Respiratory Medicine (2015) 109, 1089–1104

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW ARTICLE

Allergy and asthma: Effects of the exposure to particulate matter and biological allergens

S. Baldacci [a,*,1], S. Maio [a,1], S. Cerrai [a], G. Sarno [a], N. Baïz [b,c], M. Simoni [a], I. Annesi-Maesano [b,c,2], G. Viegi [a,2] on behalf of the HEALS Study

[a] Pulmonary Environmental Epidemiology Unit, Institute of Clinical Physiology, CNR, Pisa, Italy
[b] Sorbonne Universités, UPMC Univ Paris 06, UMR-S 1136, Institute Pierre Louis of Epidémiology and Public Health, Epidemiology of Allergic and Respiratory Diseases Department, Paris, France
[c] INSERM, UMR-S 1136, IPLESP, EPAR Department, Paris, France

Received 22 December 2014; received in revised form 8 May 2015; accepted 19 May 2015
Available online 22 May 2015

KEYWORDS
Particulate matter;
Biological allergens;
Allergic diseases;
Asthma

Abstract
The prevalence of asthma and allergies including atopy has increased during the past decades, particularly in westernized countries. The rapid rise in the prevalence of such diseases cannot be explained by genetic factors alone. Rapid urbanization and industrialization throughout the world have increased air pollution and population exposures, so that most epidemiologic studies are focusing on possible links between air pollution and respiratory diseases. Furthermore, a growing body of evidence shows that chemical air pollution may interact with airborne allergens enhancing the risk of atopic sensitization and exacerbation of symptoms in sensitized subjects. These phenomena are supported by current *in vitro* and animal studies showing that the combined exposure to air pollutants and allergens may have a synergistic or additive effect on asthma and allergies, although there is an insufficient evidence about this link at the population level.

Further research is needed in order to elucidate the mechanisms by which pollutants and biological allergens induce damage in exposed subjects.

The abatement of the main risk factors for asthma and allergic diseases may achieve huge health benefits. Thus, it is important to raise awareness of respiratory allergies as serious chronic diseases which place a heavy burden on patients and on society as a whole.

* Corresponding author. Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology, Via Trieste 41, 56126 Pisa, Italy.
E-mail address: baldas@ifc.cnr.it (S. Baldacci).
[1] Denotes equal first author contribution.
[2] Denotes equal last author contribution.

http://dx.doi.org/10.1016/j.rmed.2015.05.017
0954-6111/

Contents

1. Introduction

The prevalence of asthma and allergies has increased during the past decades, particularly in westernized countries [1,2]. The rapid rise in the prevalence of these diseases since the '60s cannot be explained by genetic factors alone [3]. Rapid urbanization and industrialization have increased air pollution and population exposures, thus most epidemiologic studies focus on possible links between air pollution and respiratory diseases [1,4,5]. Exposure to particulate matter (PM) may drive to reduced lung function, lower airways inflammation and upper airways irritation [6], as well as asthma hospital admissions, asthma incidence, asthma exacerbations, respiratory allergy/hay fever and bronchodilator usage [1]. Exposure to biological allergens may produce respiratory infections, sensitisation, respiratory allergic diseases and wheezing [7–9]. A growing body of evidence shows that chemical air pollution may interact with airborne allergens enhancing risk of atopic sensitization and exacerbation of symptoms in sensitized subjects and of asthma and asthma-like symptoms [10–13]. Current *in vitro* and animal studies showed that the combined exposure to air pollutants and allergens may have a synergistic effect on asthma and allergies, although there is still an insufficient knowledge about this link at the population level [14].

The specific aim of the present review is to gather recent evidences concerning the relationship between exposure to PM, biological allergens and allergic diseases.

2. Indoor and outdoor pollution sources

Worldwide, the main sources of outdoor pollutants are fuel combustion from vehicular transportation, construction and agricultural operations, power plants and industries. Primary pollutants coming from these sources are: carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and polycyclic aromatic hydrocarbons (PAHs). Ozone (O_3) is classified as secondary pollutant since it is formed by reaction between NO_2 and volatile organic compounds (VOCs) in the presence of heat and sunlight. PM can be either primary PM or formed from gaseous precursors (secondary PM), mainly SO_2, oxides of nitrogen (NO_x), ammonia (NH_3) and non-methane volatile organic compounds (NMVOCs) [15].

Indoor environment is also an important source of health risk factors, particularly considering that most people spend more than 90% of their time indoors [16]. The indoor environment quality depends on the air that penetrates from outdoor and on the presence of indoor air pollution sources. To improve energy efficiency, modern dwellings are often thermally insulated and scarcely ventilated, possibly resulting in deterioration of the air quality. Moreover, indoor environment is influenced by building systems, construction techniques, contaminant sources and occupants' behavior. The most frequently investigated risk factors for indoor pollution are Environmental Tobacco Smoke (ETS), biomass fuel, cleaning products and biological

allergens [1]. The main air pollutants are CO, carbon dioxide (CO_2), NO_2, SO_2, VOCs, phthalates, formaldehyde, PM and PAHs.

2.1. Particulate matter (PM)

PM is a mixture of solid and liquid particles suspended in air and it can have different sizes, shapes and chemical composition; it is divided into different categories depending on the aerodynamic diameter of the particles (Fig. 1): PM_{10} with an aerodynamic diameter of $\leq$10 μm; $PM_{2.5}$ with a diameter of $\leq$2.5 μm; $PM_{0.1}$ with a diameter of $\leq$0.1 μm. The particle size influences the capability of the PM to penetrate deeply in the lung (Table 1) [15]. Primary and secondary PM present in atmosphere can be transported over long distances and their removal may occur via rainfall, gravitational sedimentation or coagulation with other particles.

2.2. Biological allergens

Allergens are antigens that react with specific Immunoglobulin E (IgE) antibodies, inducing an allergic state. They originate from a wide range of animals, insects, mites, plants, or fungi [17,18]. Indoor allergens are mainly originated from house dust mites, furred pets (primarily cat and dog dander), cockroaches, moulds, plants and rodents [7]. Primary sources for outdoor allergens include plants, fungi, molds and yeasts [18] (Table 2).

Airborne biological particles are released from sources into the air by wind, rain, mechanical disturbance, or active discharge mechanisms; once particles have been launched into the air, their concentration decreases with increasing distance from the point of liberation. Particle dispersion is largely dependent on air mass movement, turbulence and thermal convection following the physical laws that apply to all airborne particulate [19].

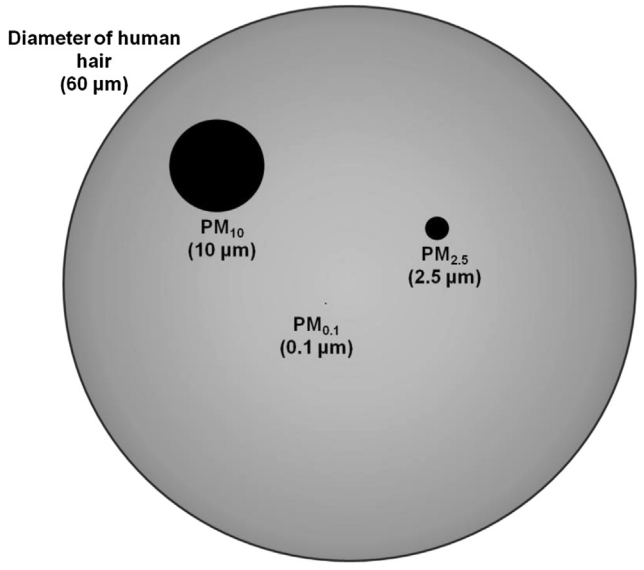

Fig. 1 Dimensional comparison between PM and human hair.

2.2.1. House dust

It is composed of organic and inorganic substances, including fibers, mold spores, pollens, insects and insect feces, mites and mite feces [20,21]. The principal domestic mite species, *Dermatophagoides* and *Euroglyphus*, are particularly abundant in mattresses, pillows, carpets or fluffy toys and proliferate in warm (above 20 °C) and humid conditions [18].

2.2.2. Pets

Cats and dogs are important sources of indoor allergens, released through secretions, excretions and danders [20,21]. The major cat allergen, *Fel d1*, is transported in the air by particles >2.5 μm and can remain airborne for long periods [18]. Dogs produce two important allergenic proteins, *Can f1* and *Can f2*, similar to those of cat allergens [20,21].

2.2.3. Cockroaches

Of the 4500 species of cockroach 4 are known to be pests: *Blatta orientalis*, *Blattella germanica*, *Periplaneta americana* and *Supella longipalpa*. Even though most of the studies on cockroaches and asthma have focused on inner-city environments, cockroaches can also be found in buildings located in suburban and rural environments, regardless of the socioeconomic status of occupants [22]. The main allergens (*Per a1*, *Bla g1*, and *Bla g2)* have been frequently found in floor dust, kitchen cabinets, bathrooms and basements [21].

2.2.4. Mould/dampness

Major indoor sources of mould growth are flood, leaks, condensation, and household moulds. They can also grow in aeration/conditioning ducts and water pipes. Microscopic fungi in homes are capable of producing spores all year round and are responsible for persistent symptoms. Moulds also grow on plants or on animal/vegetable waste, furnishings, wallpaper, mattress dust and fluffy toys [18].

2.2.5. Fungi

Fungi and yeasts can be both indoor and outdoor airborne allergens. Indoor fungi can grow in dark, humid, and poorly ventilated areas and within the cooling, heating, and humidification systems. Outdoor fungi tend to release seasonal allergens [20,21]. The most commonly studied allergenic fungi are *Alternaria*, *Aspergillus*, *Botrytis*, *Cladosporium*, *Epicoccum*, *Fusarium* and *Penicillium* [23].

2.2.6. Pollens

Pollen allergens come mainly from trees, grasses and weeds and their air concentrations varies with location and atmospheric conditions [20,21]. Common plants causing allergy in humans belong to the family Gramineae, Betulaceae, Corylaceae, Fagaceae, Oleaceae, Cupressaceae, Urticaceae, Compositae. In the last decades, the increased use of ornamental plants in parks and gardens, public and work places and houses provided new sources of aeroallergens [24].

Table 1 Main characteristics and sources of PM.

PM fraction	Characteristics	Sources
PM_{10} (*Inhalable PM*)	PM_{10} has a diameter $\leq$ 10 μm and it is able to penetrate into the upper respiratory tract (nose, throat and larynx).	*Outdoor*
$PM_{10-2.5}$ (*Coarse particles*)	$PM_{10-2.5}$ has a diameter ranging from 2.5 to 10 μm and it is able to penetrate into the upper respiratory tract (nose, throat and larynx).	• Vehicular traffic • Organic matter and fossil fuel combustion
$PM_{2.5}$ (*Fine PM*)	$PM_{2.5}$ has a diameter $\leq$ 2.5 μm and it is able to penetrate into the tracheobronchial tract (trachea, bronchi, bronchioli).	• Power stations/industry • Marine aerosol
$PM_{0.1}$ (*Ultrafine PM*)	$PM_{0.1}$ has a diameter $\leq$ 0.1 μm and it is able to penetrate into alveolar region.	• Soil erosion • Volcanic eruptions • Windblown dust from roadways, agriculture and construction • Bushfires/dust storms
		Indoor
		• Woodstoves • Organic matter and fossil fuel combustion for heating/cooking • ETS

ETS: environmental tobacco smoke.

3. Burden of asthma and allergic diseases

A wide variety of mechanisms are associated with allergic diseases, but an IgE-mediated reaction is the most frequent underlying trigger [25]. Currently, more than 25% of the European population is affected by IgE-associated allergic diseases [26]. The highest prevalence occurs in late adolescence/early adulthood.

Different manifestations of allergic diseases involve respiratory system (rhinoconjunctivitis, asthma), skin (atopic eczema, dermatitis), and gastrointestinal tract (food allergy and eosinophilic gastroenteritis) and may have systemic manifestations (anaphylactic shock) [25].

The sequential development of allergic disease manifestations during early childhood is often referred to as the "allergy march". Epidemiological and birth-cohort studies have begun to elucidate the effects of environmental factors and genetic predisposition on the "allergy march". Food allergy often precedes inhalant allergen allergy. Atopic dermatitis and asthma are linked in the "allergy march", but atopic dermatitis does not necessarily precede asthma, whereas allergic rhinitis is a risk factor for asthma [27].

Table 2 Main biological pollutants and their sources.

Sources	Allergens
Dust, beds, carpets	House dust mites
Pets, birds, insects, rodents	Specific allergens (i.e. Fel d1)
Cockroaches	Specific allergens (i.e. Bla g1)
Dampness	Moulds
Plants	Pollens
Virus, bacteria	Biological contaminants

Allergic rhinitis and asthma, the two principal closely related allergic diseases, significantly reduce the quality of life (QoL) and have a wide economic impact on patient, patient's family and society as a whole [28].

3.1. Asthma

More than 300 million people worldwide are affected by asthma [29] and asthma accounts for about 250,000 annual deaths worldwide with large differences between countries [20]. In Europe asthma affects about 30 million among children and adults under 45 yrs age, with a prevalence ranging from 3% to more than 9% in northern and western countries among 18—44 yrs adults [30]. Some European prevalence rates of diagnosed asthma are reported in Fig. 2.

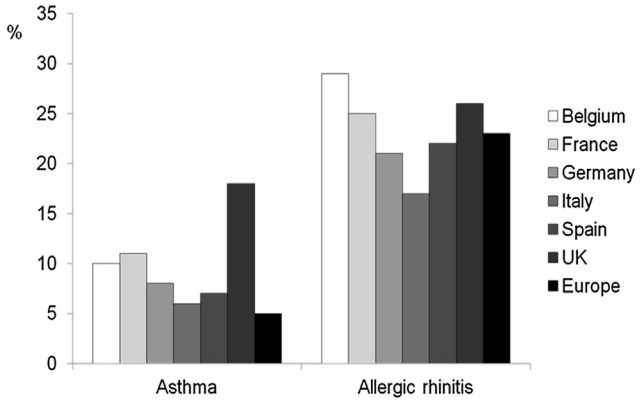

Fig. 2 Prevalence rates of asthma and allergic rhinitis in Europe (modified from [34] and [29]).

The prevalence of asthma increased worldwide in the second half of the last century until the 1990s, but since then, there has been no clear temporal pattern [31]. Although improved treatment efficiency, asthma prevalence continues to increase, particularly in low- and middle-income countries, or in some ethnic groups [32] as communities adopt modern lifestyles and become urbanized. It is estimated that there may be an additional 100 million people with asthma by 2025 [33,34]. In Italy, asthma prevalence has increased by 38% during the past 20 yrs [31]. The ISAAC (International Study of Asthma and Allergies in Childhood) study Phase Three (1999–2004) found an increasing trend in the prevalence of asthma and allergies particularly in urban areas [35].

European and USA studies indicate that about 33% of school age children with asthma may be undiagnosed. Adults and the elderly are also frequently undiagnosed. Thus, asthma is often undertreated and this may lead on to exacerbation and poor QoL [36].

Epidemiological studies have shown that rhinitis coexists in 70% of people with asthma [20]. Moreover, allergic rhinitis is a risk factor for asthma [36], such as active smoke [37] and obesity [38].

3.2. Allergic rhinitis

Hay fever characteristically occurs in three phases: sensitization, early phase reaction, and late phase reaction. The early phase reaction is initiated within minutes of a sensitized person becoming exposed to an antigen and produces the early symptoms of allergic rhinitis, including sneezing, itching and rhinorrhea. In the late phase reaction, early symptoms characteristically shift to nasal congestion and obstruction [39].

Nasal congestion is an important factor contributing to the impairment of study/work performance, since it disturbs sleep causing daytime fatigue [39]. The prevalence of allergic rhinitis ranges from 17% to 29% in Europe (Fig. 2). A conservative estimate proposes that allergic rhinitis occurs in approximately 500 million people. About 200 million people have asthma as a comorbidity [29], suggesting the concept of 'one airway one disease' [40]. However, not all patients with rhinitis have asthma and there are differences between rhinitis and asthma [29].

The worldwide incidence and prevalence of allergic rhinitis has been increasing since at least 1990 in almost all westernized countries. Increasing air pollution, indoor environment, improved hygiene practices, climatic changes could be the cause of this upward trend [31]. In Italy, from 1991 to 2010, the prevalence of allergic rhinitis increased continuously moving from 16.8% to 25.8% [31].

4. Environmental risk factors for asthma and allergic diseases

The causal link between exposure to air pollutants/allergens and allergic conditions is still debated despite its biological plausibility. The exposure-response relationship is complex, depending on several factors, such as genetic susceptibility or gene–environment interaction [4]. Even though respiratory allergic diseases show strong familial association, their rapid rise in prevalence occurred in recent decades cannot be explained by genetic factors alone [41]. Allergic diseases are more common in highly developed countries thus suggesting that urban life promotes allergy. Indeed, the susceptibility to allergens may increase in presence of chemicals and aerosols [41], or PM [42].

The present review will take into account PM, airborne perennial allergens (house dust mites, pets, cockroach), pollens and moulds/dampness as major risk factors.

4.1. Link with PM and PM sources

Considering that vast majority of European population lives in urban areas where PM levels exceed the WHO 2005 Air Quality Standards [43], and that there is no evidence of a safe level of exposure [44], pollution derived from PM creates a remarkable burden of disease.

Recently, the use of a dispersion model for estimating exposure to outdoor air pollution showed that lifetime allergic rhinitis was associated with PM_{10}, and sensitization against pollen with benzene and PM_{10} in a sample of French children [45]. In a cohort of children living in 6 French cities, an association between asthma, especially if atopic, and dwellings in areas with a concentration of $PM_{2.5}$>10 $\mu g/m^3$ was shown [46] (Table 3). These results were also confirmed in the multicentric Traffic, Asthma, and Genetics (TAG) study carried out on 6 birth-cohorts, showing a significant association between $PM_{2.5}$ and allergic rhinitis at 7–8 years of age (OR 1.37 per 5 $\mu g/m^3$ $PM_{2.5}$ mass concentration) [47] (Table 3).

Nanosize pollutants seem to have more aggressive implications than other breathable fractions of urban aerosol, both at respiratory and at molecular level: ultrafine particles (UfPs, PM $<$ 0.1 μm) can lead molecular changes and are proposed to represent the subclinical effects that manifest disease exacerbations or subjects' predisposition to pathologies onset [48].

Indoor exposure to $PM_{2.5}$ confirmed the same relationship with asthma and asthma symptoms. In two Italian general population samples, high indoor levels of $PM_{2.5}$ were associated with bronchial and asthmatic symptoms [49] (Table 3). In the 6 French cities study, a significant increased prevalence of past year asthma in the classrooms with high levels of $PM_{2.5}$ was shown (OR 1.21) (Table 3), particularly for allergic asthma (OR 1.42). A significant positive correlation was found between exercise-induced asthma and levels of $PM_{2.5}$ and acrolein in the same week [50].

Living in close proximity to PM sources like roads with high traffic density was shown to be a carrier factor for increased allergic symptoms, reduced lung function, increased sensitization to common aeroallergens [51–53]. In an Italian general population sample it was demonstrated that people living within 100 m of heavy traffic roads showed an increased adjusted risk for persistent wheeze and reduced forced expiratory volume in the first second/forced vital capacity ratio (FEV_1/FVC) in males and for positivity to skin prick test, asthma diagnosis and attacks of shortness of breath with wheeze among females [53] (Table 3). A significant association between heavy traffic on the street of residence and asthma and rhinoconjunctivitis was shown in a sample of adolescents (10–17 yrs)

Table 3 Link between allergic diseases and PM, PM sources.

Study	Country (n, sample)	Exposure	Health outcome	Measures
Annesi-Maesano I, 2007 [46]	France (5338, schoolchildren)	Outdoor $PM_{2.5}$> 10 μg/m^3		OR (95% CI):
			Asthma	1.3 (1.0—1.7)
			Atopic asthma	1.6 (1.2—2.1)
Fuertes E, 2013 [47]	Canada, Germany, Swiss, Netherlands[a] (15,299, children)	Outdoor $PM_{2.5}$ mass concentration		OR (95% CI) per 5 μg/m^3 increase:
			Allergic rhinitis	1.4 (1.0—1.9)
Simoni M, 2004 [49]	Italy (1090, adults)	Indoor $PM_{2.5}$		OR (95% CI):
			Bronchitic/asthmatic symptoms	1.4 (1.2—1.7)
Annesi-Maesano I, 2012 [50]	France (6590, schoolchildren)	Indoor $PM_{2.5}$		OR (95% CI):
			Past year asthma	1.2 (1.1—1.4)
Nuvolone D, 2011 [53]	Italy (2061, adults)	Living within 100 m of heavy traffic roads		OR (95% CI):
			Males	
			Persistent wheeze	1.8 (1.1—2.9)
			FEV_1/FVC	2.1 (1.1—3.9)
			Females	
			positivity to SPT	1.8 (1.1—3.0)
			asthma diagnosis	1.7 (1.0—2.9)
			attacks of wheeze[b]	1.7 (1.0—2.8)
Cibella F, 2011 [54]	Italy (2150, adolescents)	Heavy traffic on the street of residence		OR (95% CI):
			Asthma	1.8 (1.1—2.3)
			Rhinoconjunctivitis	1.4 (1.1—1.8)
Robinson CL, 2011 [55]	Peru (1441, adolescents)	Peri-urban environment		OR (95% CI):
			Asthma	2.6 (1.3—5.3)
Agrawal S, 2012 [63]	India (156,316, adults)	Living in households using biomass and solid fuels		OR (95% CI):
			Females	
		Combined effects of biomass and solid fuel use and tobacco smoke	Asthma	1.3 (1.1—1.5)
			Females	
			Asthma	2.2 (1.6—2.9)
			Males	
			Asthma	1.3 (1.0—1.7)
Simoni M, 2007 [64]	Italy (women, never smoker)	ETS		OR (95% CI):
			Wheeze	1.7 (1.0—2.8)
			Attacks of wheeze[b]	1.9 (1.1—3.3)
			Asthma	1.5 (1.1—2.1)
			Rhino-conjunctivitis	1.5 (1.1—1.9)
Jones LL, 2011 [66]	Meta-analysis (infants)	ETS by both parents		OR (95% CI):
			LRI	1.6 (1.4—1.9)
Graif Y, 2013 [65]	Israel (10,298, schoolchildren)	ETS at home		OR (95% CI):
			Asthma	1.3 (1.1—1.5)

$PM_{2.5}$: particulate matter with aerodynamic diameter $\leq$ 2.5 μm; FEV_1/FVC: forced expiratory volume in the first second/forced vital capacity; SPT: skin prick test; OR: odds ratio; 95% CI: 95% confidence intervals; ETS: environmental tobacco smoke; LRI: lower respiratory infections.

[a] 6 birth-cohorts from CAPPS, SAGE, BAMSE, GINIplus, LISAplus and PIAMA studies.

[b] Attacks of shortness of breath with wheeze.

living in Palermo [54] (Table 3). A recent survey carried out in Peru demonstrated how adolescents living in peri-urban setting presented a higher prevalence of asthma (13% vs 2%) and atopy (56% vs 38%) with respect to less polluted rural setting, and peri-urban environment was associated with a 2.6-fold greater odds of asthma [55] (Table 3).

Acute episodes of air pollution are clearly associated with exacerbation of respiratory symptoms and allergic events [56,57], particularly in subjects with airway diseases [58].

Worldwide, the huge use of biomass for heating, cooking and lighting, raises a particular concern and it becomes the main source of indoor PM exposure. Over two million people rely on biomass fuels to supply their household energy needs, with an estimated 3.5 million deaths annually being attributable to biomass smoke exposure [59]. Several studies have validated the association between biomass smoke exposure and respiratory diseases [60,61], even though no significant association has been found with atopic dermatitis in the ISAAC study [62]. A recent Indian study has shown that the indoor use of biomass and solid fuels is associated with a significantly higher risk of asthma for adult women [63] (Table 3).

In indoor environments frequented by smokers, tobacco smoke is the major source of PM, accounting for as much as 50–90% of the total indoor PM concentration. ETS is linked to several acute and long-term adverse respiratory effects. Some studies showed that women are at higher risk for ETS exposure than men: living with smokers has been related to asthma, attacks of shortness of breath with wheeze, wheeze, current phlegm/cough and rhinoconjunctivitis [64] (Table 3). A dose–response association study on 10,298 schoolchildren confirmed that exposure to ETS at home was significantly associated with asthma [65] (Table 3) and smoking by both parents increases the risk of lower respiratory infections (LRI) in infants [66] (Table 3).

Recent epigenetic studies have shown that the exposure to environmental factors (pollution and ETS) during early childhood, may induce a long-lasting altered genetic state, adapting to a persistent "Th2 state", thus influencing the development of asthma or atopic dermatitis [67].

Few reduction studies demonstrated how PM abatement can decrease the respiratory health risk and improve health conditions in asthmatic subjects. In a randomized controlled study, a significant reduction in indoor PM concentrations and a significant increase in symptom-free days in children with asthma were associated [68]. Some unplanned events of PM concentration decrease had a positive impact on health: the closure and reopening of a steel mill in Utah Valley, in 1986-87, resulted in a 3-fold lower prevalence of children hospital admission for bronchitis and asthma [69]; in the Swiss Study on Childhood Allergy and Respiratory Symptoms with respect to Air Pollution, Climate and Pollen, the falling levels of regional PM_{10} between 1992 and 2001 were associated with a declining prevalence of bronchitis, nocturnal dry cough and conjunctivitis symptoms [70]. Within the Swiss study on Air Pollution and Lung Disease in adults (SAPALDIA) an association between a reduced exposure to PM_{10} and an attenuated age-related lung function decline has been found [71]. The results from the extended follow-up of the Harvard Six Cities Study showed that an improved respiratory mortality was associated with a 10 $\mu g/m^3$ reduction of $PM_{2.5}$ (RR, 0.43; 95% CI, 0.16–1.13) [72].

Finally, although PM exposure and the associated respiratory and allergic risks are a concern pertaining to all people, the impact of this hazard is higher for susceptible populations, such as women and elderly subjects, who spend most of their daily-time indoor, subjects presenting pre-existent comorbidities and children, who have a morpho-structural immaturity and an underdeveloped immune defense system.

Overall, the available evidence suggests a causal association between long- and short-term PM exposure and respiratory morbidity. Further researches are still needed to fully understand how PM affects human health. While regional exposure data has become standard for PM epidemiology, studies with true individual exposure have still to be fully realized [73].

4.2. Link with biological allergens

In developed countries homes have been insulated for energy efficiency, thus creating an ideal habitat for indoor allergens [21] cause of respiratory allergic diseases.

4.2.1. House dust mites (HDM)

House dust mites have been epidemiologically associated with asthma development and exacerbations and with allergic rhinitis. In a US birth-cohort, early exposure to $\geq$10 $\mu g/g$ levels of dust mite allergens was associated with increased risk of asthma and wheeze at age 7; lower levels ($\geq$2 to $<$10 $\mu g/g$) were associated with increased risk of allergic rhinitis [74] (Table 4). Early-life exposure to carpet in dwelling was associated with early-onset asthma and ever-having asthma in Taiwan children; the study showed higher risks considering the presence of carpet in the children's bedroom [12] (Table 4). A study on an Ethiopian general population sample showed an elevated association between dust mites exposure and asthma and wheeze in the past year [75] (Table 4).

Continuous exposure to HDM may contribute to chronic bronchial hyper-responsiveness [76] (Table 4) and to pulmonary function reduction [77]; data from the European Respiratory Community Health Survey (ECRHS) have indicated that asthmatic subjects, sensitized to mites, had a lower FEV_1 and FEV_1/FVC ratio than non-sensitized asthmatics [77].

In the Chinese sample of the ISAAC study an increasing sensitization to dust mites was associated with the increased prevalence of wheeze; high degrees of sensitization were risk factors for asthma diagnosis (OR 3.44, 1.75–6.41) [78]. A German longitudinal study evaluated the predictive value of sensitization to common aeroallergens on the incidence of asthma and hay fever in children over 9 years: previous sensitization to *Dermatophagoides* was associated with hay fever incidence (relative risk- RR 2.51, 1.63–3.87) [79].

4.2.2. Pets

The ARIA guideline on allergic rhinitis reports cats and dogs as major allergens triggers in asthma, rhinitis or rhinoconjunctivitis [28]; nevertheless, contradictory results were found in the literature.

A Swedish study on an adult population sample showed an association between keeping a dog in childhood, and grade 2 dyspnoea in adulthood, as well as between keeping a cat in childhood, and attacks of dyspnoea in adulthood [80] (Fig. 3).

The Italian SIDRIA-2 Study (Italian studies on Respiratory Disorders in Childhood and the Environment) showed that cat, but not dog, exposure in the first year of life was significantly and independently associated with wheezing (OR 1.88, 1.33–2.68) and current asthma (OR 1.74, 1.10–2.78) at 7 years of age [81] (Fig. 3). Differently, a Taiwan study showed a significant association between early-life dog exposure and early asthma onset (before 5 yrs old) (OR 2.40, 1.15–5.01); the same association was found considering exposure to any pet (OR 2.50, 1.26–4.98) [12] (Fig. 3). The 9 years German longitudinal study showed associations between incident asthma, hay fever and previous sensitization to cat (RR 3.49, 1.57–7.74; RR 5.36, 2.87–9.99, respectively) [79]. On the other hand, other scientific evidences seem to suggest that intensive exposure to cat in early childhood may have a protective effect for developing asthma [82,83] and prevent allergen sensitization [84] (Fig. 3).

Table 4 Link between allergic diseases and biological allergens.

Study	Country (n, sample)	Exposure	Health outcome	Measures
Wong GW, 2002 [76]	China (608, children)	House dust mites		OR (95% CI):
			Bronchial hyper-responsiveness	3.7 (1.9–6.9)
Davey, 2005 [75]	Ethiopia (7649, general population)	House dust mites		OR (95% CI):
			Wheeze	1.2 (1.0–1.5)
			Asthma	4.1 (2.9–5.8)
Celedon JC, 2007 [74]	US (440, children)	House dust mites:		OR (95% CI):
		high levels	Wheeze	5.0 (1.5–16.4)
		low levels	Asthma	3.0 (1.1–7.9)
			Allergic rhinitis	3.2 (1.5–7.0)
Chen Y–C, 2011 [12]	Taiwan (579, children)	Carpet in house		OR (95% CI):
		Carpet in children's bedroom	Early-onset asthma	2.9 (1.5–5.6)
			Ever-having asthma	2.4 (1.4–4.1)
			Early-onset asthma	3.5 (1.4–8.4)
			Ever-having asthma	2.7 (1.3–5.6)
Silva JM, 2005 [88]	Brazil (73, children)	Cockroach		OR (95% CI):
			Wheeze	7.6 (1.4–4.1)
Davey G, 2005 [75]	Ethiopia (7649, general population)	Cockroach		OR (95% CI):
			Wheeze	1.3 (1.0–1.6)
Chen Y–C, 2011 [12]	Taiwan (579, children)	Cockroach		OR (95% CI):
			Early-onset asthma	2.3 (1.0–4.9)
			Ever-having asthma	2.2 (1.2–4.1)
Fisk WJ, 2007 [95]	Meta-analysis (children) (general population)	Mould/dampness		OR (95% CI):
			Wheeze	1.5 (1.4–1.7)
			Current asthma	1.6 (1.3–1.9)
			Wheeze	1.5 (1.4–1.6)
Pirastu R, 2009 [96]	Italy (4122, children)	Mould/dampness lifetime exposure		OR (95% CI):
		Mould/dampness current exposure	Current wheeze	2.4 (1.6–3.7)
			Current wheeze	1.9 (1.3–2.9)
Nguyen T, 2010 [13]	New York States (1412, children) (3315, adults)	Mould		OR (95% CI):
			Current asthma	2.1 (1.3–3.3)
			Current asthma	2.5 (1.8–3.4)
Chen Y–C, 2011 [12]	Taiwan (579, children)	Mould odor		OR (95% CI):
		early-life exposure	Late-onset asthma	3.2 (1.3–7.5)
		Visible mould	Ever having asthma	1.8 (1.2–2.7)
		early-life exposure		
Erbas B, 2013 [11]	Australia (620, children)	Pollens		OR (95% CI):
			Hay fever	1.1 (1.0–1.3)
			Asthma	1.4 (1.1–1.7)

OR: odds ratio; 95% CI: 95% confidence intervals.

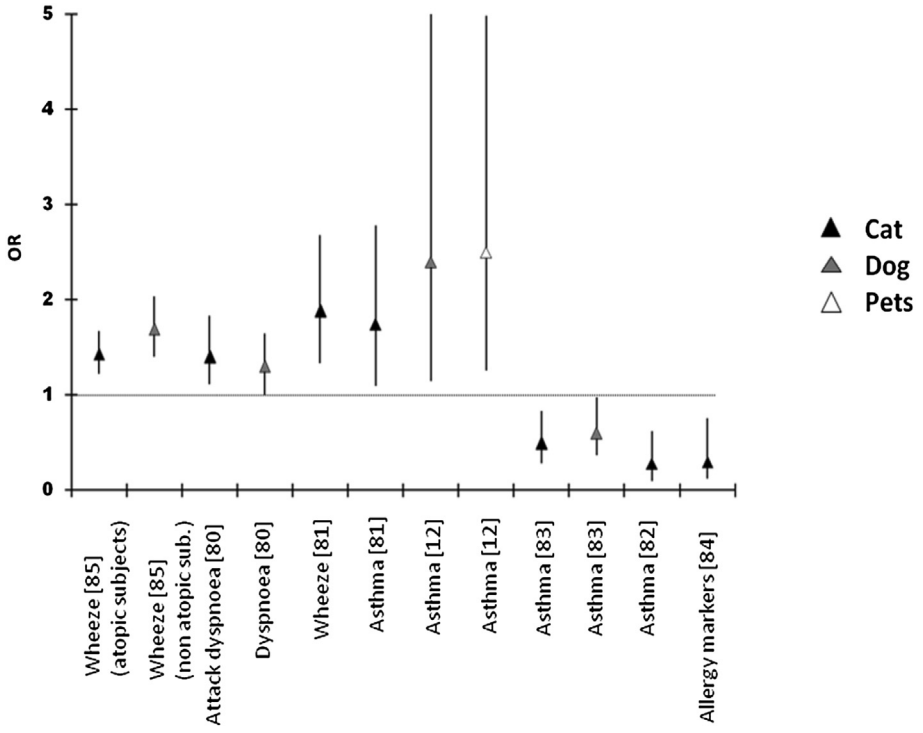

Fig. 3 Link between allergic diseases and pets exposure.

This health effect may vary according to the type of pet and to the individuals' allergic sensitization [85]. The ECRHS study showed that atopic subjects, exposed to cat in childhood, have a high risk of developing wheeze and other asthma-like symptoms. The same effects, in non atopic subjects, were due to dog exposure [85] (Fig. 3).

Such inconsistent findings may partly be due to different study designs, type of exposure, health outcome [86], recall or selection bias; further, interaction between gene and environmental exposure was proposed to be a major cause of the inconsistent observation [87].

4.2.3. Cockroach

Cockroach allergens, found in many poor inner-city areas, have been associated with asthma onset or exacerbation in many countries [75,88,12] (Table 4); 40—60% of patients with asthma in urban and inner-city areas has Immunoglobulin E (IgE) antibodies to cockroach allergens [89]. A study on 2—4 years old children showed that exposure to cockroach allergen in the kitchen was associated with three or more wheezing episodes in the past 12 months [88] (Table 4). Recently, early-life exposure to cockroach was shown to be associated with early-onset asthma and ever-having asthma in Taiwan children [12] (Table 4). In USA children, aged 2 months to 10 years, cockroach sensitivity showed a significant correlation with wheezing [90]. In Italian children, a relationship between cockroach sensitization and rhinoconjunctivis was shown in older allergic children (8—18 yrs) (OR 2.65, 1.06—6.59); the Population Attributable Risk (PAR) was computed showing that the abatement of cockroach exposure would prevent about one-fifth of rhinoconjunctivitis cases (20.6%) [91].

In a US birth-cohort, the presence of anti-cockroach IgE was linked to high risk of early wheeze (by 3 years of age) (OR 3.25, 1.69—6.24) and the presence of both anti-cockroach IgE and anti-mouse IgE was linked to rhinitis (OR 6.64, 1.50—29.45); a dose—response relationship was found between higher IgE and increased prevalence of wheeze [92]. Exposure to cockroach is also associated with asthma exacerbation: the National Cooperative Inner City Asthma Study showed that home exposure and sensitization to cockroach were associated with unscheduled visits for asthma (RR 1.48, 1.07—2.05), hospitalizations (RR 3.55, 1.60—7.90) and steroid use (RR 1.63, 1.06—2.50) [93].

4.2.4. Mould/dampness and fungi

Dampness is present in 10—50% of houses. Moulds are a source of allergens, Microbial Volatile Organic Compounds (mVOCs) and mycotoxins. Building dampness and moulds are associated with approximately 30—50% increases in respiratory and asthma-related health outcomes. Epidemiological studies and meta-analyses showed indoor dampness/mould to be associated with increased asthma development and exacerbations, current and ever asthma diagnosis, dyspnea, wheeze, allergic rhinitis, eczema and upper respiratory tract symptoms, regardless of atopy [94]. In children, an increased pooled risk for wheeze caused by indoor mould/dampness has been estimated [95] (Table 4); in Italian children, lifetime and current exposure to mould/dampness were associated with higher risk of having current wheeze [96] (Table 4). In the USA an increased risk of having current asthma was shown in children exposed to house mould [13] (Table 4). Early-life exposure to mould odor was linked to late-onset asthma (after 5 yrs old) in Taiwan children; the same study showed a relationship

between early-life exposure to visible moulds and ever-having asthma [12] (Table 4).

Similar risks for wheeze and current asthma were observed in adults and in general population samples [13,95] (Table 4).

In Italy it was estimated that avoiding an early mould/dampness exposure would abate 6% of wheeze, 7% of asthma or cough/phlegm and 4% of rhinoconjunctivitis in children and 4% of wheeze and 6% of asthma in adolescents [97].

Recently, a new method was developed to measure fungal DNA as a mould marker in dust/air. Positive significant associations were found between some specific fungal DNA and wheeze, dry cough at night, daytime breathlessness or asthma diagnosis [98,99].

4.2.5. Pollens

Pollen allergy has a remarkable clinical impact. In most European countries, grass pollen allergy is the 1st/2nd most frequent respiratory allergy, with a median prevalence value of 16.9% [100]. After grass, birch is a major allergenic threat in Northern Europe, whilst olive and Parietaria in Southern Europe [24]. In the Chinese sample of the ISAAC study was shown a significant increase in the prevalence of sensitization to mixed grass pollen from 0.5% in 2002 to 3.7% in 2010 [78].

Recent studies showed an association between pollens and allergic diseases onset and exacerbations. In the ISAAC Japanese sample there were positive correlations between cedar or cypress pollen counts and allergic rhinoconjunctivitis and between cedar pollen counts and asthma, in 6–7 years children; a positive association was found between cypress pollen counts and allergic rhinoconjunctivitis in 13–14 years children [101]. The 9 years German longitudinal study reported associations between incident asthma and hay fever with previous sensitization to grass pollen (RR 1.79, 1.01–3.19; RR 6.00, 4.04–8.90, respectively); incident hay fever was linked to previous sensitization to birch pollen too (RR 3.85, 2.31–6.40) [79]. A study on an Australian birth-cohort found the following associations at 6–7 years of age: cumulative exposure to pollen up to 3 months with hay fever; between 4 and 6 months with asthma [11] (Table 4). Grass pollen allergy was related to seasonal asthma exacerbations in a large international epidemiological study: higher risks were found for grass sensitized subjects in early summer in Southern Europe (OR March/April 2.60, 1.70–3.97; OR May/June 4.43, 2.34–8.39); a similar result was observed for birch sensitized subjects in Northern Europe (OR May/June 2.94, 1.92–4.50; OR July/August 2.01, 1.38–2.94) [102].

A French study identified a significant association between grass airborne pollens and asthma attacks requiring a General Practitioner (GP) consultation, with a 54% increase in the risk of asthma attacks for an interquartile range increase of 17.6 grains/m^3 of the Poaceae grass family [103].

4.3. Interaction between air pollution and biological allergens

Many studies about respiratory and allergic risk factors focused on the exposure to single pollutants. But in 'real life' multiple exposures frequently occur. In the environment, there are always complex mixtures of pollutants from different sources, which may jointly contribute to additive or synergic toxic effects [104,105]. Ambient inhalable PM, because of their intrinsic electrostatic properties and porous surfaces, readily adhere to free airborne allergens released from animal dander, dust mites, moulds and pollens. PM may interact with aeroallergens, promoting airway sensitization by modulating the allergenicity of airborne allergens [106,42]. In experimental conditions, Phleum pratense pollen releases more allergen-containing granules when treated with several concentrations of NO_2 and O_3 than when exposed to air only. Effects of traffic related pollutants might lead to increased bioavailability of airborne pollen allergens [107]. The airway mucosal damage and the impaired mucociliary clearance induced by air pollution per se may facilitate the access of inhaled allergens to the immune system [42]; this link enhances the risk of atopic sensitization and exacerbation of symptoms in sensitized subjects [41].

Current knowledge about the pathogenesis of asthma and allergies due to the combined exposure to air pollutants and biologicals is primarily based on *in vitro* or animal studies [14], since this kind of association is difficult to analyze in uncontrolled settings; little is known about the possible synergetic effect between air pollution and allergens at the population level [14]. Several laboratory clinical studies have demonstrated that the effect of allergen challenge on asthma is higher after prior exposure to ambient air pollutants. A recent publication [108] has demonstrated that mice co-exposed to HDM and diesel exhaust particles (DEPs) have significantly more HDM-specific memory T cells in the lungs, with respect to mice exposed to saline, DEPs, or HDM alone; these memory T cells promote in mice a strong and rapid response on secondary exposure to allergen *in vivo*. On the basis of these data, the authors hypothesized that if DEPs exposure potentiates recall responses to allergen, early-life DEP exposure might increase risk of developing allergic asthma in children. Thus, the same researchers assessed the effect of early-life exposure to high ECAT (elemental carbon attributable to traffic, a proxy of DEP exposure) levels in HDM sensitized and not sensitized children of a US birth cohort: sensitized children exposed to high ECAT level at birth had a 2-fold higher prevalence of asthma at 7 years of age compared with not sensitized ones [108].

However, the clinical significance of this effect modification in the general population is uncertain [109], indeed inconsistent results were found.

In a large French sample of patients suffering from severe seasonal allergic rhinitis the link between the allergic rhinitis severity and pollen counts, observed in clinical practice and experimental studies, was confirmed at the population level: such results persisted after controlling for various air pollutants (NO_2, SO_2, PM_{10}, O_3), showing that air pollution didn't modify this link [110] (Table 5).

A Spanish study showed a higher risk of asthma emergency room visits per 10 $\mu g/m^3$ of SO_2 and NO_2 increments; the combined exposure with both Urticaceae and Poaceae didn't change the risk level [111] (Table 5).

On the contrary, a US study showed that prenatal exposure to cockroach allergens was associated with a larger risk of allergic sensitization (RR 1.15, 1.07–1.25).

Table 5 Link between allergic diseases and combined exposures.

Study	Country (n, sample)	Health outcome	Single exposure	Combined exposure
Carlsten C, 2011 [114]	Canada (380, children)		OR (95% CI): Dog allergens	OR (95% CI): Dog allergens and NO_2
		Asthma	1.0 (0.2—5.2) NO_2 1.3 (0.4—4.5)	4.8 (1.1—21.5)
Annesi-Maesano I, 2012 [110]	France (36,397, adults)		OR (95% CI): Grass pollen	OR (95% CI): Grass pollens and air pollutants
		Allergic rhinitis	1.08 (1.04—1.11)	1.08 (1.01—1.14)
Cirera L, 2012 [111]	Spain (3939, hospital ER visits)		RR% (95% CI): SO_2	RR% (95% CI): SO_2 and pollens
		Asthma ER visits	5.2 (0.5—10.1) NO_2	5.7 (0.9—10.6) NO_2 and pollens
		Asthma ER visits	2.6 (0.3—5.0)	2.7 (0.4—5.1)
Perzanowski MS, 2013 [112]	US (727, young adults)		RR (95% CI): Cockroach allergens	RR (95% CI): Cockroach allergens and nPAH
		Allergic sensitization	1.15 (1.07—1.25)	1.22 (1.08—1.36)

OR: odds ratio; RR: relative risk; 95% CI: 95% confidence intervals; ER: emergency room; SO_2: sulphur dioxide; NO_2: nitrogen dioxide; nPAH: nonvolatile polycyclic aromatic hydrocarbons.

This risk was increased by exposure to nonvolatile PAHs (RR 1.22, 1.08—1.36), in particular in children null for the glutathione-S-transferase μ GSTM1 mutation (RR 1.54, 1.18—2.01) [112] (Table 5). The results of a study performed in 11 Canadian cities between 1994 and 2007 showed a higher association between fungi and pollens exposure and hospitalizations for asthma in the days of higher air pollution (NO_2, SO_2, PM_{10}, $PM_{2.5}$) [109] (Fig. 4).

Early-life exposure to smoke and aeroallergens may influence pulmonary function development in childhood: a US birth-cohort showed that exposure to second-hand smoke in early-life produce a reduction in lung function (Forced expiratory flow between 25% and 75% of forced vital capacity-FEF_{25-75}) in childhood; the number of aeroallergen-positive skin prick tests at age 2 modified this relationship: FEF_{25-75} −0.06 in total sample; −0.09 in subjects with 1 sensitization; −0.30 in subjects with more than 2 sensitizations [113].

In a study on a birth-cohort at high risk for asthma, co-exposure to dog allergen and NO_2, or to dog allergen and ETS, appears to increase the risk for asthma (OR 4.8, 1.1—21.5 and OR 2.7, 1.1—7.1, respectively) [114] (Table 5). A letter commenting these results reported that in 'real life' it is unrealistic to separate the role of dog allergens from that of other allergens commonly found indoors. The importance of both cat and dog allergens as risk factors for induction of allergic sensitization and bronchial asthma is not limited to shared indoor environments: *in vitro* studies have shown cross-reactivity between these allergens [115].

5. Research needs and conclusions

Although largely avoidable, asthma and allergic rhinitis tend to occur as epidemics and hit young people both in industrialized and in developing countries. Reasons for increased susceptibility to developing allergy in response to exposure to pollen allergens remain elusive, but environmental and life style factors appear to drive these increases [41]. Scientific evidences showed that air pollution and biologicals are important risk factors for allergic diseases onset and exacerbation; current *in vitro* and animal studies showed a link between pathogenesis of asthma and allergies and combined exposure to air pollutants and biologicals, but little is known about this possible synergetic effect at the population level [14]. A growing body of evidence shows that components of air pollution interact with airborne allergens and enhance risk of atopic sensitization and exacerbation of symptoms in sensitized subjects [10].

More research is needed in order to elucidate the mechanisms by which pollutants and biologicals induce damage in exposed subjects. Some recent evidences showed that biological allergens can induce not only allergic response, through the production of immunoglobulins, but also non-atopic reactions like inflammation and irritation [116]. Few data have taken into account the separation between allergic and non-allergic asthma\rhinitis, underlying mechanisms and management variation. Considering that air pollution is the main risk factor for non-allergic respiratory diseases, research on this topic is advisable in order to evaluate relative weight of this factor on the two sides of the coin (e.g. allergic and non-allergic asthma) and to define the better strategy leading to their optimal management. Important omic techniques are now available for a deeper assessment of various biochemical pathways operative in health and disease [117].

The abatement of the main risk factors for asthma and allergic diseases may achieve huge health benefits. Thus, it is important to raise awareness of respiratory allergies as serious chronic diseases which place a heavy burden on patients and on society as a whole. Meanwhile, the ability of patients and their caregivers to identify early symptoms in order to ensure an early diagnosis of allergic diseases should be increased.

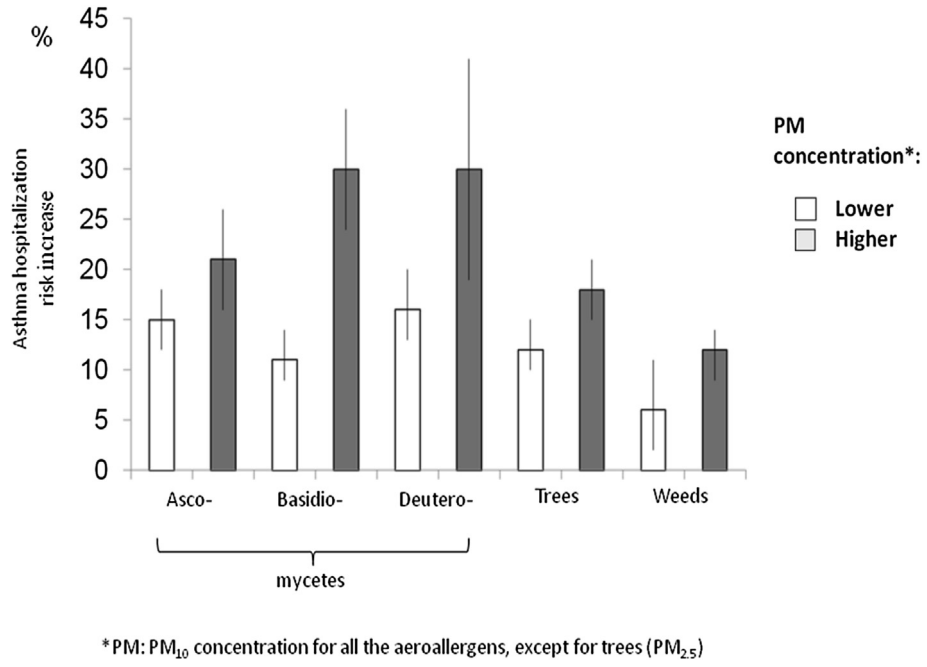

Fig. 4 Percentage increase of relative risk of asthma hospitalization for an interquartile range increase in aeroallergen concentration by particulate matter concentration (modified from [109]).

Prevention of chronic diseases should start early in life including healthy lifestyles in the school curricula; the concept of exposure standards for allergens and respiratory irritants must be promoted as a major primary prevention initiative. Air pollution can influence the plant allergenic content, and by affecting plant growth it can affect both the amount of pollen produced and the amount of allergenic proteins contained in pollen grains. Thus, acting on air pollution abatement will trigger a virtuous circle with beneficial effects on air quality, climate, allergen exposure and health status.

The WHO had suggested several options for achieving acceptable indoor air quality [118,119]. Guidelines and recommendations on indoor air quality in dwellings are also reported in the EFA (European Federation of Allergy and Airways Diseases Patients Associations) final document of the THADE (Towards Healthy Air in Dwellings in Europe) project [120,121]. Guidelines on indoor air quality cannot be enforced in private buildings, but it is important that people be aware of the health risks due to indoor pollution, so that they can try to adopt healthy behaviors.

Within the 2013 EU Year of Air, a WHO technical report from the REVIHAAP project (Review of evidence on health aspects of air pollution) was published with the aim to review and discuss the newly accumulated scientific evidence on the health adverse effects of air pollution [43,14]. European Respiratory Society Environment and Health Committee developed 10 concise principles for clean air, which summarize the scientific state of the art and provide guidance for public health policy [122]; in particular, the principles highlighted that citizens are entitled to clean air and that outdoor air pollution is one of the biggest environmental health threats in Europe today, leading to significant reductions of life expectancy and productivity. EU policies to reduce air pollution are needed for having clean air and no longer significant adverse effects on the health of European citizens. The benefits of such policies outweigh the costs by a large amount [122].

Conflict of interest

None.

Acknowledgment

This publication arises in the frame of the project HEALS which has received funding from the European Union, in the framework of FP7-ENV (contract number 603946).

References

[1] Maio S, Cerrai S, Simoni M, Sarno G, Baldacci S, Viegi G. Environmental risk factors: indoor and outdoor pollution. In: Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss MS, editors. White Book on Allergy: Update. World Allergy Organization (WAO); 2013. p. 91—8.

[2] Lee SY, Chang YS, Cho SH. Allergic diseases and air pollution. Asia Pac. Allergy 2013;3:145—54.

[3] Dijk FN, de Jongste JC, Postma DS, Koppelman GH. Genetics of onset of asthma. Curr. Opin. Allergy Clin. Immunol. 2013; 13:193—202.

[4] Jenerowicz D, Silny W, Dańczak-Pazdrowska A, Polańska A, Osmola-Mańkowska A, Olek-Hrab K. Environmental factors and allergic diseases. Ann. Agric. Environ. Med. 2012;19: 475—81.

[5] Anderson H, Favarato G, Atkinson RW. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. Air Qual. Atmos. Health 2013;1:47—56.

[6] Viegi G, Simoni M, Maio S, Cerrai S, Sarno G, Baldacci S. Indoor and outdoor pollution. In: Palange P, Simonds A, editors.

ERS Handbook: Respiratory Medicine. 2nd ed. Plymouth (UK): Charlesworth Press (UK), Latimer Trend & Co. Ltd; 2013. p. 345—51.
[7] Hulin M, Simoni M, Viegi G, Annesi-Maesano I. Respiratory health and indoor air pollutants based on quantitative exposure assessments. Eur. Respir. J. 2012;40:1033—45.
[8] Simoni M, Annesi-Maesano I, Viegi G. Indoor environment. In: Gibson GJ, Loddenkemper R, Sibille Y, Lundback B, editors. European Lung White Book Respiratory Health and Disease in Europe; 2013. p. 112—23. Wakefield (UK).
[9] Stoltz DJ, Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Gern JE, et al. Specific patterns of allergic sensitization in early childhood and asthma & rhinitis risk. Clin. Exp. Allergy 2013;43:233—41.
[10] D'Amato G, Cecchi L, D'Amato M, Liccardi G. Urban air pollution and climate change as environmental risk factors of respiratory allergy: an update. J. Investig. Allergol. Clin. Immunol. 2010;20:95—102.
[11] Erbas B, Lowe AJ, Lodge CJ, Matheson MC, Hosking CS, Hill DJ, et al. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. Clin. Exp. Allergy 2013;43:337—43.
[12] Chen YC, Tsai CH, Lee YL. Early-life indoor environmental exposures increase the risk of childhood asthma. Int. J. Hyg. Environ. Health 2011;215:19—25.
[13] Nguyen T, Lurie M, Gomez M, Reddy A, Pandya K, Medvesky M. The national asthma survey—New York State: association of the home environment with current asthma status,. Public Health Rep. 2010;125:877—87.
[14] World Health Organization WHO. Review of Evidence on Health Aspects of Air Pollution. REVIHAAP Project: final technical report. 2013. Accessed 7 Aug 2014, http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report.
[15] Künzli N, Perez L, Rapp R. Pollutants, sources and levels. In: Künzli N, Perez L, Rapp R, editors. Air Quality and Health. Lausanne (Switzerland): European Respiratory Society; 2010. p. 9—22.
[16] Richardson G, Eick S, Jones R. How is the indoor environment related to asthma?, literature review. J. Adv. Nurs. 2005;52:328—39.
[17] European Environment Agency (EEA). http://glossary.eea.europa.eu/terminology/concept_html?term=allergen. Accessed 7 Aug 2014.
[18] Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63.8—160.
[19] Lancey ME, West JS. The aerobiological pathway. In: Lancey ME, West JS, editors. The Air Spora, A Manual for Catching and Identifying Airborne Biological Particles. Netherland: Springer; 2007. p. 15—34.
[20] The Global Initiative for Asthma (GINA). http://www.ginasthma.org. Accessed 7 Aug 2014.
[21] Maio S, Simoni M, Baldacci S, Sherrill D, Viegi G. Indoor air pollution and airway disease. In: Pawankar R, Holgate ST, Rosenwasser LJ, editors. Allergy Frontiers: Epigenetics, Allergens and Risk Factors, 1. Tokyo: Springer; 2009. p. 387—401.
[22] Portnoy J, Chew GL, Phipatanakul W, Williams PB, Grimes C, Kennedy K, et al. Joint taskforce on practice parameters; practice parameter workgroup. Environmental assessment and exposure reduction of cockroaches: a practice parameter. J. Allergy Clin. Immunol. 2013;132:802—8.
[23] Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, et al. Fungi and allergic lower respiratory tract diseases. J. Allergy Clin. Immunol 2012;129:280—91.
[24] D'Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, Liccardi G, Popov T, van Cauwenberge P. Allergenic pollen and pollen allergy in Europe. Allergy 2007;62:976—90.
[25] Bousquet J, Anto J, Auffra C, Akdis M, Cambon-Thomsen A, Keil T, et al. MeDALL (Mechanisms of the development of ALLergy): an integrated approach from phenotypes to systems medicin. Allergy 2011;66:596—604.
[26] Valenta R, Campana R, Mart K, van Hage M. Allergen-specific immunotherapy: from therapeutic vaccines to prophylactic approaches. J. Intern. Med. 2012;272:144—57.
[27] Zhen T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. Allergy Asthma Immunol. Res. 2011;3:67—73.
[28] Bousquet J, Van Cauwenberge P, Khaltaev N. ARIA workshop group, World health Organization, allergic rhinithis and its impact on asthma. J. Allergy Clin. Immunol 2001;108:1s—334s.
[29] Ozdoganoglu T, Songu M. The Burden of allergic rhinitis and asthma. Ther Adv. Resp. Dis 2012;6:11—23.
[30] Gibson GJ, Loddenkemper R, Sibille Y, Lundback B. Adult asthma. In: Gibson GJ, Loddenkemper R, Sibille Y, Lundback B, editors. European Lung White Book - Respiratory Health and Disease in Europe. Wakefield (UK): European respiratory Society; 2013. p. 138—47.
[31] De Marco R, Cappa V, Accordini S, Rava M, Antonicelli L, Bortolami O, et al., GEIRD Study Group. Eur. Respir. J. 2012;39:883—92.
[32] Baïz N, Annesi-Maesano I. Is the asthma epidemic still ascending? Clin. Chest Med 2012;33:419—29.
[33] World Health Organization. Global surveillance. In: Bousquet J, Khaltaev NG, editors. Prevention and Control of Chronic Respiratory Diseases: A Comprehensive Approach. , Geneva: World Health Organization; 2007.
[34] To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. BMC Public Health 2012;12:204. http://www.ncbi.nlm.nih.gov/pubmed/22429515.
[35] Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al., ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 2006;368:733—43.
[36] Valovirta E, editor. EFA Book on Respiratory allergies. Raise Awareness, Relieve the Burden. Napoli: Scientific Communication Srl; 2011. http://www.efanet.org/wp-content/documents/EFABookonRespiratoryAllergiesFINAL.pdf.
[37] Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. Eur. Respir. J. 2013;41:716—26.
[38] Ramasamy AK, Gupta N, Kumar R. Impact of obesity on bronchial asthma in Indian population. Lung India 2014;31:121—6.
[39] Ferguson BJ. Influences of allergic rhinitis on sleep. Otolaryngol Head Neck Surg. 2004;130:617—29.
[40] Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy 2003;58:691—706.
[41] D'Amato G. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. MRM 2011;6:28—37.
[42] D'Amato G. Environmental urban factors (air pollution and allergens) and the rising trends in allergic respiratory diseases. Allergy 2002;57:30—3.
[43] World Heath Organization. WHO Air Quality Guidelines Global Updates. 2005. Accessed 7 Aug 2014, http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf?ua=1.

[44] World health Organization. Health Effects of Particulate Matter. Policy Implications for Countries in Eastern Europe. Caucasus and central Asia: WHO; 2013. Accessed 7 Aug 2014, http://www.euro.who.int/__data/assets/pdf_file/0006/189051/Health-effects-of-particulate-matter-final-Eng.pdf?ua=1.
[45] Pénard-Morand C, Raherison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. Eur. Respir. J. 2010;36:33—40.
[46] Annesi-Maesano I, Moreau D, Caillaud D, Lavaud F, Le Moullec Y, Taytard A, Pauli G, et al. Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. Respir. Med. 2007;101:1721—9.
[47] Fuertes E, Brauer M, MacIntyre E, Bauer M, Bellander T, von Berg A, et al. TAG study group. Childhood allergic rhinitis, traffic-related air pollution, and variability in the GSTP1, TNF, TLR2, and TLR4 genes: results from the TAG Study. J. Allergy Clin. Immunol. 2013;132:342—52.
[48] Kumar S, Verma MK, Srivastava AK. Ultrafine particles in urban ambient air and their health perspectives. Rev. Environ. Health 2013;28:117—28.
[49] Simoni M, Scognamiglio A, Carrozzi L, Baldacci S, Angino A, Pistelli F, et al. Indoor exposures and acute respiratory effects in two general population samples from a rural and an urban area in Italy. J. Expo Anal. Environ. Epidemiol 2004;14:S144—52.
[50] Annesi-Maesano I, Hulin M, Lavaud F, Raherison C, Kopferschmitt C, de Blay F, et al. Poor air quality in classrooms related to asthma and rhinitis in primary school-children of the French 6 cities Study. Thorax 2012;67:682—8.
[51] Urman R, McConnell R, Islam T, Avol EL, Lurmann FW, Vora H, et al. Associations of children's lung function with ambient air pollution: joint effects of regional and near-roadway pollutants. Thorax 2014;69:540—7.
[52] Kim BJ, Lee SY, Kwon JW, Jung YH, Lee E, Yang SI, et al. Traffic-related air pollution is associated with airway hyperresponsiveness. J. Allergy Clin. Immunol. 2014;133:1763—5.
[53] Nuvolone D, Della Maggiore R, Maio S, Fresco R, Baldacci S, Carrozzi L, et al. Geographical information system and environmental epidemiology: a cross-sectional spatial analysis of the effects of traffic-related air pollution on population respiratory health. Environ. Health 2011;10:12.
[54] Cibella F, Cuttitta G, La Grutta S, Melis MR, Lospalluti ML, Uasuf CG, et al. Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. Pediatr. Allergy Immunol. 2011;22:60—8.
[55] Robinson CL, Baumann LM, Romero K, Combe JM, Gomez A, Gilman RH, et al. Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting. Thorax 2011;66:1051—7.
[56] Lemke LD, Lamerato LE, Xu X, Booza JC, Reiners Jr JJ, Raymond Iii DM, et al. Geospatial relationships of air pollution and acute asthma events across the Detroit-Windsor international border: study design and preliminary results. J. Expo. Sci. Environ. Epidemiol. 2014;24:346—57.
[57] Song S, Paek D, Park C, Lee C, Lee JH, Yu SD. Exposure to ambient ultrafine particles and urinary 8-hydroxyl-2-deoxyguanosine in children with and without eczema. Sci. Total Environ. 2013;458—460:408—13.
[58] Manney S, Meddings CM, Harrison RM, Mansur AH, Karakatsani A, Analitis A, et al. Association between exhaled breath condensate nitrate + nitrite levels with ambient coarse particle exposure in subjects with airways disease. Occup. Environ. Med. 2012;69:663—9.
[59] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2224—60.
[60] Jagger P, Shively G. Land use change, fuel use and respiratory health in Uganda. Energy Policy 2014;67:713—26.
[61] Trevor J, Antony V, Jindal SK. The effect of biomass fuel exposure on the prevalence of asthma in adults in India - review of current evidence. J. Asthma 2014;51:136—41.
[62] Vicedo-Cabrera AM, García-Marcos L, Llopis-González A, López-Silvarrey-Varela Á, Miner-Canflanca I, Batlles-Garrido J, et al. Atopic dermatitis and indoor use of energy sources in cooking and heating appliances. B.M.C. Public Health 2012;12:890.
[63] Agrawal S. Effect of indoor air pollution from biomass and solid fuel combustion on prevalence of self-reported asthma among adult men and women in India: findings from a nationwide large-scale cross-sectional survey. J. Asthma 2012;49:355—65.
[64] Simoni M, Baldacci S, Puntoni R, Pistelli F, Farchi S, Lo Presti E, et al. Respiratory symptoms/diseases and environmental tobacco smoke (ETS) in never smoker Italian women. Respir. Med. 2007;101:531—8.
[65] Graif Y, German L, Ifrah A, Livne I, Shohat T. Dose-response association between smoking and atopic eczema: results from a large cross- sectional study in adolescents. Dermatology 2013;226:195—9.
[66] Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. Respir. Res. 2011;12:5.
[67] Tezza G, Mazzei F, Boner A. Epigenetics of allergy. Early Hum. Dev. 2013;89:S20—1.
[68] Butz AM, Matsui EC, Breysse P, Curtin-Brosnan J, Eggleston P, Diette G, et al. A randomized trial of air cleaners and a health coach to improve indoor air quality for inner-city children with asthma and secondhand smoke exposure. Arch. Pediatr. Adolesc. Med. 2011;165:741—8.
[69] Pope III CA. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public. Health 1989;79:623—8.
[70] Bayer-Oglesby L, Grize L, Gassner M, Takken-Sahli K, Sennhauser FH, Neu U, et al. Decline of ambient air pollution levels and improved respiratory health in Swiss children. Environ. Health Perspect 2005;13:1632—7.
[71] Downs SH, Schindler C, Liu LJ, Keidel D, Bayer-Oglesby L, Brutsche MH, Gerbase MW, et al., SAPALDIA Team. Reduced exposure to PM10 and attenuated age-related decline in lung function. N. Engl. J. Med. 2007;357:2338—47.
[72] Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am. J. Respir. Crit. Care Med. 2006;173:667—72.
[73] Anderson JO, Thundiyil GJ, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. J. Med. Toxicol. 2012;8:166—75.
[74] Celedón JC, Milton DK, Ramsey CD, Litonjua AA, Ryan L, Platts-Mills TA, et al. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. J. Allergy Clin. Immunol. 2007;120:144—9.
[75] Davey G, Vennw A, Belete H, Berhane Y, Brittonw J. Wheeze, allergic sensitization and geohelminth infection in Butajira, Ethiopia. Clin. Exp. Allergy 2005;35:301—7.
[76] Wong GW, Li ST, Hui DS, Fok TF, Zhong NS, Chen YZ, et al. Individual allergens as risk factors for asthma and bronchial hyperresponsiveness in Chinese children. Eur. Respir. J. 2002;19:288—93.

[77] Jaen A, Sunyer J, Basagana X, Chinn S, Zock JP, Antó JM, et al., on behalf of European Community Respiratory Health Survey. Specific sensitization to common allergens and pulmonary function in the European community respiratory health Survey. Clin. Exp. Allergy 2002;32:1713—9.
[78] Li J, Wang H, Chen Y, Zheng J, Wong GW, Zhong N. House dust mite sensitization is the main risk factor for the increase in prevalence of wheeze in 13- to 14-year-old schoolchildren in Guangzhou city, China. Clin. Exp. Allergy 2013;43:1171—9.
[79] Schäfer T, Wölke G, Ring J, Wichmann HE, Heinrich J. Allergic sensitization to cat in childhood as major predictor of incident respiratory allergy in young adults. Allergy 2007; 62:1282—7.
[80] Skorge TD, Eagan TML, Eide GE, Gulsvik A, Bakke PS. Indoor exposures and respiratory symptoms in a Norwegian community sample. Thorax 2005;60:937—42.
[81] Lombardi E, Simoni M, La Grutta S, Viegi G, Bisanti L, Chellini E, et al., SIDRIA-2 Collaborative Group. Effects of pet exposure in the first year of life on respiratory and allergic symptoms in 7-yr-old children. The SIDRIA-2 study. Pediatr. Allergy. Immunol. 2010;21:268—76.
[82] Oberle D, von Mutius E, von Kries R. Childhood asthma and continuous exposure to cats since the first year of life with cats allowed in the child's bedroom. Allergy 2003;58:1033—6.
[83] Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among pre-teenage children. Am. J. Respir. Crit. Care Med. 2002;166:696—702.
[84] Oryszczyn MP, Annesi-Maesano I, Charpin D, Kauffmann F. Allergy markers in adults in relation to the timing of pet exposure: the EGEA study. Allergy 2003;58:1136—43.
[85] Svanes C, Heinrich J, Jarvis D, Chinn S, Omenaas E, Gulsvik A, et al. Pet-keeping in childhood and adult asthma and hay fever: European community respiratory health Survey. J. Allergy Clin. Immunol. 2003;112:289—300.
[86] Almqvist C, van Hage-Hamsten M. Cat and dog allergens—can intervention studies solve their inscrutable riddle? Clin. Exp. Allergy 2003;33:1167—70.
[87] Heinrich J. Influence of indoor factors in dwellings on the development of childhood asthma. Int. J. Hyg. Environ. Health 2011;214:1—25.
[88] Silva JM, Camara AA, Tobias KRC, Macedo IS, Cardoso MRA, Arruda E, et al. A prospective study of wheezing in young children: the independent effects of cockroach exposure, breast-feeding and allergic sensitization. Pediatr. Allergy Immunol. 2005;16:393—401.
[89] Sohn MH, Kim KE. The cockroach and allergic diseases. Allergy Asthma Immunol. Res. 2012;4:264—9.
[90] De Vera MJ, Drapkin S, Moy JN. Association of recurrent wheezing with sensitivity to cockroach allergen in inner-city children. Ann. Allergy Asthma Immunol. 2003;91:455—9.
[91] La Grutta S, Cibella F, Passalacqua G, Cuttitta G, Liotta G, Ferlisi A, et al. Association of Blattella germanica sensitization with atopic diseases in pediatric allergic patients. Pediatr. Allergy Immunol. 2011;22:521—7.
[92] Donohue KM, Al-alem U, Perzanowski MS, Chew GL, Johnson A, Divjan A, et al. Anti-cockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. J. Allergy Clin. Immunol. 2008;122:914—20.
[93] Wang J, Visness CM, Calatroni A, Gergen PJ, Mitchell HE, Sampson HA. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. Clin. Exp. Allergy 2009;39:1381—9.
[94] Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. Environ. Health Perspect 2011;119:748—56.
[95] Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-analyses of the associations of respiratory health effects with dampness and mould in homes. Indoor Air 2007;17:284—96.
[96] Pirastu R, Bellu C, Greco P, Pelosi U, Pistelli R, Accetta G, et al. Indoor exposure to environmental tobacco smoke and dampness: respiratory symptoms in Sardinian children—DRIAS study. Envir. Res. 2009;109:59—65.
[97] Simoni M, Lombardi E, Berti G, Rusconi F, La Grutta S, Piffer S, et al., the SIDRIA-2 Collaborative Group. Mould/-dampness exposure at home is associated with respiratory disorders in Italian children and adolescents: the SIDRIA-2 Study. Occup. Environ. Med. 2005;62:616—22.
[98] Simoni M, Cai GH, Norback D, Annesi-Maesano I, Lavaud F, Sigsgaard T, et al. Total viable molds and fungal DNA in classrooms and association with respiratory health and pulmonary function of European schoolchildren. Pediatr. Allergy Immunol. 2011;22:843—52.
[99] Cai GH, Hashim JH, Hashim Z, Ali F, Bloom E, Larsson L, et al. Fungal DNA, allergens, mycotoxins and associations with asthmatic symptoms among pupils in schools from Johor Bahru, Malaysia. Pediatr. Allergy Immunol. 2011;22:290—7.
[100] Bousquet PJ, Chinn S, Janson C, Kogevinas M, Burney P, Jarvis D, European Community Respiratory Health Survey I. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European community respiratory health survey I. Allergy 2007;62:301—9.
[101] Yoshida K, Adachi Y, Akashi M, Itazawa T, Murakami Y, Odajima H, et al. Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren. Allergy 2013;68:757—63.
[102] Canova C, Heinrich J, Anto JM, Leynaert B, Smith M, Kuenzli N, et al. The influence of sensitisation to pollens and moulds on seasonal variations in asthma attacks. Eur. Respir. J. 2013;42:935—45.
[103] Huynha BT, Tuala S, Turbelin C, Pelat C, Cecchi L, D'Amato G, et al. Short-term effects of airborne pollens on asthma attacks as seen by general practitioners in the Greater Paris area, 2003-2007. Prim. Care Respir. J. 2010;19: 254—9.
[104] Billionnet C, Sherrill D, Annesi-Maesano I, on behalf of the Gerie study. Estimating the health effects of exposure to Multi-pollutant mixture. Ann. Epidemiol. 2012;22:126—41.
[105] Eggleston PA. Complex interactions of pollutant and allergen exposures and their impact on people with asthma. Pediatrics 2009;123:S160—7.
[106] García-Gallardo MV, Algorta J, Longo N, Espinel S, Aragones A, Lombardero M, et al. Evaluation of the effect of pollution and fungal disease on Pinus radiata pollen allergenicity. Int. Arch. Allergy Immunol. 2013;160:241—50.
[107] Motta AC, Marliere M, Peltre G, Sterenberg PA, Lacroix G. Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen. Int. Arch. Allergy Immunol. 2006;139:294—8.
[108] Brandt EB, Biagini Myers JM, Acciani TH, Ryan PH, Sivaprasad U, Ruff B, LeMasters GK, Bernstein DI, Lockey JE, LeCras TD, Khurana Hershey GK. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. J. Allergy Clin. Immunol 2015 [Epub of print].
[109] Cakmak S, Dales RE, Coates F. Does air pollution increase the effect of aeroallergens on hospitalization for asthma? J. Allergy Clin. Immunol 2012;129:228—31.
[110] Annesi-Maesano I, Rouve S, Desqueyroux H, Jankovski R, Klossek JM, Thibaudon M, et al. Grass pollen counts, air pollution levels and allergic rhinitis severity. Int. Arch. Allergy Immunol 2012;158:397—404.
[111] Cirera L, García-Marcos L, Giménez J, Moreno-Grau S, Tobías A, Pérez-Fernández V, et al. Daily effects of air

pollutants and pollen types on asthma and COPD hospital emergency visits in the industrial and mediterranean Spanish city of Cartagena. Allergol. Immunopathol. (Madr.) 2012;40:231—7.

[112] Perzanowski MS, Chew GL, Divjan A, Jung KH, Ridder R, Tang D, et al. Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children. J. Allergy Clin. Immunol. 2013;131:886—93.

[113] Brunst KJ, Ryan PH, Lockey JE, Bernstein DI, McKay RT, Khurana Hershey GK, et al. Unraveling the relationship between aeroallergen sensitization, gender, second-hand smoke exposure, and impaired lung function. Pediatr. Allergy Immunol. 2012;23:479—87.

[114] Carlsten C, Brauer M, Dimich-Ward H, Dybuncio A, Becker AB, Chan-Yeung M. Combined exposure to dog and indoor pollution: incident asthma in a high-risk birth cohort. Eur. Respir. J. 2011;37:324—30.

[115] Liccardi G, Annesi-Maesano I, Salzillo A, D'Amato G. Can dog allergen alone, if combined with indoor pollution, be responsible for asthma in children? Eur. Respir. J. 2011;38:744—5.

[116] Hulin M, Moularat S, Kirchner S, Robine E, Mandin C, Annesi-Maesano I. Positive associations between respiratory outcomes and fungal index in rural inhabitants of a representative sample of French dwellings. Int. J. Hyg. Environ. Health 2013;216:155—62.

[117] Fens N, van der Schee MP, Brinkman P, Sterk PJ. Exhaled breath analysis by electronic nose in airways disease. Established issues and key questions. Clin. Exp. Allergy 2013;43:705—15.

[118] World Heath Organization. WHO Guidelines for Indoor Air Quality: Dampness and Mould. 2009. Accessed 7 Aug 2014, http://www.euro.who.int/__data/assets/pdf_file/0017/43325/E92645.pdf.

[119] World Heath Organization. WHO Guidelines for Indoor Air Quality: Selected Pollutants. 2010. Accessed 7 Aug 2014, http://www.who.int/indoorair/publications/9789289002134/en/.

[120] European Federation of Allergy and Airways Diseases Patients' Association (EFA). Towards Healthy Air in Dwellings in Europe, 2004. Brussels, Belgium: EFA; 2004. Accessed 10 March 2014, www.efanet.org.

[121] Franchi M, Carrer P, Kotzias D, Rameckers EM, Seppanen P, van Bronswijk JE, et al. Working towards healthy air in dwellings in Europe. Allergy 2006;61:864—8.

[122] Brunekreef B, Annesi-Maesano I, Ayres JG, Forastiere F, Forsberg B, Künzli N, et al. Ten principles for clean air. Eur. Respir. J. 2012;39:525—8.