style="list-style-type: none"> Evidence particles chemical composition 	

			<ul style="list-style-type: none"> ▪ Population health impacts ▪ Toxicological and pathogenetic mechanisms 	
Temperature -pollutant interaction	All respiratory diseases (mortality, HA, ED visits) Asthma (ED visits)	Adult, elderly Children	<ul style="list-style-type: none"> ▪ Interaction between air pollutants and cold temperature ▪ Interaction of temperature on specific pollutants ▪ Effect on specific diseases/morbidity outcomes ▪ Pathogenetic mechanisms 	<ul style="list-style-type: none"> ▪ Increase potential for interaction due to increases in specific pollutants and in the frequency of hot extremes and heat waves

HA: Hospital admissions
ED: Emergency Room
GPs: General Practitioners
COPD: Chronic Obstructive Pulmonary Disease

