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HEALS

HEALS

Health and Environment-wide Associations based on Large population Surveys

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1 Summary

The overall aim of WP14 is to develop approaches, methods, protocols and a knowledge base for converting information on joint exposures to particulate matter (PM) and allergens into quantitative estimates of their effects on allergy and asthma.

In this framework, the 'Report on the implementation of the HEALS methodology for country-based assessment of all health and exposure outcomes of interest' is the first deliverable of this WP. Data on health and exposure assessments from the various studies contributing to the HEALS project, namely population studies and twins studies, had to be prepared to be dealt with the HEALS methodology. A HEALS database including data from these various studies on exposure to particulate matter (PM), as assessed objectively or estimated, and to biological allergens (pollens and moulds for outdoors and house dust mite, pets, moulds…for indoors), presence of asthma and allergies and potential confounders and modifiers, is being implemented by WP12 ('Exposure and Health data management').

The obtained HEALS datasets on asthma and allergies and risk factors constitute a main deliverable for this WP and in the present report the essential steps to reach this aim will be listed and described.

2 Updated review about the relationship between PM, biological allergens, asthma and allergy

A thorough research of the most recent scientific publications was performed consulting the Medline database ('Pubmed'). In particular, the research was focused on: a) characteristics and sources of PM; b) characteristics and sources of biological allergens (house dust mites, pets, cockroaches, mould/dampness, fungi, pollens); c) burden of asthma and allergic diseases; d) relationship between asthma/allergy and PM; e) relationship between asthma/allergy and biological allergens; f) interaction between air pollution and biological allergens and their effects on asthma and allergy.

Over 140 publications were selected and analyzed, delivering a detailed review including tables and figures summarizing the main obtained results (**attachment 1**).

Thanks to this updated review and to the expertise of the WP14 lead beneficiary and project coordinators, a selection of the main parameters to be collected and analyzed in order to fulfill the purpose of the WP14 was done.

Attachment 1

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

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2.1 Introduction

The prevalence of asthma and allergies including atopy has increased during the past decades, particularly in westernized countries [Lee S-Y, Asia Pac Allergy 2013; Maio S, White Book on Allergy 2013]. The rapid rise in the prevalence of these diseases since the '60s cannot be explained by genetic factors alone [Djik FN, Curr Opin Allergy Clin Immunol 2013]. Rapid

urbanization and industrialization throughout the world have increased air pollution and population exposures, so that most epidemiologic studies focus on possible links between air pollution and respiratory disease [Jenerowicz D, Ann Agric Environ Med 2012; Maio S, White Book on Allergy 2013]; traffic-related air pollution exposure was shown to play an important role in the development of incident asthma in children [Anderson H, Air Qual Atmos Health 2013].

A growing body of evidence shows that chemical air pollution may interact with airborne allergens and enhance risk of atopic sensitization and exacerbation of symptoms in sensitized subjects [D'Amato G, J Investig Allergol Clin Immunol 2010]. Particulate matter (PM) and biological allergens are major components of the environmental exposure leading to increased allergic symptoms/diseases, in particular asthma and asthma-like symptoms [D'Amato G, Clin Exp Allergy 2005; D'Amato G, J Investig Allergol Clin Immunol 2010; Erbas B, Clin Exp Allergy 2013; Chen Y-C, Int J Hyg Environ Health 2011; Nguyen T, Publich Health Rep 2010]. Exposure to PM may produce reduced lung function, lower airways inflammation and upper airways irritation [Viegi G, ERS Handbook 2013], as well as asthma hospital admissions, asthma incidence, asthma exacerbations, respiratory allergy/hay fever and bronchodilator usage [Maio S, White Book on Allergy 2013]. Exposure to biological allergens may produce respiratory infections, sensitisation, respiratory allergic diseases (asthma and rhinitis) and wheezing [Hulin M, ERJ 2012; Simoni M, Lung White Book 2013; Stoltz DJ, Clin Exp Allergy 2013].

Moreover, current *in vitro* and animal studies showed that the combined exposure to air pollutants and allergens may have a synergistic or additive effect on asthma and allergies, but there is insufficient knowledge about this link at the population level [WHO 2013-REVIHAAP].

Regardless of the existence of nonallergic asthma and rhinitis, this review is focused on allergic diseases for which numerous epidemiological data are available. Therefore, the specific aim is to gather recent evidences concerning the relationship between exposure to PM, biological allergens and allergic diseases.

2.2 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, primarily

refineries. The primary pollutants, directly emitted into the atmosphere, 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 because it is formed in the atmosphere by reaction between NO_2 and volatile organic compounds (VOCs) in the presence of heat and sunlight. PM can be either emitted directly into the air (primary PM) or formed in the atmosphere from gaseous precursors, mainly SO_2, oxides of nitrogen (NO_x), ammonia (NH_3) and non-methane volatile organic compounds (NMVOCs) (secondary PM).

Indoor environment (dwellings, workplaces, schools, day care centres, bars and discotheques) is a source of health risk factors; most people, in industrialized countries, spend more than 90% of their time indoors, and more than half of this time at home [Richardson G, J Adv Nurs 2005]. The indoor environment quality depends on the air that penetrates from outdoors and on the presence of indoor air pollution sources. To improve energy efficiency, modern dwellings often are thermally insulated and scarcely ventilated, possibly resulting in deterioration of the air quality. Moreover, the indoor environment is influenced by the interaction between building systems, construction techniques, contaminant sources and building occupants. The most frequently investigated risk factors for indoor pollution are Environmental Tobacco Smoke (ETS), biomass (wood/coal) fuel, cleaning and washing products and biological allergens [Maio S, White Book on Allergy 2013]. The main indoor air pollutants are CO, carbon dioxide (CO_2), NO_2, SO_2, VOCs, phthalates, formaldehyde, PM and PAHs.

PM and biological allergens play a key role in the environmental exposure that can lead to increased allergic symptoms/diseases [Jenerowicz D, Ann Agric Environ Med 2012].

2.2.1 Particulate Matter (PM)

PM, also known as particulate matter or particle pollution, is a collective name for fine solid or liquid particles added to the atmosphere by processes at the earth's surface. Particulate matter includes dust, smoke, soot, pollen and soil particles [EEA website]. PM can have different sizes and shapes and can be made up of hundreds of different chemicals (figure 1, US EPA website). The sizes and chemical composition of this mixture can change in time and space, depending on emission sources and atmospheric and weather conditions.

PM is present in atmosphere as: primary particle, emitted directly (*primary PM*); "secondary" particle, produced as a result of chemical reactions involving PM forming (precursor) gases after

their emission: SO_2, NO_X, NH_3 and NMVOCs (*secondary PM)* [EEA 2013]. The residence time of PM varies from few minutes to several days depending on the particulate size and the concerned atmospheric layer. The particles can also be transported over long distances and their removal may occur via rainfall, gravitational sedimentation or coagulation with other particles [Baldacci S, Epid Prev 2009; Sarno G, Epid Prev 2013].

PM is divided into different categories depending on the aerodynamic diameter of the particles; the penetration depth depends on the particle size (figure 2) (table 1) [Künzli N, ERS 2010].

2.2.2 Biological allergens

Allergens are antigens that react with specific Immunoglobulin E (IgE) antibodies, inducing an allergic state in humans or animals. They originate from a wide range of animals, insects, mites, plants, fungi or occupational sources [EEA website; Bousquet J, Allergy 2008]. Indoor allergens are mainly originated from house dust mites (e.g. *Dermatophagoides pteronyssimus* and *Dermatophagoides farinae*), furred pets (primarily cat and dog dander), cockroaches (e.g. *Periplaneta americana*, *Blattella germanica* and *Blatta orientalis*), moulds (e.g. *Alternaria, Cladosporium, Aspergillus, Penicillium* and *Fusarium*) and, to a lesser extent, plants and rodents [Hulin M, ERJ 2012]. Primary sources for outdoor allergens include plants (grasses, weeds and trees pollens), fungi, molds and yeasts [Bousquet J, Allergy 2008] (table 2). The presence of water, nutrients or elevated temperature facilitates the proliferation of moulds, cockroaches and mites, thus increasing the concentration of allergens. Endotoxins are components of the outer membrane of various Gram-negative bacteria and they originate from contaminated humidifiers, pet keeping and contact with livestock, or storage of food waste [Hulin M, ERJ 2012].

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 [Burge HA, Envir Health Perspect 2000; Lancey ME, Springer 2007].

2.2.2.1 House Dust Mites

House dust is composed of several organic and inorganic compounds, including fibers, mold spores, pollen grains, insects and insect feces, mites and mite feces [GINA website; Maio S, Allergy Frontiers 2009]. The principal domestic mite species, *Dermatophagoides* and *Euroglyphus*, are particularly abundant in mattresses, box springs, pillows, carpets, or fluffy toys. Mites proliferate in warm (above 20°C) and humid conditions (80% or higher relative humidity). When humidity is lower than 50%, mites dry out and die [Bousquet J, Allergy 2008].

Pets

Cats and dogs are another important source of indoor allergens, released through secretions (saliva), excretions (e.g., urine) and danders [GINA website; Maio S, Allergy Frontiers 2009].

The principal sources of cat allergen are the sebaceous glands, saliva and the peri-anal glands, but the main reservoir is the fur. The major cat allergen, *Fel d1*, is transported in the air by particles > 2.5 μm and can remain airborne for long periods [Bousquet J, Allergy 2008]. Dogs produce two important allergenic proteins (C*an f1* and *Can f2*): their characteristics (allergen carrying particles, ubiquity, etc.) are similar to those of cat allergens [GINA website; Maio S, Allergy Frontiers 2009].

Cockroaches

Of the 4500 species of cockroach, approximately 30 are associated with human dwelling, and 4 are known to be pests, including the *Blatta orientalis*, *Blattella germanica*, *Periplaneta americana* and *Supella longipalpa*. Cockroaches can be found in any building that has a mean of access, a source of water, food, adequate temperature, and shelter for their survival. While most of the studies of cockroaches and asthma have focused on inner-city environments, it is clear that cockroaches can also be found in homes, schools, and other buildings that are located in suburban and rural environments regardless of the socioeconomic status of occupants [Portnoy J, J Allergy Clin Immunol 2013]. The main allergens (*Per a1*, *Bla g1*, and *Bla g2)*, produced by dead bodies and fecal matter, have been frequently found in floor dust, kitchen cabinets, bathrooms and basements [Maio S, Allergy Frontiers 2009].

2.2.2.2 Mould/Dampness

Domestic moulds are very important allergens and are commonest in humid areas. Major sources of mould growth indoors are flood, leaks in building fabric, condensation, unattended plumbing leaks and household moulds. They can also grow in aeration and conditioning ducts

(central heating and air conditioning) and water pipes. Microscopic fungi present in homes are capable of producing spores all year round and are responsible for persistent symptoms, especially in hot and humid dwellings. They are particularly abundant in bathrooms and kitchens. Moulds also grow on plants, which are watered frequently, or on animal or vegetable waste, furnishings, wallpaper, mattress dust and fluffy toys [Bousquet J, Allergy 2008].

2.2.2.3 Fungi

Moulds and yeasts can be both indoor and outdoor airborne allergens. Dark, humid, and poorly ventilated areas are optimal for indoor fungal growth. Indoor fungi can grow within the systems used for cooling, heating, and humidification. Outdoor fungi tend to be seasonal allergens in temperate zones, where some fungi sporulate on warm, dry summer days, and others prefer the rainy nights of fall [GINA website; Maio S, Allergy Frontiers 2009].

Aerobiological studies have shown the majority of fungal spores in outdoor air to be from the phyla *Ascomycota* and *Basidiomycota*. The most commonly studied allergenic fungi are conidia-producing anamorphs of ascomycetes, such as *Alternaria*, *Aspergillus*, *Botrytis*, *Cladosporium*, *Epicoccum*, *Fusarium* and *Penicillium* species [Knutsen AP, J Allergy Clin Immunol 2012].

2.2.2.4 Pollens

Pollen allergens come mainly from trees, grasses and weeds. The air concentration of pollens varies with location and atmospheric condition, but in general, tree pollens predominate in the early spring, grass pollens in the late spring and summer, and weed pollens during summer and fall [GINA website; Maio S, Allergy Frontiers 2009]. 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 [D'Amato G, Allergy 2007].

2.3 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 [Bousquet J, Allergy 2011].

Currently, more than 25% of the European population are affected by IgE-associated allergic diseases depending on age group [Valenta R, J Intern Med 2012]. The highest prevalence occurs in late adolescence/early adulthood, with, for example, between 4.5% and

29.2% of young adults in European countries having sensitization to grass pollen [Bousquet J, Allergy 2007].

The different manifestations of allergic diseases involve the respiratory system (asthma, rhinoconjunctivitis), the skin (atopic eczema, dermatitis), and the gastrointestinal tract (food allergy and eosinophilic gastroenteritis) and may have systemic manifestations involving different organs (life-threatening anaphylactic shock) [Bousquet J, Allergy 2011].

The sequential development of allergic disease manifestations during early childhood is often referred to as the “allergy march”. Various epidemiological and birth-cohort studies have begun to elucidate the evolution of allergic disease manifestations and to identify populations at risk for disease. These studies emphasize the effects of environmental factors and genetic predisposition on the “allergy march”. In many patients, food allergy precedes inhalant allergen allergy. In the “allergy march”, atopic dermatitis and asthma are linked, but atopic dermatitis does not necessarily precede asthma, whereas allergic rhinitis is a risk factor for asthma and can precede asthma [Zheng T , Allergy Asthma Immunol Res 2011].

Allergic rhinitis and asthma, the two principal closely related allergic diseases, significantly reduce quality of life (QoL) and have a significant economic impact on society [Bousquet J, J Allergy Clin Immunol 2001].

In particular, allergic rhinitis and asthma have a significant economic impact on the patient, the patient’s family and the society as a whole. According to a European survey of diagnosed allergy sufferers, around 80% of respondents found that their disease considerably affects their daily activities. The growing prevalence of allergy also has major economic consequences for society by absence from education or work or by impaired performance, thereby placing a greater burden on healthcare resources and increasing medication costs. For example, economic costs due to ragweed-related allergy in Germany amount to €32 million per year [Reinhardt F, Federal Ministry Report 2013].

2.3.1 Food allergy

According to the World Health Organization (WHO), food allergy concerns 4-10% of children (including 6-8% and 3-5%, respectively, of infants and children up to the age of 8 years) and 2-4% of adults. Severe, generalized allergic reactions to food can be classified as anaphylaxis [Jenerowicz D, Ann Agric Environ Med 2012].

Patients sensitized to pollen allergens may present cross-reactivity with certain foods [Jenerowicz D, Ann Agric Environ Med 2012]. It has been observed that adolescent or adult patients suffering from pollinosis associated with birch pollen allergens, in 50%-70% also show immediate symptoms upon ingestion of birch pollen-related fruit and vegetables (e.g. apple, hazelnut, carrot, and celery) [Jenerowicz D, Ann Agric Environ Med 2012].

2.3.2 Atopic eczema, dermatitis

Atopic eczema is a clinically well-defined inflammatory, chronically relapsing, highly itchy skin disease with a typically age-related distribution and morphology. It occurs often in families with other atopic diseases (bronchial asthma and/or allergic rhinoconjunctivis). Atopic eczema is one of the most common skin diseases which affects up to 20% of children and 1–3% of adults in most countries of the world [Ring J, J Eur Acad Dermatol Venereol 2012].

As a multifactorial disease with a genetic background, atopic eczema has a large number of individually different trigger factors.

No overall trend for the incidence or prevalence of atopic eczema has been found worldwide. However, in Africa [e.g. from 9.9% (1995) to 20.9% (2001–02) in Morocco in 13-14 years old children], eastern Asia [e.g. from 10.1% (1996) to 13.6% (2006) in Japan in a wider-ranged age group 7–15], western Europe [e.g. from 11.7% (1992) to 17.4% (2001) in 5–7 year old children in Switzerland] and parts of northern Europe [e.g. from 17.8% (1995–96) to 21.0% (2001–02) in 6–7 year old boys in the UK] trends in atopic eczema prevalence were mainly increasing [Deckers IA, PLoS One 2012].

2.3.3 Asthma

Several studies have shown that rates for asthma vary considerably from one country to another and there are more than 300 million people worldwide who are affected by asthma [Ozdoganoglu T, Ther Adv Resp Dis 2012]. In Europe, it is estimated that asthma affects about 30 million of children and adults under 45 yrs age, with a prevalence ranging from less than of 3% to more than 9% in northern and western countries among adults aged 18-44 yrs [ERS white book 2013].

Whithin the World Health Survey, the global prevalence rates of doctor diagnosed asthma, clinical/treated asthma and wheezing in adults were 4.3%, 4.5%, and 8.6% respectively, and varied by as much as 21-fold amongst the 70 countries investigated; in Europe the prevalence

rates were 5.1%, 5.3% and 10.7% respectively. Australia reported the highest rate of doctor diagnosed, clinical/treated asthma, and wheezing (21.0%, 21.5%, and 27.4%) [To T, BMC Public Health 2012].

Some European prevalence rates of diagnosed asthma are reported in figure 3.

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 [De Marco R, ERJ 2012]. Although treatment for asthma has improved substantially, the prevalence of asthma continues to increase, particularly in low- and middle-income countries, or in some ethnic groups in which prevalence was previously low [Baïz N, Clin Chest Med 2012] as communities adopt modern lifestyles and become urbanized. With a projected increase in the proportion of the world's population living in urban areas, it is estimated that there may be an additional 100 million people with asthma by 2025 [WHO 2007; To T, BMC Public Health 2012].

In Italy, during the past 20 yrs, asthma prevalence has increased by 38%, in parallel with a similar increase in asthma-like symptoms and allergic rhinitis [De Marco R, ERJ 2012].

The ISAAC (International Study of Asthma and Allergies in Childhood) study Phase Three (1999-2004) also found an increasing trend in the prevalence of asthma and allergies particularly in urban areas, where children were found to have more allergic reactions to outdoor and indoor allergens, except those where the prevalence was already extremely high [Asher MI, Lancet 2006]. In addition, the incidence of allergic symptoms in children was associated to allergens in indoor environments with poor air quality [EFA Book 2011].

The burden of asthma assessed by disability-adjusted life years (DALYs), which ranks 22 worldwide, is similar to that of other chronic diseases such as diabetes or Alzheimer disease [WHO 2007].

It is estimated that asthma accounts for about 250000 annual deaths worldwide with large differences between countries. Mortality shows higher rates in countries where access to essential medical care is problematic. The countries with the highest death rates are those in which asthmatic people do not have access to controller therapy [GINA website].

Childhood asthma accounts for many lost school days and may deprive the affected children of both academic achievement and social interaction [WHO 2007].

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 quality of life. Undertreatment may also increase the economic and social burden of the disease in terms of direct costs, and school and work day losses [EFA Book 2011].

Epidemiological studies have consistently shown that asthma and rhinitis often co-exist in the same patients: over 70% of people with asthma have concomitant rhinitis [GINA website]. Moreover, allergic rhinitis is a risk factor for asthma [EFA Book 2011].

In most low and middle income countries, the prevalence of active smoking in adults with asthma is about 25%. Compared to nonsmokers with asthma, active smokers have more severe asthma symptoms, an accelerated decline in lung function and a reduced response to corticosteroid therapy [Polosa R, ERJ 2013]. Obesity aggravates inflammation in asthma leading to increased severity of asthma and decreased responsiveness to the treatment, thus leading to increased morbidity and mortality in obese asthmatics compared to non-obese asthma patients [Ramasamy AK, Lung India 2014].

2.3.4 Allergic rhinitis

Hay fever characteristically occurs in three phases: sensitization, early phase reaction, and late phase reaction. Susceptible individuals become sensitized on initial exposure to an antigen. An antigen is a substance (usually protein) that elicits an immune response, causing the production of antibodies. 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, which include sneezing, itching and rhinorrhea (discharge from the nasal mucous membrane). The late phase reaction begins 4 to 6 hours after antigen exposure and can last up to 24 hours. In this late phase reaction, symptoms characteristically shift from mainly sneezing and rhinorrhea to nasal congestion and obstruction [Ferguson BJ, Otolaryngol Head Neck Surg 2004].

The symptoms of seasonal rhinitis may significantly reduce the ability to study and work of an affected individual. Nasal congestion associated with late phase reaction is an important factor contributing to impairment of performance, because it disturbs sleep causing daytime fatigue [Ferguson BJ, Otolaryngol Head Neck Surg 2004]. Other complications associated with allergic rhinitis and increasing the likelihood of problems when studying and working are: recurrent middle ear infections, Eustachian tube dysfunction, allergic conjunctivitis, sinusitis, conductive hearing loss, sleep disorders, frequent respiratory infections, chronic cough and asthma [Bousquet J, J Allergy Clin Immunol 2001]. Severe allergic rhinitis negatively impacts school

performance in fact, in a French study, 40% of students with allergic rhinitis reported to have been disturbed in their schoolwork [Institut CSA 2009].

The prevalence of allergic rhinitis is estimated to range from 17% to 29% in Europe (figure 3). Using a conservative estimate, it is proposed that allergic rhinitis occurs in approximately 500 million people. About 200 million people also have asthma as a comorbidity [Ozdoganoglu T, Ther Adv Resp Dis 2012].

Most patients with asthma have rhinitis suggesting the concept of 'one airway one disease' [Bousquet J, Allergy 2003]. The presence of allergic rhinitis commonly exacerbates asthma, increasing the risk of asthma attacks, emergency visits and hospitalizations for asthma. However, not all patients with rhinitis have asthma and there are differences between rhinitis and asthma [Ozdoganoglu T, Ther Adv Resp Dis 2012].

Despite recognition that allergic rhinitis and asthma are global health problems, there are insufficient and heterogeneous epidemiologic data. The clinical definition of rhinitis is difficult to apply in the epidemiologic settings of large populations due to the lack of economic resources to visit each individual or to obtain the laboratory confirmation of each immune response. In fact, beyond allergic rhinitis, nonallergic rhinitis is also very common (from 17 to 52% of all rhinitis cases in adults) [Lieberman P, Curr Allergy Asthma Rep 2014]. It seems that there is an overestimation of allergic rhinitis using questionnaires only. The attributable fraction of IgE-mediated allergy in patients diagnosed with allergic rhinitis by questionnaires has been reported to be slightly over 50% [Arshad SH, Acta Paediatr 2002]. Thus, using only questionnaires in epidemiologic studies may overestimate the true prevalence of allergic rhinitis.

The worldwide incidence and prevalence of allergic rhinitis has been increasing since at least 1990 in almost all westernized countries. One or more factors among increasing air pollution, indoor environment, improved hygiene practices, climatic changes could be the cause of this upward trend [De Marco R, ERJ 2012]. In Italy, from 1991 to 2010, the prevalence of allergic rhinitis increased continuously moving from 16.8% to 25.8% [De Marco R, ERJ 2012].

2.3.5 Direct and indirect costs of respiratory allergies

Very few national statistics are available about the cost of respiratory allergies, particularly of allergic rhinitis. Available data vary greatly from country to country which may be also due to different reimbursement policies.

Even if few data are available, there is evidence that the more severe the symptoms of asthma, the greater the costs. The economic cost of asthma is considerable both in terms of direct medical costs (such as hospital admissions and the cost of pharmaceuticals) and indirect medical costs (such as time lost from work and premature death) [IUATLD 2011]. In Europe, costs for asthma were €72.2 billion, of which €19.5 billion for direct costs and €14.4 billion for indirect costs, in 2011 [ERS lung white book 2013]. Indeed, prevention programs and good control of the disease can considerably reduce costs [Haahtela T, Thorax 2006].

A recent European EFA (European Federation of Allergy and Airways Diseases Patients' Associations) survey showed relevant direct costs for respiratory allergy: e.g. in Germany, direct costs for allergic rhinitis were €220Millions per year of which €179M for medication and €41M for doctor and hospital visits [EFA Book 2011].

A recent study of Swedish patients suffering from allergic rhinitis estimated that the mean productivity loss was 5.1 days equivalent to €653 per worker per year, resulting in a total productivity loss of €2.7 billion a year. It has been also computed that a decrease in productivity loss of 1 day per patient per year could lead to save €528M [Hellgren J, Allergy 2010].

However, it is difficult to estimate indirect costs for patients with allergic rhinitis since few patients (about 45%) seek medical advice. On the contrary, allergic patients make large use of over-the-counter therapies [EFA Book 2011].

The National Asthma Control Program (NACP) has made significant progress in controlling asthma in the U.S: over the last 12 years, costs due to asthma illness and death have decreased by $23.1 billion. These savings reflect a shift from visits in more costly medical settings (hospitals and emergency rooms) to less expensive primary care settings (doctor offices and outpatient clinics). In addition, asthma death rates have decreased by 27% since 1999 [CDC 2013]. Integrated national programmes (specific training for primary care doctors and appropriate communication flows within a network of specialists, pharmacies and patients' organizations of asthma and allergies), such as those launched in Finland and in the Czech Republic, have proven to be effective in terms of an improved quality of life for patients and reduced costs despite the increase of allergy in the population [EFA Book 2011].

2.4 Risk factors for asthma and allergic diseases

Risk factors for asthma were classified as host factors, if involved in the development of asthma, and environmental factors, if may influence the susceptibility to the development of asthma in predisposed individuals, cause exacerbations of asthma, and/or cause symptoms to persist. Host factors include the genetic predisposition to the development of either asthma or allergic sensitization, airway hyperresponiveness, gender and race; environmental factors include allergens, occupational sensitizers, tobacco smoke, air pollution, respiratory (viral) infections, diet, socioeconomic status, and family size [GINA website].

As regard allergic rhinitis, the best established risk factor is a family history and exposure to allergens; changes in lifestyle, increase in exposure to allergens, pollution and irritants, modification in diet responsible for the diminution of protective nutrient intake and decrease in infections were associated to the increase in the prevalence of allergic rhinitis observed over the last 40 years [Bousquet J, J Allergy Clin Immunol 2001].

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 and can involve many different organs (typical allergic symptoms include asthma, rhinoconjunctivitis, allergic rhinitis and skin lesions) and any age group [Jenerowicz D, Ann Agric Environ Med 2012]. Even if respiratory allergic diseases show strong familial association, the rapid rise in the prevalence of these diseases occurred in recent decades cannot be explained by genetic factors alone [D'Amato G, MRM 2011]. Allergic diseases are more common in highly developed countries and less common in low-middle income countries. There are suggestions that urban life promotes allergy through an interaction of genetic and environmental factors. Indeed, the human susceptibility to allergens may increase in presence of chemicals and aerosols, e.g. diesel exhausts, O_3 and NO_2 [D'Amato G, MRM 2011], as well as PM [D'Amato G, Allergy 2002].

Among the main risk factors for allergic diseases will be taken into account PM, airborne perennial allergens (house dust mites, pets, cockroach) and seasonal allergens (moulds and dampness, pollens).

2.4.1 Link with PM and PM sources

In the past decades an important increase in the prevalence of asthma and allergic respiratory diseases has been documented in most countries of the world, with large differences being reported within different areas [Jie Y, Rev Environ Contam Toxicol 2013], particularly in industrialized countries. The large differences in prevalence of reported asthma and allergic diseases may partly be explained taking into account the crucial variations in the level of particulate air pollution from motor vehicles, due, for instance, to different air quality policies adopted by different countries. Nonetheless, it is also important to consider that a wide inter-individual variability in exposure and response to air pollutants exists, and that further researches are needed to deeply understand the etiology for the development of atopic diseases.

Considering that vast majority of European population lives in urban areas where PM levels exceed the WHO 2005 Air Quality Standards [WHO 2005], and that there is no evidence of a safe level of exposure below which no adverse health effects occur [WHO 2013], pollution derived from PM creates a remarkable burden of disease. Even though it is not always simple to identify causal associations between specific environmental contamination and health effects, there is clear evidence that allergic diseases are influenced by environmental factors [Jenerowicz D, Ann Agric Environ Med 2012].

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 4907 French children [Pénard-Morand C, ERJ 2010]. In a cohort of 5338 children living in 6 French cities, an association between asthma, especially if atopic, and dwelling in areas with a concentration of $PM_{2.5}$ > 10 µg/m^3 was shown; this association was stronger in children who lived in the same house for more than 8 years [Annesi-Maesano I, Respir Med 2007] (table 3). These results were also confirmed in the multicentric Traffic, Asthma, and Genetics (TAG) study carried out on 6 birth cohorts. The study showed a significant association between $PM_{2.5}$ and allergic rhinitis at 7 or 8 years of age (OR 1.37 per 5 µg/m^3 $PM_{2.5}$ mass concentration) [Fuertes E, J Allergy Clin Immunol 2013] (table 3).

The nanosize pollutants seem to have more aggressive implications than other respirable fractions of urban aerosol, both at respiratory level and at molecular level: ultrafine particles (UfPs, PM<0.1 µm) can lead molecular changes, such as immunoregulation, reactive oxygen

species generation to trigger histaminic response, mast cell activation etc. and are proposed to represent the subclinical effects that manifest disease exacerbations or subjects' predisposition to pathologies onset [Kumar S, Rev Environ Health 2013]. Few studies assessed the effects of indoor UFPs, even though many indoor sources have been identified. The potential respiratory effects of such exposure could be really important because these particles cause oxidative stress and inflammation in the lungs. Thus, indoor UFPs exposure may contribute to the exacerbation of asthma symptoms in susceptible individuals [Weichenthal S, Indoor Air 2007].

In two general population samples, studied in Italy during the '90s, high indoor levels of $PM_{2.5}$ were associated with bronchial and asthmatic symptoms [Simoni M, JEAEE 2004] (table 3). In the 6 French cities study, the impact of classroom air quality was analyzed, showing a significant increased prevalence of past year asthma in the classrooms with high levels of $PM_{2.5}$ (OR 1.21) (table 3). The relationship was observed mostly for allergic asthma (OR 1.42). A significant positive correlation was found between exercise-induced asthma and the levels of $PM_{2.5}$ and acrolein in the same week [Annesi-Maesano I, Thorax 2012].

Although PM pollution generated by industry and vehicle exhausts from car traffic may be an carrier factor for atopic sensitization, the evidence in support of this assumption remains inconsistent.

Epidemiological studies have demonstrated a strong association between people living in close proximity to roads with high traffic density and increased allergic symptoms, reduced lung function, increased sensitization to common aeroallergens [Urman R, Thorax 2013; Brender JD, Am J Public Health 2011; Kim BJ, J Allergy Clin Immunol 2014; McConnell R, Environ Health Perspect 2010; Jacquemin B, Semin Respir Crit Care Med 2012; Cakmak S, Envir Int 2012]. In an Italian general population sample it was demonstrated that people living within 100m of heavy traffic roads showed an increased adjusted risks for persistent wheeze in males and for positivity to skin prick test, asthma diagnosis and attacks of shortness of breath with wheeze among females [Nuvolone D, Environ Health 2011] (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 years) living in Palermo [Cibella F, PAI 2011] (table 3). A recent survey carried out on 1441 adolescents 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 [Robinson CL, Thorax 2011] (table 3).

Acute episodes of air pollution are clearly associated with exacerbation of respiratory symptoms and allergic events [Lemke LD, J Expo Sci Environ Epidemiol 2013; Song S, Sci Total Environ 2013], particularly in subjects with airway diseases [Manney S, Occup Environ Med 2012].

Worldwide, the huge use of biomass for heating, cooking and lighting, raises a particular concern. Over two million people worldwide rely on biomass fuels to supply their household energy needs, with an estimated 3.5 million deaths annually being attributable to biomass smoke exposure [Lim SS, Lancet 2012], even though a recent review article on the global burden of disease showed a decrease from 2nd to 3rd rank for household air pollution derived from solid fuels [Murray CJ, NEJM 2013]. Several studies have validated the association between biomass smoke exposure and respiratory diseases [Bihari V, J Environ Biol 2013; Jagger P, Energy Policy 2014; Trevor J, J Asthma 2014], even though no significant association has been found between the type of indoor energy sources used and the presence of atopic dermatitis in the ISAAC study [Vicedo-Cabrera AM, BMC Public Health 2012].

In indoor settings, a recent Indian study has shown that the use of biomass and solid fuels is associated with a significantly higher risk of asthma for adult women with respect to the use of cleaner fuels [Agrawal S, J Asthma 2012] (table 3). Furthermore, kerosene, often advocated as a cleaner alternative to solid fuels, may impair lung function and increase asthma [Lam NL, J Toxicol Environ Health B Crit Rev 2012].

The indoor PM levels and composition are influenced by fuels combustion and pollutants that enter the confined environments from outdoor, but a major concern is addressed to environmental tobacco smoke (ETS) as source of indoor PM.

In a dose-response association study on 10298 schoolchildren, exposure to ETS at home was significantly associated with asthma [Graif Y, Dermatology 2013] (table 3).

Recent epigenetic studies have shown that the exposure to environmental factors during early childhood, such as environmental pollution and ETS, may induce a long-lasting altered genetic state, adapting to a persistent "Th2 state", thus influencing the development of asthma or atopic dermatitis [Tezza G, Early Hum Dev 2013].

Few reduction studies demonstrated how the abatement of PM levels can decrease the respiratory health risk and improve health conditions in asthmatic subjects. In a randomized

controlled study, aimed at testing the use of air cleaners and a health coach intervention to reduce secondhand smoke exposure in reducing PM levels at home, a significant reduction in indoor PM concentrations and a significant increase in symptom-free days in children with asthma were shown [Butz AM, Arch Pediatr Adolesc Med 2011]. Some unplanned events of PM concentration decrease in specific areas had a positive impact on health: in 1986-87, the closure and reopening of a steel mill in Utah Valley resulted in a three times lower prevalence of children hospital admission for bronchitis and asthma as reported by Pope [Pope CA, Am J Public Health 1989]; 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 various respiratory symptoms, including bronchitis, nocturnal dry cough and conjunctivitis symptoms [Bayer-Oglesby L, Environ Health Perspect 2005]. 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, even though this association appears to be not equally distributed across the population, but modified by the individual genetic arrangement determining oxidative stress defense [Curjuric I, ERJ 2010].

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; CI, 0.16-1.13) [Laden F, AJRCCM 2006].

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.

Another important topic to be taken into account is that PM, apart from being a widespread air pollutant presents wherever people live, is often combined with or is a vehicle for other pollutants, such as chemicals, allergens, pollens etc., thus creating a complex synergistic matrix of interactions and health hazards.

In conclusion, as reported in a recent review about the health effects of PM, a dose–response relationship between exposure and adverse effects has been identified and improvement in health endpoints is observed when the PM exposures are reduced. 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 [Anderson JO, J Med Toxicol 2012].

2.4.2 Link with biological allergens

2.4.2.1 House dust mites

In developed countries, homes have been insulated for energy efficiency and carpeted, heated, cooled and humidified, thus creating an ideal habitat for indoor allergens [Maio S, Allergy Frontiers 2009].

House dust mites have been epidemiologically associated with asthma development and exacerbations and allergic rhinitis. In a US birth cohort, early exposure to high levels of dust mite allergens (≥10 µg/g) was associated with increased risks of asthma and wheeze at age 7 years; lower levels (≥2 to <10 µg/g) were associated with increased risks of allergic rhinitis [Celedón JC, J Allergy Clin Immunol 2007] (table 4). Early life exposure to carpet in house was associated with early-onset asthma (before 5 yrs old) and ever-having asthma in Taiwan children; the study showed higher risks considering the presence of carpet in the children's bedroom [Chen YC, Int J Hyg Environ Health 2011] (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 [Davey G, Clin Exp Allergy 2005] (table 4).

Continuous exposure to house dust mites may contribute to chronic bronchial hyper-responsiveness [Wong GW, ERJ 2002] (table 4) and to reduction of the pulmonary function [Jaen A, Clin Exp Allergy 2002]; data from the European Respiratory Community Health Survey (ECRHS) have indicated that asthmatic subjects, sensitized to mites, had a lower FEV_1 (forced expiratory volume in the first second) and FEV_1/FVC (FEV_1/forced vital capacity) ratio than non-sensitized asthmatics [Jaen A, Clin Exp Allergy 2002].

In the Chinese sample of the ISAAC study an increasing sensitization to dust mites was associated with the increase in prevalence of wheeze; high degrees of sensitization were risk factors for asthma diagnosis (OR 3.44, 1.75–6.41) [Li J, Clin Exp Allergy 2013]. 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) [Schäfer T, Allergy 2007].

2.4.2.2 Pets

The ARIA guideline on allergic rhinitis reports that cats and dogs are major allergens triggers in asthma, rhinitis or rhino-conjunctivitis [Bousquet J, J Allergy Clin Immunol 2001]; 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 [Skorge TD, Thorax 2005] (figure 4). 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 [Lombardi E, PAI 2010] (figure 4). Differently, a Taiwan study showed a significant association between early-life dog exposure and early onset of asthma (before 5 yrs old) (OR 2.40, 1.15-5.01); the same association was found considering exposure to any pet (including dogs, cats, birds, mice and rabbits) (OR 2.50, 1.26-4.98) [Chen YC, Int J Hyg Environ Health 2011] (figure 4). 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) [Schäfer T, Allergy 2007]. 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 [Oberle D, Allergy 2003; Perzanowski MS, AJRCCM 2002] and prevent allergen sensitisation [Oryszczyn MP, Allergy 2003] (figure 4). A reason could be that pet keeping may increase the exposure to bacterial components that may enhance lymphocytes development and so protecting children from the allergy development [Heinrich J, Int J Hyg Environ Health 2011].

This health effect may vary according to the type of pet and to the individuals' allergic sensitization [Svanes C, J Allergy Clin Immunol 2003]. 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 [Svanes C, J Allergy Clin Immunol 2003] (figure 4).

Such inconsistent findings may partly be due to different study design (cohort, case-control, cross-sectional studies), type of exposure (early or current pet ownership, allergen concentrations), health outcome (sensitization, presence of wheeze or asthma) [Almqvist C, Clin Exp Allergy 2003], recall or selection bias; further, interaction between gene and environmental exposure was proposed to be a major cause of the inconsistent observation [Heinrich J, Int J Hyg Environ Health 2011].

2.4.2.3 Cockroach

Cockroach allergens, which are found in many poor inner city areas, have been repeatedly associated with asthma onset or exacerbation in many countries [Davey G, Clin Exp Allergy 2005; Silva JM, PAI 2005; Chen YC, Int J Hyg Environ Health 2011] (table 4); 40%-60% of patients with asthma in urban and inner-city areas have Immunoglobulin E (IgE) antibodies to cockroach allergens [Sohn MH, Allergy Asthma Immunol Res 2012]. A study on 2-4 year old children sample showed that exposure to cockroach allergen in the kitchen was associated with three or more wheezing episodes in the past 12 months [Silva JM, PAI 2005] (table 4). Recently, early-life exposure to cockroach was shown to be associated with early-onset asthma (before 5 yrs old) and ever-having asthma in Taiwan children [Chen YC, Int J Hyg Environ Health 2011] (table 4). In USA children aged 2 months to 10 years, although dust mite was the most common allergen to which the children were sensitised, only cockroach sensitivity showed a significant correlation with wheezing [De Vera MJ, Ann Allergy Asthma Immunol 2003]. In an Italian sample of children, a relationship between cockroach sensitization and rhinoconjunctivis was shown in older allergic children (8-18 yrs) (OR 2.65, 1.06–6.59); moreover, the Population Attributable Risk (PAR) was computed showing that the abatement of cockroach exposure would prevent about one-fifth of rhinoconjunctivitis cases (20.6%) [La Grutta S, PAI 2011].

In a US birth cohort, presence of anti-cockroach IgE was linked to high risk of early wheeze (by 3 yrs of age) (OR 3.25, 1.69-6.24) and presence of both anti-cockroach IgE and anti-mouse IgE was linked to rhinitis (OR 6.64, 1.50-29.45); moreover, a dose-response relationship was found between higher IgE and increased prevalence of wheeze [Donohue KM, J Allergy Clin Immunol 2008]. Exposure to cockroach is also associated with asthma exacerbation: the National Cooperative Inner City Asthma Study showed that exposure in the home 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) [Wang J, Clin Exp Allergy 2009].

2.4.2.4 Mould/dampness and fungi

Dampness is present in 10–50% of houses. Moulds are the source of allergens, Microbial Volatile Organic Compounds (mVOCs) and mycotoxins. Building dampness and moulds are associated with approximately 30-50% increases in a variety of respiratory and asthma-related health outcomes. Unfortunately, no distinction between allergic and non-allergic asthma was done in most studies. 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 [Mendell MJ, Environ Health Perspect 2011]. In children, an increased pooled risk for wheeze caused by indoor mould/dampness has been estimated [Fisk WJ, Indoor Air 2007] (table 4); in Italian children, lifetime and current exposure to mould or dampness were associated with higher risk of having current wheeze [Pirastu R, Envir Res 2009] (table 4). Recently, in the USA an increased risk of having current asthma was shown in children exposed to mould in their house [Nguyen T, Public Health Rep 2010] (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 [Chen YC, Int J Hyg Environ Health 2011] (table 4).

Similar risks for wheeze and current asthma were observed in adults and in general population samples [Nguyen T, Public Health Rep 2010; Fisk WJ, Indoor Air 2007] (table 4).

Associations between moulds and wheezing, asthma, rhino-conjunctivitis, eczema, cough and phlegm are more evident in children than in adolescents, particularly when the exposure occurs early in life. Through the measurement of PAR, 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 [Simoni M, Occup Environ Med 2005].

Recently, a new method was developed to measure fungal DNA as a mould marker in dust/air. The main benefit of using DNA is the possibility of identifying also dead or dormant organisms. Positive significant associations were found between some specific fungal DNA and wheeze,

dry cough at night, daytime breathlessness or asthma diagnosis [Simoni M, PAI 2011, Cai GH, PAI 2011].

2.4.2.5 Pollens

Pollen allergy has a remarkable clinical impact throughout Europe. A body of evidence suggests that prevalence of pollen-related allergic respiratory diseases has increased in past decades. In most European countries, grass pollen allergy is the 1st/2nd most frequent respiratory allergy, with a median prevalence value of 16.9% [Bousquet PJ, Allergy 2007]. After grass, birch is a major allergenic threat in Northern Europe, whilst olive and Parietaria in Southern Europe [D'Amato G, Allergy 2007]. 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 [Li J, Clin Exp Allergy 2013].

Recent studies showed an association between pollens and allergic diseases onset and exacerbations. In the ISAAC Japanese sample there were positive correlations between cedar and cypress pollen counts and allergic rhinoconjunctivitis and between cedar pollen counts and asthma, in children aged 6–7 years; moreover, a positive association was found between cypress pollen counts and allergic rhinoconjunctivitis, in children aged 13–14 years [Yoshida K, Allergy 2013]. The 9 year 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) [Schäfer T, Allergy 2007]. A very recent study on an Australian birth cohort found the following associations at 6-7 yrs of age: cumulative exposure to pollen up to 3 months, with hay fever; between 4 and 6 months, with asthma [Erbas B, Clin Exp Allergy2013] (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) [Canova C, ERJ 2013].

A French study investigated the short-term effects of airborne pollens on asthma attacks: a significant association has been identified 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 [Huynha BT, Prim Care Respir J 2010].

2.4.3 Interaction between air pollution and biological allergens

Many studies about respiratory and allergic risk factors focused on the exposure to a single pollutant. But in 'real life' multiple exposures frequently occur. In the environment, there are always complex mixtures of particle and gas phase pollutants from different sources, which may jointly contribute to the toxic effects: additive or synergic effects are plausible [Billionnet C, Ann Epidemiol 2012; Eggleston PA, Pediatrics 2009]. In particular, ambient inhalable PM, because of their intrinsic electrostatic properties and porous surfaces, readily adhere to free airborne allergens released from animal dander, dust mites, mould and pollen. PM may interact with aeroallergens, promoting airway sensitization by modulating the allergenicity of airborne allergens, in particular influencing plant allergenicity [García-Gallardo MV, Int Arch Allergy Immunol 2013; D'Amato G, Allergy 2002]. In experimental conditions, Phleum pratense (timothy grass) 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 these traffic related pollutants might lead to increased bioavailability of airborne pollen allergens [Motta AC, Int Arch Allergy Immunol 2006]. Further, the airway mucosal damage and the impaired mucociliary clearance induced by air pollution may facilitate the access of inhaled allergens to the immune system [D'Amato G, Allergy 2002]; this link enhances the risk of atopic sensitization and exacerbation of symptoms in sensitized subjects [D'Amato G, MRM 2011].

Much of current knowledge about the pathogenesis of asthma and allergies due to the combined exposure to air pollutants and biologicals is based on *in vitro* or animal studies [WHO 2013-REVIHAPP], because this kind of association is difficult to analyze in uncontrolled setting; little is known about the possible synergetic effect between air pollution and allergens at the population level [WHO 2013-REVIHAPP]. Several laboratory clinical studies demonstrated that the effect of allergen challenge on asthma is higher after prior exposure to an ambient air pollutant; but the clinical significance of this effect modification in the general population is uncertain [Cakmak S, J Allergy Clin Immunol 2012].

In a large Indian study (about 100,000 women and 57,000 men, aged 20-49 years), a combined effects of biomass and solid-fuel use and tobacco smoke on the risk of asthma was found (OR 2.16, 1.58-2.94, in females; OR 1.34, 1.04-1.72, in males) [Agrawal S, J Asthma 2012]. Early

life exposure to smoke and aeroallergens may influence pulmonary function development in childhood: a US birth cohort showed that children exposed to second-hand smoke in early life have 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 [Brunst KJ, PAI 2012].

With regard to the combined effects between air pollution and aeroallergens, inconsistent results were found at population level. In a large French sample of patients suffering from severe seasonal allergic rhinitis the link between the severity of allergic rhinitis 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 [Annesi-Maesano I, Int Arch Allergy Immunol 2012] (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 [Cirera L, Allergol Immunopathol 2012] (table 5). On the contrary, a US study showed that prenatal exposure to cockroach allergen was associated with a larger risk of allergic sensitization (RR 1.15, 1.07-1.25). This risk was increased by exposure to nonvolatile polycyclic aromatic hydrocarbons (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) [Perzanowski MS, J Allergy Clin Immunol 2013] (table 5). The results of a study performed in 11 Canadian cities between 1994 and 2007 showed a higher association between aeroallergens (fungi and pollens) exposure and hospitalizations for asthma in the days of higher air pollution (NO_2, SO_2, PM_{10}, $PM_{2.5}$) [Cakmak S, J Allergy Clin Immunol 2012] (figure 6).

In a recent study on a birth cohort at high risk for asthma, co-exposure to dog allergen and NO_2, or to dog allergen and environmental tobacco smoke, appears to increase the risk for asthma (OR 4.8, 1.1-21.5 and OR 2.7, 1.1-7.1, respectively) [Carlsten C, ERJ 2011] (table 5). A letter commenting these results reported that in 'real life' it is not realistic to separate the role of dog allergens from that of other allergens commonly found indoors (house dust mite and cat allergens); some studies have shown that indoor air pollution, particularly NO_2, enhances the risk of asthma exacerbations in asthmatic children sensitised to dust mite allergens. The importance of both cat and dog allergens as risk factor for induction of allergic sensitisation and

bronchial asthma is not limited to shared indoor environments: in vitro studies have shown cross-reactivity between these allergens [Liccardi G, ERJ 2011].

2.5 Research needs

Although largely avoidable, asthma and allergic rhinitis tend to occur as epidemics and hit young people both in industrialized and developing countries. Reasons for increases in susceptibility to developing allergy in response to exposure to pollen allergens remain elusive, but environmental and life style factors appear to drive these increases [D'Amato G, MRM. 2011]. 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 [WHO 2013-REVIHAPP].

A growing body of evidence shows that components of air pollution interact with airborne allergens and enhance risk of atopic sensitisation and exacerbation of symptoms in sensitised subjects [D'Amato G, J Investig Allergol Clin Immunol 2010].

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 [Hulin M, Int J Hyg Environ Health 2013]. 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 nonallergic 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 nonallergic asthma) and to define the better strategy leading to their optimal management.

Advances in exposure assessment through computational models, in conjunction with validation studies that use targeted monitoring campaigns, can provide a more efficient way to enhance the research on health effects [WHO 2013-REVIHAPP]. Important omics techniques are now available for a deeper assessment of various biochemical pathways operative in health and disease [Fens N, Clin Exp Allergy 2013].

In this framework, the ongoing European project HEALS (Health and Environment-wide Associations based on Large population Surveys) will permit to obtain new evidences about the causal associations between health status and environmental stressors introducing a novel approach based on the integrated use of advanced statistical tools, novel technologies and modeling tools; this model will permit to perform environment-wide association studies in support of EU-wide environment and health assessments.

The abatement of the main risk factors for asthma and allergic diseases and, in particular, of outdoor air pollution, allergens and environmental tobacco smoke, 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. At national and international level, policy makers, physicians' associations and patients' organizations should implement comprehensive preventive programmes and set targets for reducing the burden of respiratory allergies. Meanwhile, the ability of patients and their caregivers and healthcare professionals to identify early symptoms in order to ensure an early diagnosis of allergic diseases should be increased.

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 virtuos 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 [WHO 2009; WHO 2010]. 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 [EFA 2004; Franchi M, Allergy 2006]. 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. The report highlights that new evidences support the scientific conclusions that health effects in some cases occur at air pollution concentrations lower than those serving to establish the air quality WHO guidelines [WHO 2005; WHO 2013-REVIHAPP]. 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 [Brunekreef B, ERJ 2012]; 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 [Brunekreef B, ERJ 2012].

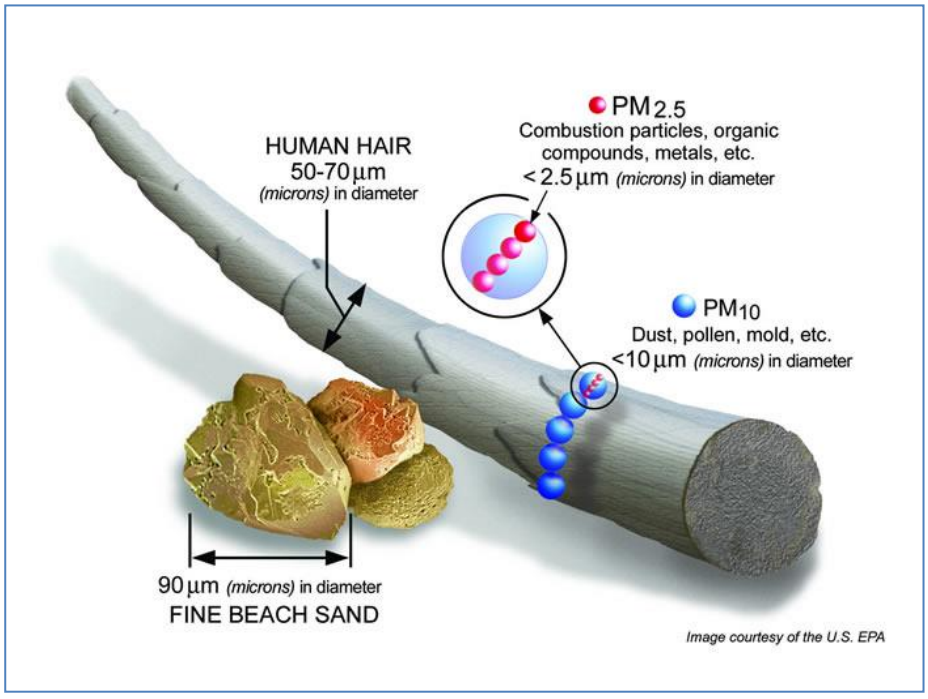


Figure 1. How Big is Particle Pollution? **(**U.S. EPA website)

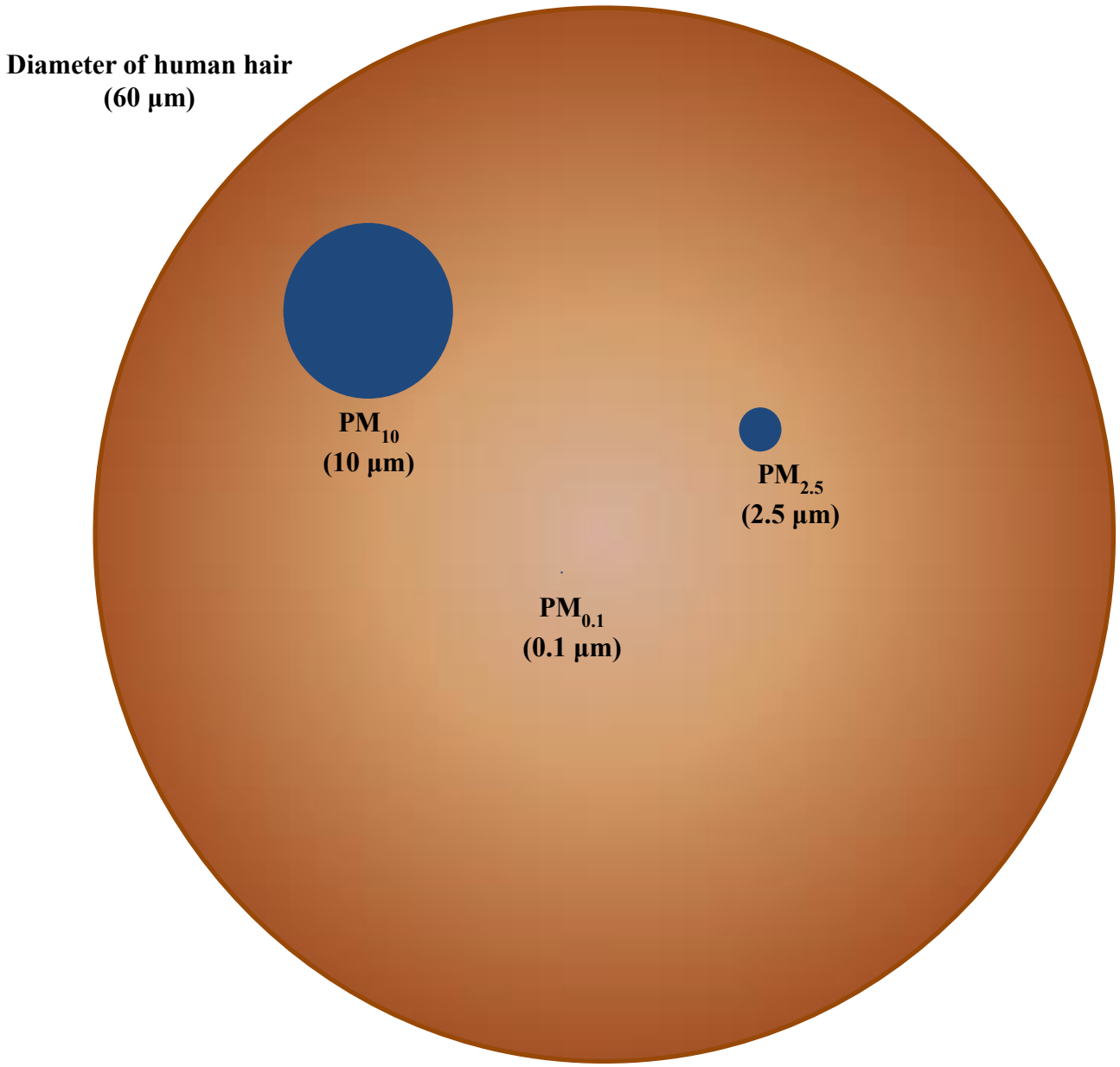


Figure 2. Dimensional comparison between PM and human hair

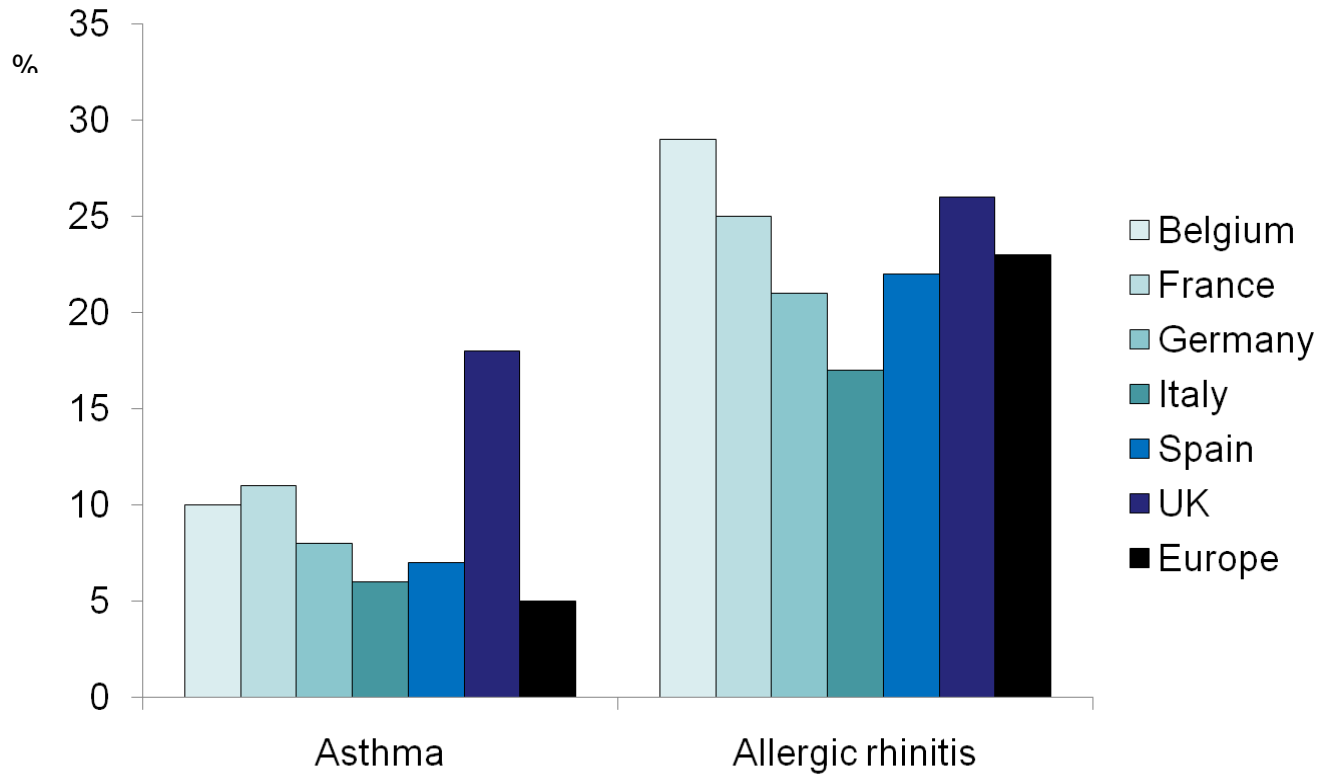


Figure 3. Prevalence rates of asthma and allergic rhinitis in Europe (modified from To T, BMC Public Health 2012 and Ozdoganoglu T, Ther Adv Resp Dis 2012)

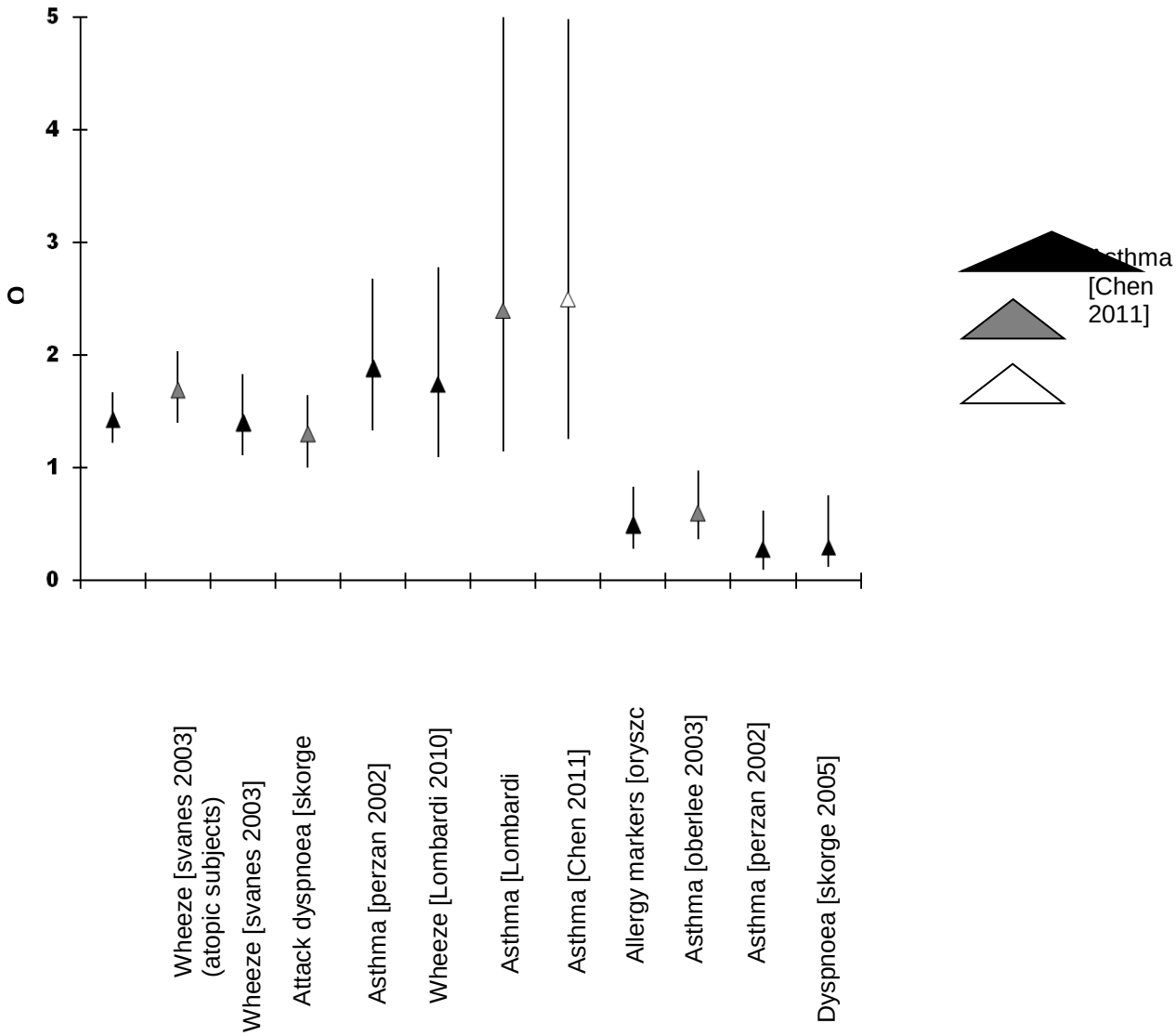
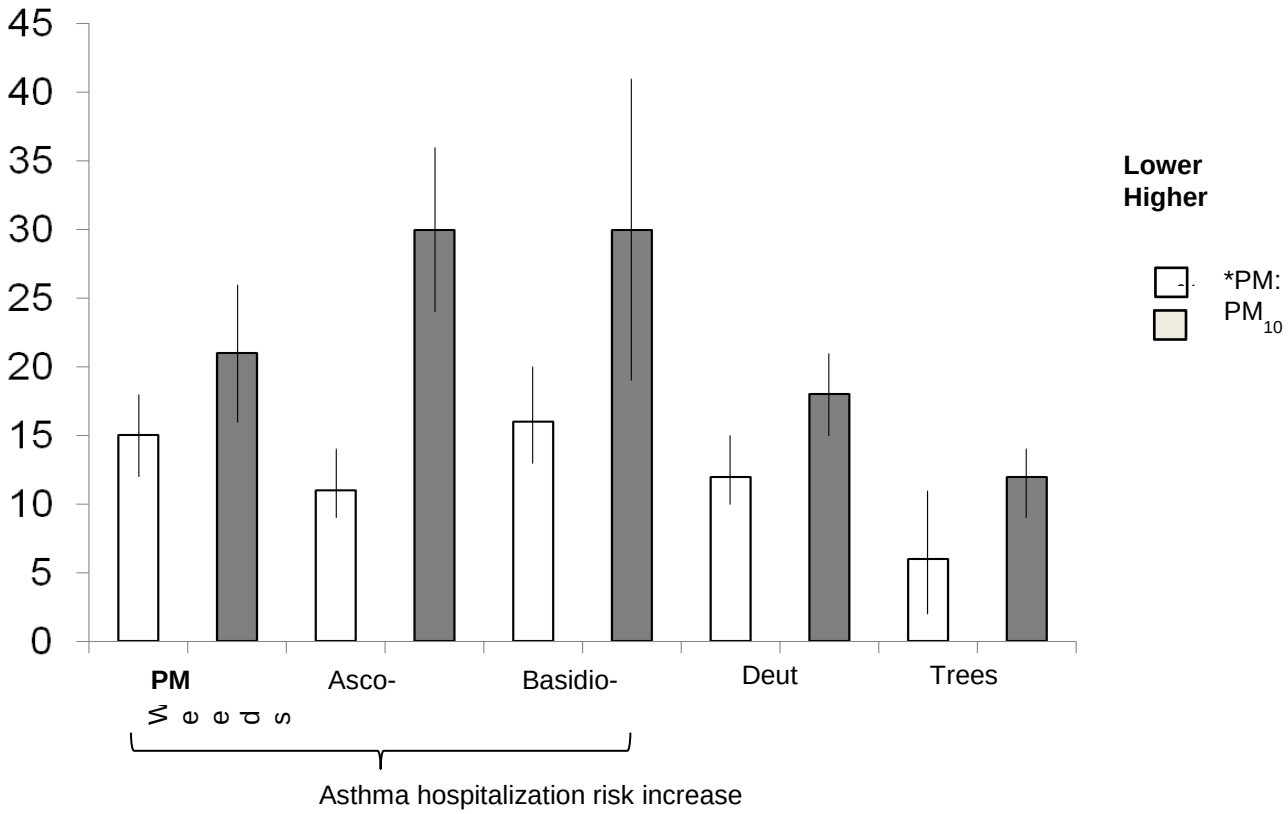


Figure 4. Link between allergic diseases and pets exposure

m



Cakmak S, J Allergy Clin Immunol 2012)

Figure 5. Percentage increase of relative risk of asthma hospitalization for an interquartile range increase in aeroallergen concentration by particulate matter concentration (modified from

Table 1. Main characteristics and sources of PM (Sarno G, Epidemiol Prev 2013)

PM fraction	Characteristics	Sources
PM_{10} **(*Inhalable PM*)**	PM_{10} has a diameter ≤ 10 µm and it is able to penetrate into the upper respiratory tract (nose, throat and larynx).	**Outdoor** • Vehicular traffic • Woodstoves • Organic matter and fossil fuel combustion • Power stations/industry • Marine aerosol • 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
$PM_{10-2.5}$ **(*Coarse particles*)**	$PM_{10-2.5}$ has a diameter ranging from 2.5 to 10µm and it is able to penetrate into the upper respiratory tract (nose, throat and larynx).	
$PM_{2.5}$ **(*Fine PM*)**	$PM_{2.5}$ has a diameter ≤ 2.5 µm and it is able to penetrate into the tracheobronchial tract (trachea, bronchi, bronchioli).	
$PM_{0.1}$ **(*Ultrafine PM*)**	$PM_{0.1}$ has a diameter ≤ 0.1 µm and it is able to penetrate into alveolar region.	

ETS: environmental tobacco smoke

Table 2. Main biological pollutants and their sources

Sources	**Allergens**
Dust, beds, carpets	Acarides (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

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

Study	**Country (n, sample)**	**Exposure**	**Health outcome**	**Measures**
Annesi-Maesano I, 2007	France (5338, schoolchildren)	Outdoor $PM_{2.5}$> 10 $\mu g/m^3$	Asthma Atopic asthma	OR (95% CI): 1.31 (1.04-1.66) 1.58 (1.17-2.14)
Fuertes E, 2013	Canada, Germany, Swiss, Netherlands† (15299, children)	Outdoor $PM_{2.5}$ mass concentration	Allergic rhinitis	OR (95% CI) per 5 $\mu g/m^3$: 1.37 (1.01-1.86)
Simoni M, 2004	Italy (1090, adults)	Indoor $PM_{2.5}$	Bronchitic/asthmatic symptoms	OR (95% CI): 1.39 (1.17-1.66)
Annesi-Maesano I, 2012	France (6590, schoolchildren)	Indoor $PM_{2.5}$	Past year asthma	OR (95% CI): 1.21 (1.05-1.39)
Nuvolone D, 2011	Italy (2061, adults)	Living within 100 m of heavy traffic roads	*Males* Persistent wheeze *Females* positivity to SPT asthma diagnosis attacks of wheeze*	OR (95% CI): 1.76 (1.08-2.87) 1.83 (1.11-3.00) 1.68 (0.97-2.88) 1.67 (0.98-2.84)
Cibella F, 2011	Italy (2150, adolescents)	Heavy traffic on the street of residence	Asthma Rhinoconjunctivitis	OR (95% CI): 1.84 (1.14-2.95) 1.39 (1.08-1.79)
Robinson CL, 201	Peru (1441, adolescents)	Peri-urban environment	Asthma	OR (95% CI): 2.6 (1.3-5.3)
Agrawal S, 2012	India (156316, adults)	Living in households using biomass and solid fuels Combined effects of biomass and solid fuel use and tobacco smoke	*Females* Asthma *Females* Asthma *Males* Asthma	OR (95% CI): 1.26 (1.06-1.49) 2.16 (1.58-2.94) 1.34 (1.04-1.72)
Graif Y, 2013	Israel (10298, schoolchildren)	ETS at home	Asthma	OR (95% CI): 1.25 (1.1-1.5)

$PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 μm; SPT: skin prick test; OR: odds ratio; 95% CI: 95% confidence intervals; ETS: environmental tobacco smoke

† 6 birth cohorts from CAPPS, SAGE, BAMSE, GINIplus, LISAplus and PIAMA studies

* attacks of shortness of breath with wheeze

Table 4. Link between allergic diseases and biological allergens

Study	Country (n, sample)	Exposure	Health outcome	Measures
Wong GW, 2002	China (608, children)	House dust mites	Bronchial hyper-responsiveness	OR (95% CI): 3.67 (1.93-6.97)
Davey, 2005	Ethiopia (7649, general population)	House dust mites	Wheeze Asthma	OR (95% CI): 1.21 (1.00-1.51) 4.09 (2.86-5.84)
Celedon JC, 2007	US (440, children)	House dust mites: high levels low levels	Wheeze Asthma Allergic rhinitis	OR (95% CI): 5.0 (1.5-16.4) 3.0 (1.1-7.9) 3.2 (1.5-7.0)
Chen Y-C, 2011	Taiwan (579, children)	Carpet in house Carpet in children's bedroom	Early-onset asthma Ever-having asthma Early-onset asthma Ever-having asthma	OR (95% CI): 2.88 (1.47-5.64) 2.36 (1.38-4.05) 3.46 (1.44-8.35) 2.69 (1.31-5.55)
Silva JM, 2005	Brazil (73, children)	Cockroach	Wheeze	OR (95% CI): 7.6 (1.4-4.1)
Davey G, 2005	Ethiopia (7649, general population)	Cockroach	Wheeze	OR (95% CI): 1.27 (1.00-1.62)
Chen Y-C, 2011	Taiwan (579, children)	Cockroach	Early-onset asthma Ever-having asthma	OR (95% CI): 2.26 (1.03-4.95) 2.16 (1.15-4.07)
Fisk WJ, 2007	Meta-analysis (children) (general population)	Mould/dampness	Wheeze Current asthma Wheeze	OR (95% CI): 1.53 (1.39-1.68) 1.56 (1.30-1.86) 1.50 (1.38-1.64)
Pirastu R, 2009	Italy (4122, children)	Mould/dampness lifetime exposure Mould/dampness current exposure	Current wheeze Current wheeze	OR (95% CI): 2.41 (1.59-3.65) 1.96 (1.34-2.88)
Nguyen T, 2010	New York States (1412, children) (3315, adults)	Mould	Current asthma Current asthma	OR (95% CI): 2.1 (1.3-3.3) 2.5 (1.8-3.4)
Chen Y-C, 2011	Taiwan (579, children)	Mould odor early life exposure Visible mould early life exposure	Late-onset asthma Ever having asthma	OR (95% CI): 3.16 (1.33-7.52) 1.75 (1.15-2.67)
Erbas B, 2013	Australia (620, children)	Pollens	Hay fever Asthma	OR (95% CI): 1.14 (1.01-1.29) 1.35 (1.07-1.72)

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

Table 5. Link between allergic diseases and combined exposures

Study	**Country (n, sample)**	**Health outcome**	**Single exposure**	**Combined exposure**
Carlsten C, 2011	Canada (380, children)	Asthma	OR (95% CI): Dog allergens 1.0 (0.2-5.2) NO_2 1.3 (0.4-4.5)	OR (95% CI): Dog allergens and NO_2 4.8 (1.1-21.5)
Annesi-Maesano I, 2012	France (36397, adults)	Allergic rhinitis	OR (95% CI): Grass pollen 1.08 (1.04-1.11)	OR (95% CI): Grass pollens and air pollutants 1.08 (1.01-1.14)
Cirera L, 2012	Spain (3939, hospital ER visits)	Asthma ER visits Asthma ER visits	RR% (95% CI): SO_2 5.2 (0.5-10.1) NO_2 2.6 (0.3-5.0)	RR% (95% CI): SO_2 and pollens 5.7 (0.9-10.6) NO_2 and pollens 2.7 (0.4-5.1)
Perzanowski MS, 2013	US (727, young adults)	Allergic sensitization	RR (95% CI): Cockroach allergens 1.15 (1.07-1.25)	RR (95% CI): Cockroach allergens and nPAH 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

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3 Matrix implementation for data collection

According to the information obtained through step 1, a matrix containing all the variable names useful for the analyses to be performed within WP14 was prepared. Moreover, being the focus of WP16 (obesity and childhood diabetes) strictly linked with asthma, it was decided to prepare a common matrix for WP14 and WP16 to be sent to the other partners.

In particular, the matrix contains the following groups of variable names (**attachment 2**):

- cohort profile (acronym, country, period, age range, number of investigated subjects)
- individual characteristics (i.e. sex, age, body mass index, birth weight…)
- health data by questionnaire on asthma, allergic rhinitis, diabetes (i.e. symptoms, diagnosis, use of health services, daily limitation, absenteeism…)
- medications for asthma, allergic rhinitis and diabetes
- clinical assessments (i.e. IgE, skin prick test, spirometry, glycemia…)
- risk or protective factors and environmental exposure by questionnaire (i.e. socio-economic status, smoking habits, exposure to passive smoke, indoor/outdoor pollutants, type of diet…)
- exposure assessments by objective measurements (i.e. data from pollen and air monitoring stations…)

The matrix was sent to the WP14-WP16 partners to be filled in, so to obtain information about availability of environmental and health data to be used for the analyses.

Attachment 2

Instructions: Please place an "X" in columns corresponding to the age/period when indicated tests were performed or samples/data were collected. The column 'general population' was insterted for studies performed on general population samples (from young , adult to elderly).

COHORT PROFILE
ACRONYM:
COUNTRY:
PERIOD:
AGE RANGE of the investigated sample:

Number of investigated subjects:

INDIVIDUAL CHARACTERISTICS

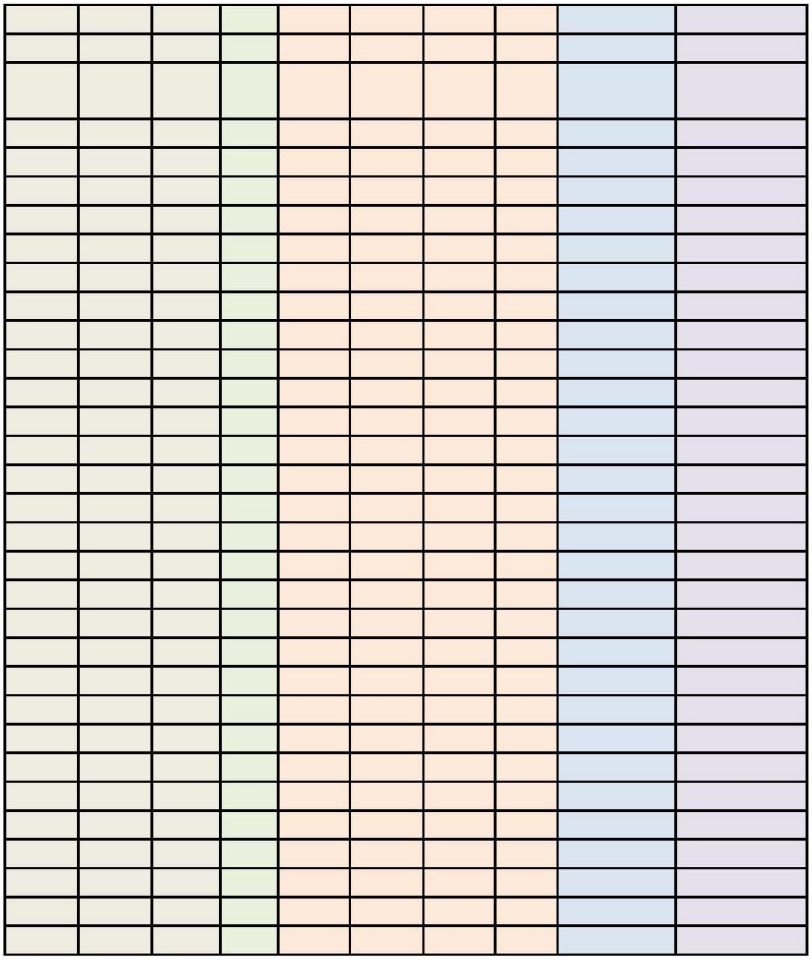
	Prenatal			Post natal	Childhood				Adulthood	General population
	1st Trim	2nd Trim	3rd Trim	Birth	1 year	2-3 years	4-6 years	After		
birth date or age										
sex										
ethnic group										
height										
weight										
BMI (in the case height and weight do not exist isolately)										
fat mass										
lean body mass										
skin folders										
head circumferences										
abdominal circumference										
birth weight										
birth head circumference										
birth skin folders										
mode of delivery										
preterm/at term delivery										

birth difficulties/fetal suffering
weight of the mother first and at the end of the pregnancy
mother's diseases during pregnancy (i.e. diabetes, asthma, infectious diseases, gestosis)

HEALTH DATA
by questionnaire

Asthma, rhinitis and allergies

asthma diagnosis
age of asthma occurrence
wheezing
dry cough
chest tightness
attacks of shortness of breath
nocturnal awakenings because of asthma like symptoms
age of first asthma attacks
age of last asthma attacks
emergency department visit for an asthma exacerbation
hospitalization for an asthma exacerbation
visits of the specialist for asthma
visits of the family doctor for asthma
school/work absenteeism for asthma
daily limitations for asthma
No. of asthma exacerbations in the last year
level of asthma severity
allergic rhinitis diagnosis
sneezing nose
runny nose
itchy nose
blocked nose
itchy/watery eyes
age of first allergic rhinitic symptoms
age of last allergic rhinitic symptoms
Itchy rash



eczema										
food allergy										
visits of the specialist for allergic rhinitis										
visits of the family doctor for allergic rhinitis										
school/work absenteeism for allergic rhinitis										
daily limitations for allergic rhinitis										
level of allergic rhinitis severity										
chronic obstructive pulmonary diseases										
cardiovascular diseases										
other comorbidities										
Diabetes										
diabetes diagnosis										
type of diabetes										
MEDICATIONS										
systemic corticosteroids use for asthma exacerbations										
salbutamol use for asthma										
antihistaminics use for allergies										
inhaled corticosteroids use for allergies										
insulin use										
CLINICAL ASSESSMENTS										
results of skin prick tests										
results of IgE assessment (Total)										
results of IgE assessment (specific)										
results of peripheral blood eosinophilia										
results of measurement of nasal nitric oxide										
results of bronchial hyper-responsiveness assessment										
results of spirometry										
results of glycemia level										
results of insulin assessment										
results of leptin assesment										
RISK OR PROTECTIVE FACTORS AND ENVIRONMENTAL EXPOSURE (by questionnaire)										
socio-economic status (i.e.crowding index)										

work position
level of education
worked for a year or more a in a dusty job

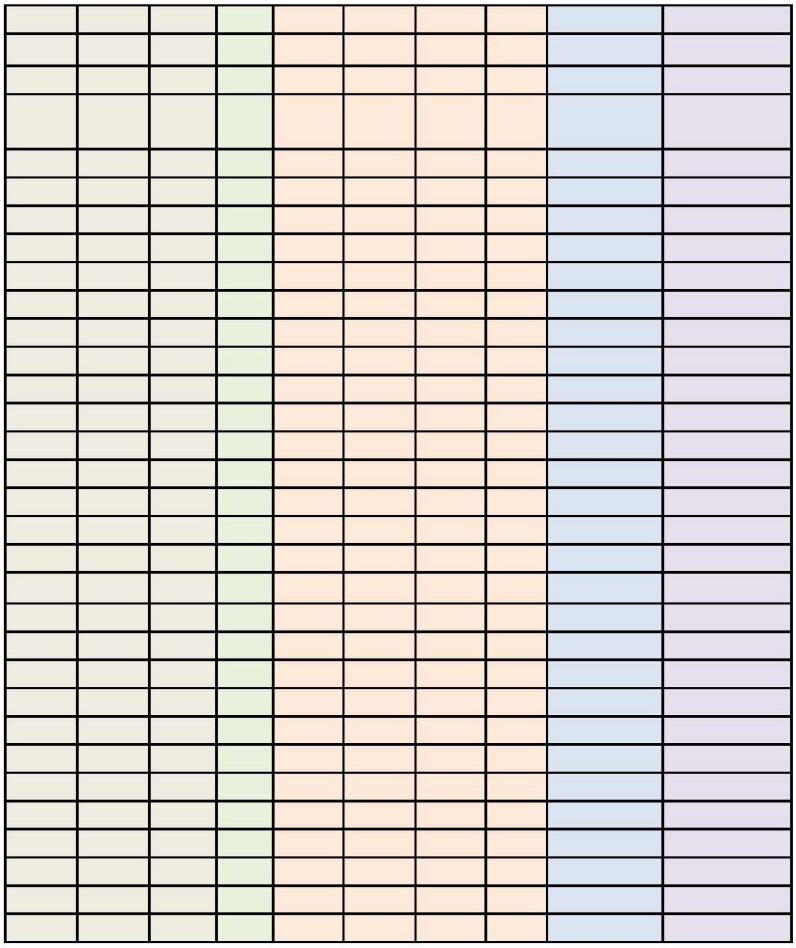
worked for a year or more exposed to fumes gases or chemicals
smoking habits
smoking habits during pregnancy
passive smoke exposure
passive smoke exposure during pregnancy
childhood infections

diet
diet during pregnancy
diet in the first months of life
vitamin D consumption
coffee
alcohol

physical activity and sports
excercise
stress
behavioural factors

exclusive breast feeding
length of exclusive breastfeeding
mixed breastfeeding

number of brothers/sisters
asthma history of parents and siblings
allergic rhinitis history of parents and siblings
sexual development
parental lifestyle
parental mental health



parental psycoafectivity

reported visible moulds or dampness in homes/classrooms
reported odor of moulds or dampness in homes/classrooms
presence of cats and dogs in homes/classrooms

presence of other pets with furs or feathers in homes/classrooms
presence of cockroaches in homes/classrooms
type of fuel for heating in homes/classrooms
type of fuel for cooking in homes/classrooms
presence of carpets in homes/classrooms
homes/classrooms renovation
presence of sources of air pollutants near homes/classrooms (industries, major road, bus/truck traffic, bad smells…)
proximity of the house to traffic by questionnaire
homes/classrooms's distance from main roads
how often vehicle pass near homes/classrooms

characteristics of the residence area (urban, rural, industrial…)
exposure to organochlorines, PBDE, phatlates, phenols
number of hours spent at home
time of residence in the last home

EXPOSURE ASSESSMENTS

by objective assessments

data from air monitoring stations on air pollutants
Please specifiy the pollutants
data from pollen monitoring stations (counts)
data from pollen monitoring stations (allergens)
biological allergens concentration in dust samples
indoor PM2.5 concentration (homes/classrooms)
outdoor PM2.5 concentration (near homes/classrooms)
indoor PM10 concentration (homes/classrooms)
outdoor PM10 concentration (near homes/classrooms)

indoor Temperature (homes/classrooms)
outdoor Temperature (near homes/classrooms)
indoor relative humidity (homes/classrooms)
outdoor relative humidity (near homes/classrooms)
indoor VOC concetration (homes/classrooms)
exposure to organochlorines, PBDE, phatlates , phenols
indoor dichlorodiphenyldichloroethylene (p,p'-DDE),
indoor hexachlorobenzene (HCB)
indoor polychlorinated biphenyls (PCBs)
lead exposure
mercury exposure
chrome exposure
chlorinated pesticides exposure
georeferenced home address

4 Collection of the filled tables and selection of the cohorts to be included in the analyses

After receiving the completed tables from the involved partners, a new summary table was elaborated with the cohort profiles in columns and the variable names in rows, in order to have a complete picture of the variables available in the studies selected according to the HEALS protocol.

In particular, two main types of studies were categorized:

a) adult/general population studies from 4 different countries (**attachment 3**): 1 from Australia (QIMR), 2 from Denmark (LSADT and MADT), 5 from Italy (PI1, PI2, IMCA, SEASD, Indoor PI2) and 1 from Spain (CHIS2000).

b) studies on children from 9 different countries and 1 European study were selected (attachment 3): 6 from Italy (MUBICOS, ITR, Indoor-School CCM, RESPIRA, PEGGS, ARPA), 1 from Finland (FinnTwin12), 1 from Norway (MoBa), 1 from Poland (REPRO_PL), 1 from Slovenia (PHIME-SI), 2 from Portugal (Generation XXI and EPITeen), 1 from France (EDEN), 1 from UK (MAAS) and 1 from Europe (SINPHONIE).

Attachment 3

Tab 1. Summary table of pre-existing cohort (adulthood-general population) **Attachment 3**

	Australia		Denmark		Italy-CNR					Spain
	QIMR 1995-98 age 7-73, 412 subjects		LSADT 1995-2007 age 70-103, 5845 subjects	MADT 1998 age 45-67, 4314 subjects	PI1 1985-88, age 4–97 years, 3865 subjects,	PI2 1991-93, age 8-97 years, 2841 subjects	IMCAII study, 2009 - 2011, age 18-103, 1620 subjects	SEASD 1997-98, age 13-99, 640	Indoor PI2 1993-94, age ≥ 15, 707	CHIS 2000 Catalonia, 2002, 18-74 yrs, 919 subjects
	Birth-childhood	General population	Adulthood	Adulthood	General population	General population	General population	General population	General population	Adulthood
Individual characteristics										
Age/sex/ Anthropom. measure		x	x	x	x	x	x	x	x	x
Ethnic group		x	x	x						
Delivery information				x weight						
Asthma										
Asthma diagnosis		x	x	x	x	x	x	x		x
Asthma symptoms		x	x	x	x	x	x	x	x	
Allergic rhinitis										
Allergic rhinitis diagnosis		x			x	x	x	x		x
Allergic rhinitis symptoms		x			x	x	x	x	x	
Clinical assessments										
skin prick tests		x				x				
IgE assessment (Total)		x				x				
IgE assessment (specific)										
peripheral blood eosinophilia		x				x				
nasal nitric oxide										
bronchial hyper-responsiveness		x				x				
spirometry		x	x	x		x	x		X PEF	
*Confounders (by Q)**	x	x	x	x	x	x	x	x	x	x
Allergens exposure (by Q)		x			x	x	x	x	x	
*Allergens exposure (objective)***										
*PM exposure (by Q)****		x			x	x	x			
*PM exposure (objective)*****						TSP	PM10 out, PM2.5 out		X PM2.5 in	
Georeferenced home address						x	x			

in gray: specific information missing in specific studies (neither by Q nor by objective measurements); * SES, work position, education, work exposure, smoke, childhood infections, breast feeding, familiarity, number of brothers/sisters; ** data pollen from monitoring stations or biological allergens in dust samples; *** sources of air pollution near home, proximity to traffic, characteristics of the residence area; **** data from air monitoring stations (MS) on air pollutants or field measurements

Tab 2a. Summary table of pre-existing cohort (childhood)

	ISS-Italy			Finland		Norway		Poland	Italy				
	MUBICOS 2009- birth cohort, 360 families	ITR since 2011, 25000 subjects		FinnTwin12 1994 onwards, 5 birth cohorts of twins born 1983-1987 and their parents, follow-up at age 11, 14, 17 and young adults (mean 22yrs), max 5000 subjects		MoBa Recruitment 1999-2009, follow-up ongoing at age 11, 14, 17 and young adults (mean 22yrs) 100.000 subjects		REPRO_PL mother's at recruitment (18-45 yrs) children'12 and 24 months, 1700 mother child pairs, 540 children	Indoor-School CCM 2011-13, age 6-15 years, 800 pupils		PEGGS 2007-09, age 11-18, 300 subjects Sicily	RESPIRA May 2012-Feb 2013, age 10-16, 1190 subjects Sicily	ARPA 2005-06, age 10-17, 1600 subjects Sicily
	Birth/ CH	CH	Adulthood	Birth/ CH	Adulthood	Birth/ CH	Parents	Pre-natal/birth/ CH	CH	parents	CH	CH	CH
Individual characteristics													
Age/sex/anthropom	x	x		x	x	x	x	x	x	x	x	x	x
Ethnic group				x				x	x		x	x	x
Delivery information	x	x		x		x	x	x	x			x	
Asthma													
Asthma diagnosis	x	x		x	x	x	x		x		x	x	x
Asthma symptoms	x	x				x	x	x	x		x	x	x
Allergic rhinitis													
Allergic rhinitis diagnosis		x		x	x	x	x		x			x	
Allergic rhinitis symptoms	x	x				x		x	x		x	x	x
Clinical assessments													
skin prick tests									x		x	x	x
IgE assessment (Total)												x	
IgE assessment (specific)												x	
peripheral blood eosin													
nasal nitric oxide			x									x	x
BHR													
spirometry			x						x		x	x	x
*Confounders (by Q)**	x	x		x	x	x	x	x	x	x	x	x	x
Allergens exposure (by Q)						x	x	x	x		x	x	x
*Allergens exposure (objective)***												x	
*PM exposure (by Q) ****	x	x						x	x		x	x	x
*PM exposure (objective)*****								x PM10 out, PM2.5 out	x PM2.5 in/out		x PM10 out	x PM2.5 in/out	x PM10out
Georeferenced address	x			x				x			x	x	x

Tab 2b. Summary table of pre-existing cohort (childhood)

	Slovenia		Portugal		France	Europe		UK
	PHIME-SI 2006-11, mother (18-45 years) -child (0-18 months) pairs, 286 subjects		Generation XXI - G21, 2005/2006 - 2009-2011 - 2012-2013, 0y/4y/7y, 8647 subjects at baseline (not for all waves)	EPITeen, (same sample as G21), 2003 - 2007 - 2012, 13y/17y/21y, 2943 subjects (not for all waves)	EDEN, 0-5 y (8 y soon), 1140 subjects	SINPHONIE, 23 European Countries, 2011-2012, children 3-14 years, parents 22-72 years, 5175 subjects		MAAS 1996 to present, 0-16 yrs
	Birth/CH	Pre-natal/birth/CH	Birth	CH	Pre-natal/birth/CH	CH	parents	Birth/ CH
Individual characteristics								
Age/sex/anthrop	x	x	x	x	x	x	x	x
Ethnic group					x	x		x
Delivery information	x	x	x	x	x			x
Asthma								
Asthma diagnosis	x	x	x	x	x	x		x
Asthma symptoms			x	x	x	x		x
Allergic rhinitis								
Allergic rhinitis diagnosis			x	x		x		x
Allergic rhinitis symptoms			x	x		x		x
Clinical assessments								
skin prick tests						x		x
IgE assessment (Total)					x			x
IgE assessment (specific)					x			x
peripheral blood eosinophilia								
nasal nitric oxide						x		
bronchial hyper-responsiveness								x
spirometry			x	x	x	x		x
*Confounders (by Q)**		x	x	x	x	x	x	x
Allergens exposure (by Q)					x	x	x	x
*Allergens exposure (objective)***						x		x
*PM exposure (by Q)****	x	x			x	x	x	
PM exposure (objective)					x PM10 out	xPM2.5 in/out		x PM10 in/out, PM2.5 out
Georeferenced home address	x	x	x	x				x

According to the received information a table was prepared highlighting the main environmental data missing in each study (PM or biological allergens), be that by questionnaire or objective measurements (**attachment 4**). The aim of the table was to try to overcome these gaps with the collaboration of HEALS partners with special expertise in environmental studies and data management. In particular, the best solution could be to obtain the missing information using external data, for example by using satellite data for PM exposure or national/local data on pollution/pollens concentration levels coming from ground monitoring stations. This information can be retrieved by the Environmental Data Management System put together in WP8 and used after applying the data fusion techniques applied and/or developed in WP11.

Attachment 4

Pre-existing cohorts with missing environmental information

Study	Period	Missing allergens	Missing PM	Georeferenced home address
Pisa study-CNR	1991-1993 2009-2011		x	x
SEASD-CNR-Italy	1997-98		x	
LSDAT-Denmark	1995-2007	x	x	
MADT-Denmark	1998	x	x	
CHIS2000-Spain	2002	x	x	
MUBICOS-ISS-Italy	2009	x		x
ITR-ISS-Italy	Since 2011	x		
FinnTwin12-Finland	Since 1994	x	x	x
MoBa-Norway	1999-2009		x	
PHIME-Slovenia	2006-2011	x		x
GenerationXXI-Portugal	2005-2009-2011-2013	x	x	x
EPITeen-Portugal	2003-2007-2013	x	x	x

5 Transfer of the information to the WP12

All these collected information about eligible studies for the WP14-WP16 and the variables to be taken into account for the statistical analyses, were sent to the project coordinators and WP12 partners in order to be used for the implementation of the HEALS GeoDatabase platform, which will systematically support the collection of and access to all the datasets collected/developed for HEALS environment-wide association studies.

Moreover, a specific procedure to obtain the variables of selected studies from the databases and to obtain a global harmonized database will be implemented by WP12 and project coordinators. This procedure will guarantee the better way to perform statistical analyses of high standard quality in order to assess the relationship between asthma/allergic rhinitis and PM and biological allergens (i.e. the main focus of WP14).