

External exposome and allergic respiratory and skin diseases



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Allergies are complex diseases that result from interactions between multiple genetic and environmental factors. However, the increase in allergies observed in the past decades is explained exclusively by environmental changes occurring in the same period. Presently, the exposome, the totality of specific and nonspecific external environmental exposures (external exposome) to which a subject is exposed from preconception onward and their consequences at the organ and cell levels (internal exposome), is being considered to explain the inception, development, and exacerbations of allergic diseases. Among the best-studied environmental factors of the specific external exposome, indoor and outdoor aeroallergens and air pollutants play a key role in the etiopathogenesis of the inflammatory response to allergens and in clinical manifestations of allergic disease. Climate change, urbanization, and loss of biodiversity affect sources, emissions, and concentrations of main aeroallergens and air pollutants and are among the most critical challenges facing the health and quality of life of the still increasing number of allergic patients today and in the coming decades. Thunderstorm-related asthma is a dramatic example of the effects of combined environmental factors and an *in vivo* model for understanding the mechanisms at work in respiratory allergy. Environment- or lifestyle-driven aberrancies in the gut and skin microbiome composition represent key mediators of allergic diseases. A better knowledge of the effect of the external exposome on allergy development is crucial for urging patients, health professionals, and policymakers to take actions to mitigate the effect of environmental changes and to adapt to them. (*J Allergy Clin Immunol* 2018;141:846-57.)

Key words: Aeroallergens, air pollution, airway hyperreactivity, allergens, asthma, atopic dermatitis, biocontaminants, climate change, biodiversity, exposome, microbiome, rhinitis, thunderstorm

Allergic diseases affect a considerable segment of the population, resulting in significant socioeconomic burden, and their prevalence has been increasing in the past decades. As shown

Abbreviations used

AD:	Atopic dermatitis
CO ₂ :	Carbon dioxide
GHG:	Greenhouse gas
HDM:	House dust mite
NO ₂ :	Nitrogen dioxide
O ₃ :	Ozone
PM:	Particulate matter
PM _{2.5} :	Particulate matter of less than 2.5 µm in diameter

below, this is due to environmental changes, although their precise role is not yet established. Worldwide, according to the World Health Organization (WHO), there are now at least 300 million persons with asthma and more than 300 million persons with allergic rhinitis, and half of the global population will have had an allergic disease by 2050.¹ Up to 50% of the general population already presents with allergic sensitization to at least 1 allergen, as defined by skin prick test response positivity or positive specific IgE levels. In terms of annual mortality, globally, there are almost 300,000 avoidable allergy-related deaths caused by asthma, food allergy, or anaphylaxis.¹

Although recognized as the result of an interaction between multiple genetic and environmental factors,² allergies are mainly considered an environmental disease. Indeed, as suggested in a recent review published in this *Journal*,³ pure genetic factors are unable to explain the dramatic increase in allergy-related diseases observed in the past decades. Various environmental factors have been involved in exacerbations (eg, viruses, tobacco smoking, air pollutants, and allergens) and development (eg, allergens, *in utero* tobacco smoking, air pollutants, and dietary factors) of allergic diseases.⁴ However, the initiation and development of allergic diseases result from the interplay, duration, and timing of several environmental exposures. In the context of allergic diseases, it has become apparent that the period of early life is of the

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Terms in boldface and italics are detailed in the glossary on page 847.

most importance for inception. This is referred to as the developmental origins of health and disease hypothesis according to which intergenerational vulnerability for disease is established before and in the first 1000 days after conception.⁵

Recently, it has become evident that the exposome (ie, the totality of the external and internal environment from preconception onward, complementing the genome to which the subject is exposed) needs to be considered to fully explain development and thus allergy epidemics. The exposome includes 3 broad domains: specific external, nonspecific external, and internal domains.

The external exposome encompasses exposures to specific external environmental factors (namely chemical, biological, occupational, and physical exposures, including diet, drug, and consumer products), as well as nonspecific general exposures (eg, climate, biodiversity, and socioeconomic factors; Fig 1). However, an informative assessment of a subject's exposure might need the combination of aspects of the 2 domains because these can be viewed as both overlapping and intertwining, and it is sometimes difficult to place a particular exposure into one domain or another.

The internal exposome includes internal chemical environments determined by internal processes (eg, metabolic and inflammatory), as assessed through evaluation of proteins, lipid mediators, xenobiotics, and their metabolites through *ad hoc* omics tools (Fig 1). The internal exposome is specific to each subject because it depends on age, physiology, body morphology, health status, and the genome among others.

There is also evidence that various environmental factors can influence the epigenome thus promoting changes in a chromosome that affect gene activity and expression, and thus modifying the risk of allergic diseases.⁶ Recent data have shown that air pollution is able to change the epigenome in peripheral blood in prenatal life.⁷ However, very few data are available on the effects of the relationship between allergen exposure and allergic sensitization and changes of the epigenome.⁶ These changes might have a transgenerational effect, like those caused by prenatal exposure to tobacco smoke.⁸ Finally, it is widely accepted that both host microbiome and external microbial exposure are critical in increasing susceptibility to allergic diseases, especially during early life, as reviewed recently by Burbank et al.⁴

Here we review recent advances in the macromechanisms and micromechanisms underlying the effects of the external specific exposome on allergic diseases, with specific emphasis on fresh data on aeroallergens and air pollutants and their effects on respiratory and skin allergies. Successively, we will stress the part played by the nonspecific external exposome by detailing the role of climate change, **urbanization**, and loss of biodiversity, which act indirectly on allergies by increasing their risk factors. These constitute the most critical challenges to be faced in the near future because of their dramatic progression observed in the past decades (Table I). Unless we act now to reduce **greenhouse gas** (GHG) emissions and air pollution, climate change, urbanization, and biodiversity loss will get worse, and the burden of allergies will increase.⁹

GLOSSARY

GREENHOUSE GASES: Gases that trap heat in the atmosphere. The major contributor to this group is carbon dioxide (CO₂), but others include methane, nitrous oxide, and fluorinated gases.

HEAT WAVES: The World Meteorological Organization is specific in its definition by stating that a heat wave occurs when the daily maximum temperature for more than 5 consecutive days exceeds the average maximum temperature by 9°. Per the National Weather Service, a heat wave is a period of abnormally and uncomfortably hot and unusually humid weather. Typically, a heat wave lasts 2 or more days.

LAG EFFECT: Temporal effect estimated by an analysis that correlates exposures occurring at different time points with an outcome (eg, asthma exacerbation). Lagged exposure can be analyzed often as either the amount of exposure on a certain day preceding the outcome or a cumulative exposure for a number of days preceding the outcome (ie, spore counts on one day 3 days before the admission or cumulative spore counts in the 3 days leading up to admission). This analysis allows multiple different correlations to be looked at for a given exposure/outcome relationship.

NANOTECHNOLOGY: The study and manipulation of matter at dimensions between approximately 1 and 100 nm for the purposes of building microscopic devices, such as computer chips.

NITROGEN DIOXIDE (NO₂): Outdoors, NO₂ forms from fuel burning emissions from automobiles, power plants, and off-road equipment. A highly reactive gas, it contributes to both ozone and particulate matter pollution, as well as acid rain.

OZONE: A gas composed of 3 oxygen atoms. Ground-level ozone (smog) is formed when volatile organic compounds combine with nitrogen oxides in the presence of heat and sunlight.

PARTICULATE MATTER (PM): PM is the sum of all solid and liquid particles suspended in air many of which are hazardous. This complex mixture includes both organic and inorganic particles, such as dust, pollen, molds, soot, smoke, and liquid droplets. Created by both natural (volcanoes, dust storm, dryness, etc) and man-made causes (combustion, traffic, industries, etc), particulates impact the earth's climate, precipitation levels and can have (those of less than 2.5 mm in diameters [PM_{2.5}]) substantial negative effects on human health (allergies included).

PHENOLOGY: A branch of science dealing with the relation between climate and periodic biological phenomena (eg, bird migration or plant flowering).

POLYCYCLIC AROMATIC HYDROCARBONS (PAHs): Also known as polyaromatic hydrocarbons, these are volatile substances produced by combustion. Traffic vehicles are a main source of PAH emission in urban areas.

URBANIZATION: The process of a population becoming more urban. The definition of urban varies by country. In the United States the Census Bureau identifies 2 types of urban areas: urbanized areas of 50,000 or more persons and urban clusters of at least 2,500 and less than 50,000 persons. The United States contains 486 urbanized areas and 3,087 urban clusters.

VOLATILE ORGANIC COMPOUNDS (VOCs): Emitted gases from solids or liquids that contain chemicals that might have health effects. Concentrations are higher indoors than outdoors. Household products that are sources of volatile organic compounds include paints, wood preservatives, aerosol sprays, disinfectants, air fresheners, dry-cleaned clothing, and pesticides. Volatile organic compounds are also released from burning fuel and are emitted from diesel exhaust. VOCs exposure has been associated with allergies.

Exposome involvement in allergy

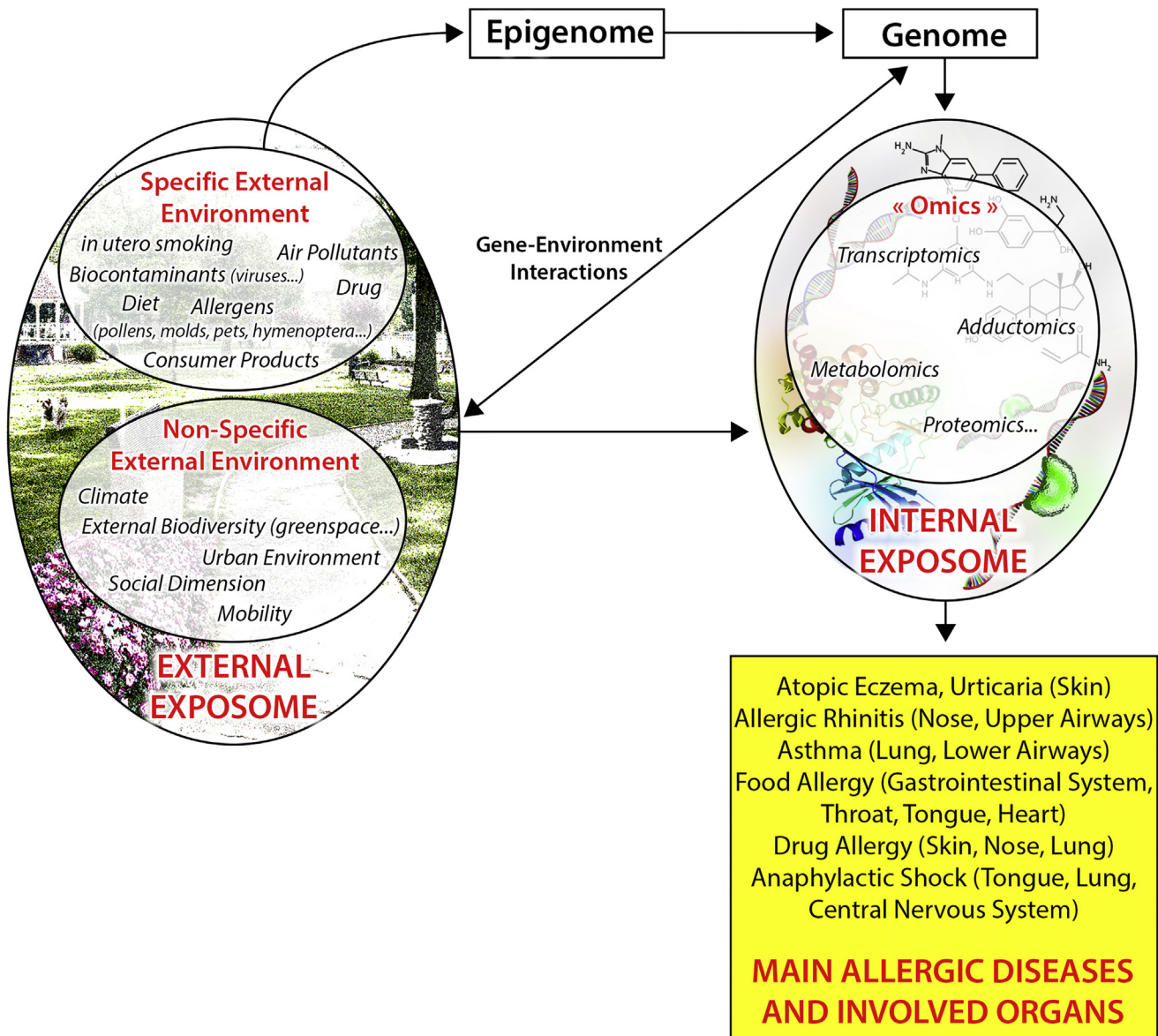


FIG 1. An overview of the concept of the exposome in allergic diseases.

SPECIFIC EXTERNAL EXPOSOME

Allergens and air pollutants are well-established ubiquitous risk factors for allergic diseases. Everyone is exposed to a mixture of allergens and air pollutants, which changes many times a day, moving between indoor and outdoor spaces and urban and rural areas during different seasons of the year (Fig 2). Indoor environments are usually not hermetically sealed, and outdoor air and its content “contaminate” indoor spaces¹⁰; in addition, meteorological and indoor conditions affect concentrations and the exchange of these factors in and between the 2 environments.¹¹ To make it more complicated, all these factors can interact before coming into contact with human beings or synergistically on the mucosa.¹¹

Chemical air pollutants

Among the environmental changes suspected to be major drivers of the increasing trend of allergic diseases, there are chemical air pollutants with levels that are still of concern, even in industrialized countries.¹² These air pollutants are produced by both natural and human sources and include *nitrogen dioxide* (NO₂), *ozone* (O₃), *volatile organic compounds*, and especially particulate matter (PM), which is heterogeneous in size and composition. For instance, fine PM from diesel exhaust contains *polycyclic aromatic hydrocarbons* (PAHs).

Today there is sufficient evidence that various indoor and outdoor air pollutants are not only exacerbating but also causing an increase in allergic diseases. Exposure to particulate matter of

TABLE I. Key factors for climate change, urbanization, and biodiversity loss

	Situation	Remediation/challenges of the 21st century
Climate change	Occurrence, duration, and intensity of extreme weather events, such as heat waves or flooding, are increasing and will continue to increase in the near future under current climate change scenarios. Similarly, air pollutant concentrations and pollen and mold levels will increase.	Mitigation and adaptation measures. Mitigation (reducing climate change) involves reducing greenhouse gases into the atmosphere, either by reducing sources of these gases or by enhancing the sinks (oceans, forests, soils) that store these gases. Adaptation (adapting to life in a changing climate) involves adjusting to new climate by reducing individual vulnerability to the harmful effects of climate change.
Urbanization	The urban population in 2014 accounted for 54% of the total global population, up from 34% in 1960, and continues to grow. The world's urban population is expected to surpass six billion by 2045. Much of the expected urban growth will take place in countries of developing regions, particularly Africa. Already in 2016, the World Health Organization reported that 92% of the world's population lives in places where air quality levels exceed the WHO's ambient air quality guidelines for annual mean PM _{2.5} . This is going to increase.	Managing urban areas ("smart cities")
Biodiversity loss	Decreasing biodiversity in terms of species as a consequence of industrialization, air pollution, and use of chemicals that have affected the environment and microorganisms with which human subjects have lived since time immemorial is occurring.	Protect biodiversity by reducing its causes. Mobilize knowledge. Ensure that the available knowledge is presented in ways that can be used by decision makers.

less than 2.5 μm in diameter (PM_{2.5}) (called fine particles) and 10 μm in diameter, O₃, or NO₂ is associated consistently with increased asthma exacerbations and higher medication use,¹³ as well as aggravation of atopic dermatitis (AD).¹⁴ Several studies have also suggested a contribution of air pollutants to new-onset asthma.¹³ The strength of the evidence is variable and depends on the pollutant. However, the most recent systematic reviews on cross-sectional and prospective studies reported an increased risk of traffic-related air pollution to asthma and allergic outcomes, including sensitization.^{15,16} Moreover, a very recent review summarizing the state of the art from birth cohort studies, the most informative studies for establishing causation, indicated an increased risk between early-life traffic-related air pollution (mostly PM_{2.5} or NO₂) exposure and incident asthma.¹⁷ Only a trend was found for hay fever.¹⁷ However, a significant positive association was observed for sensitization to aeroallergens in the case of PM_{2.5} in birth cohort studies.¹⁷ The existence of a causal association is strongly supported by the results of laboratory studies and human exposure experiments for PM, in particular PM_{2.5}, whereas it is weaker for NO₂, possibly because it has been less investigated.¹³ The involved mechanisms include oxidative injury to the airways, leading to inflammation, remodeling, and increased risk of sensitization.

A detailed review,¹⁴ as well as data from 3 birth cohorts,¹⁸⁻²⁰ indicated that a variety of air pollutants (environmental tobacco smoke, volatile organic compounds, formaldehyde, toluene, NO₂, and PM) act as risk factors for the development of AD. These air pollutants can induce oxidative stress in the skin, leading to skin barrier dysfunction or immune dysregulation.¹⁴ However, these results need to be confirmed because of the low number of studies and limitations in methods. Recently, concerns have been raised about the detrimental effects of nanomaterials, including ultrafine particles, which were defined as having at least 1 dimension less than 100 nm, from diesel exhaust, cooking, heating, and wood burning and from increasing use of *nanotechnology*,²¹ which possess not only chemical but also physical

characteristics with the potential to modify disease risk and outcome. Although some toxicological studies on animals and experimental *in vitro* tests on lung cells are available, exhaustive data on the effects of nanoparticles and nanomaterials on allergies are still lacking.²² Lastly, environmental chemicals, such as phthalate esters, which are commonly used as plasticizers, or persistent organic pollutants have also been related to asthma and allergy.²³⁻²⁵

Overall, all these effects happen at even low doses of air pollutants, sometimes at much lower levels than air quality standards, and are stronger in subjects who are highly sensitive to allergies.¹²

Aeroallergens

It is generally accepted that aeroallergen exposure is associated with exacerbations and development of clinical allergy. In general, indoor allergens are linked more strongly to the development of asthma than outdoor allergen sensitization related to hay fever. The understanding of the skin immune response to allergens has started only recently. Several properties of allergens facilitate barrier disruption and skin sensitization. In addition, there is evidence that the skin route can promote allergen tolerance in undisturbed skin.^{26,27} However, the relationship between allergen exposure, sensitization, and allergy is likely much more complex than previously assumed.²⁸ For example, in a recent review on risk factors for asthma, data supporting the hypothesis of sensitization and exposure to allergens as a major risk factor for the development of asthma were classified as inconsistent.²⁹ Birth cohort studies show that timing, type of allergen, and degree of sensitization are all relevant³⁰ and that they can account for the inconsistent results of studies on risk factors for allergic disease development.

Pollen. Although pollen is a well-known risk factor for nasal allergies and asthma exacerbations,³¹⁻³³ quite surprisingly, its role in the development of respiratory allergy is still to be fully

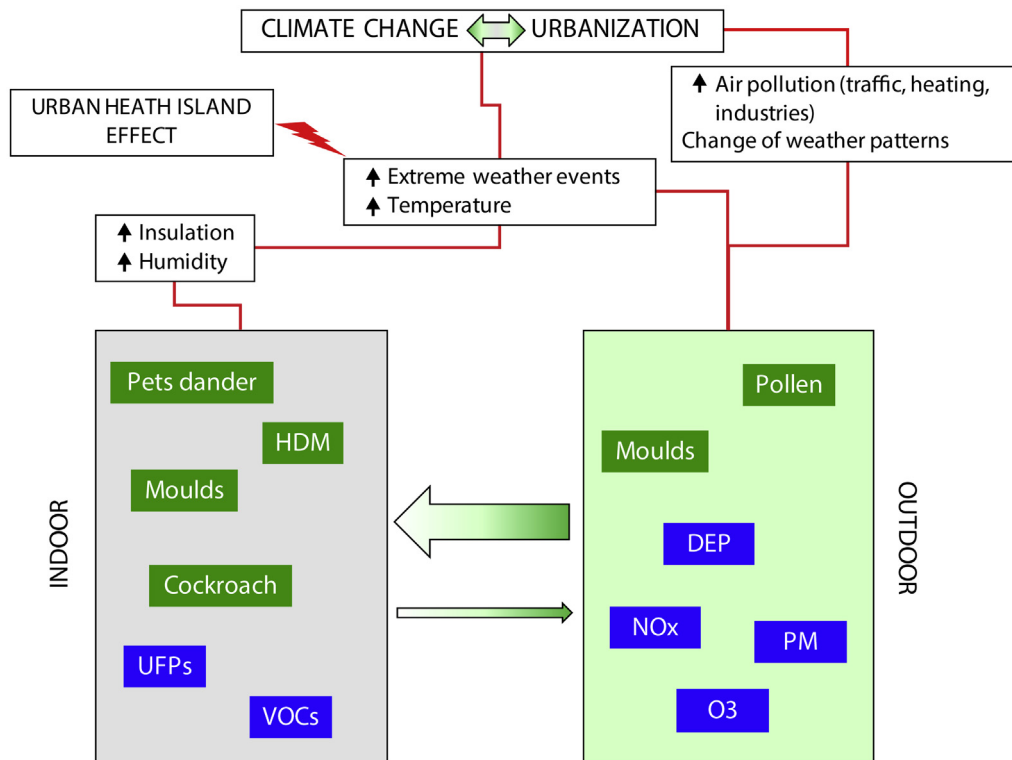


FIG 2. Indoor and outdoor exposures to aeroallergens and air pollutants and environmental factors affecting their production and concentrations. *NOx*, Nitrogen oxides; *UFPs*, ultrafine particles; *VOCs*, volatile organic compounds.

elucidated.^{34,35} Studies conducted thus far suggest that different patterns of sensitization to outdoor allergens have different effects on the risk of allergic rhinitis and asthma.³⁶ The heterogeneity of these patterns is mainly due to the different sets of allergen extracts used for assessing sensitization *in vivo*. As in the case of sensitization to mite allergens (see below), standardized measurement of specific IgE to the pollen-derived allergenic molecules (with a standardized set of allergens being in singleplex or multiplex) can be particularly useful for collecting and comparing findings from different birth cohorts.³⁷

Molds and house dust mites. The efforts to make houses more energy efficient and the effects of extreme flooding increase the risk of dampness and fungal contamination. Mold spores are small (1–20 μm in diameter) and therefore can enter deep in the airways; characterization of allergenic molecules and diagnostics for mold allergy are still surprisingly neglected, as brilliantly underlined in a recent review.³⁸

Exposure to mold and dampness has been suggested to increase the risks and exacerbations of asthma and allergic diseases in several studies.³⁹ Recent findings from the BAMSE birth cohort confirm that exposure to mold or dampness during infancy increases the risk of asthma, particularly persistent asthma, and rhinitis through 16 years of age.⁴⁰ The effect of mold exposure on the development of childhood asthma was confirmed in a high-risk birth cohort followed from infancy to 7 years of age in which molds were assessed objectively in a study in which a high index of indoor exposure based on DNA analysis of 36 molds (Environmental Relative Moldiness Index) at 1 year of age was

associated with an increased risk of asthma at 7 years of age.⁴¹ Using a case-crossover approach, Tham et al⁴² found that exposures to spores of several outdoor fungal taxa, including *Alternaria*, *Leptosphaeria*, *Coprinus*, and *Drechslera* species, were associated with the risk of asthma exacerbations in children and adolescents, regardless of their sensitization to *Alternaria* and *Cladosporium* species.⁴² The *lag effect* was different for each spore.

The combination of birth cohort blood samples and molecular diagnostics provided new data supporting the key role of house dust mite (HDM) sensitization as a risk factor for the development of respiratory allergy. In the German Multicenter Allergy Study birth cohort, sensitization to the HDM molecules Der p 1 or Der p 23, but not Der p 2, at age 5 years or less predicted asthma at school age. Asthmatic children had more complex molecular patterns of sensitization to HDM allergens.⁴³ Similar results were shown in the Manchester Asthma and Allergy Study birth cohort, in which specific IgEs to the HDM allergens Der p 1 and Der f 1 at the ages of 3, 5, 8, and 11 years were associated with a higher risk of asthma, rhinitis, or both at age 16 years.⁴⁴ Interestingly, these findings were not confirmed when testing specific IgE while using a different method for IgE measurement, in the Swedish birth cohort (BAMSE).⁴⁵ Recently, new routes of penetration of aeroallergens have been explored. As a consequence, early oral exposure to HDM allergens through breast milk was found to be a risk factor for allergic sensitization and respiratory allergies in children on follow-up.⁴⁶

NONSPECIFIC EXTERNAL EXPOSOME

Climate

Among nonspecific factors, climate is of paramount importance for allergic diseases by acting on them directly or influencing their risk factors. Increases in the production and concentration of aeroallergens and chemical air pollutants and of their geographic distribution are due to changes in climate and weather patterns.

Climate as a nonspecific exposure factor. Recently, for the first time, by linking US National Health Interview Survey data from 1997 to 2013 and data on the occurrence of *heat waves* (the “daily maximum temperature of more than five consecutive days exceeding the average maximum temperature by 5°C, the normal period being 1961-1990” according to World Meteorological Organization), an association was found between extreme heat events, especially when occurring in the spring, and hay fever prevalence.⁴⁷ Although this association was only slightly significant, the size of the survey makes the result dramatically important from a public health point of view. Earlier studies confirmed the positive association between temperature and hay fever prevalence in the United States⁴⁸ but not in Australia⁴⁹ and Italy.⁵⁰ AD was also related to climate.⁵¹ Although there is evidence showing that climate plays a role, even in initiation of allergic diseases, the complexity of the mechanisms and dramatic importance of local-regional factors indicate that climate is only one aspect of the complex multifactorial etiology of allergic diseases.

Effects of climate change on chemical air pollutants.

Climate change can affect air quality and *vice versa* because many pollutants are GHGs.⁵² Global warming will lead to longer episodes of O₃ peaks through stronger sunlight and higher temperatures overall in urban settings. Higher concentrations of gases and particles are expected because of increased human activity and traffic in large cities where, in the long term, a large majority of the world population will be forced to live as a result of climate change-related factors, with sea level rise among them. Lastly, particle concentrations will increase because of desertification and wildfires.⁵³ The effect of climate change on indoor air quality had received relatively little attention in spite of the fact that buildings that were designed to operate under the “old” climatic conditions might not be performant under new conditions, thus affecting the health of their occupants. Indoor chemical matter, organic matter, and PM can increase because of changes in outdoor concentrations of a pollutant cause by alterations in atmospheric chemistry or measures to reduce energy use in buildings, such as decreasing ventilation rates.

Effects of climate change on pollen and molds. The effect of climate change on pollen and pollen allergy is well established. Outdoor climate and pollen count were associated with the prevalence of hay fever in 91,642 children aged 0 to 17 years from the 2007 National Survey of Children's Health. A lower prevalence of allergy was found in areas characterized by wetter conditions, lower temperatures, and lower pollen counts, whereas a higher prevalence was observed in states with extremely dry, hot, and sunny conditions with high pollen counts or wet and rainy conditions.⁴⁸

Macromechanisms, which influence plant distribution and production, include increases in air temperature and carbon dioxide (CO₂). Temperature is a key factor affecting plant distribution and *phenology*, although with regional differences,⁵⁴ and therefore geographic distribution and atmospheric concentrations

of allergenic pollen.⁵⁵ The increase in atmospheric CO₂ supplies more carbon for photosynthesis, biomass production, and plant growth. Ragweed (*Ambrosia* species) has been studied thoroughly in the past 20 years for its effect on the environment, agriculture, and public health.⁵⁶

Stinson et al⁵⁷ grew common ragweed plants (*Ambrosia artemisiifolia*) at 3 latitudes in the northeastern United States at different levels of CO₂. They found that plants from northern latitudes produced more flowers than plants from southern parts of the region as a result of longer and earlier flowering periods. Also, because the effect was more evident at increased CO₂ levels, an increase in flower production, duration, and possibly pollen output, can be expected in the northeastern United States in the near future.⁵⁷

Interestingly, these effects could be enhanced by increased vegetation and forestation in the northern temperate zones, which in turn result in an increase in CO₂ levels (reverse causation). A multicentric study on 242 pollen traps over Europe showed that ragweed pollen counts were on the increase in few areas but that the direction of trends varied locally, depending of the sources of pollen and adoption of containment measures.⁵⁸ Earlier start of the flowering season and increase in pollen production were found for several trees producing allergenic pollen, such as birch,⁵⁹ oak,⁶⁰ and olive tree,⁶¹ effectively increasing the duration of exposure to pollen.⁶² However, a large European study did not find consistent trends toward changes in duration and exposure to allergenic pollen.⁶³ Changes in grass phenology and pollen distribution is complicated because of the several species producing allergenic pollen combined with environmental factors, such as weather variables, land use, and management of green spaces; however, a general trend toward an earlier start of flowering season of grass was observed, likely because of the increase in temperature and CO₂ levels.⁶⁴

A recent study conducted on 6 allergenic fungal species (*Alternaria alternata*, *Aspergillus niger*, *Botrytis cinerea*, *Cladosporium cladosporioides*, *Cladosporium oxysporum*, and *Epicoccum purpurascens*) showed that all fungal species grew faster but produced surprisingly fewer spores at higher temperatures, and this effect was more pronounced for temperature projections in 2100.⁶⁵ In addition, extreme weather conditions associated with climate change might lead to more frequent breakdowns in the building envelopes, followed by infiltration of water into indoor spaces and thus dampness that encourages mold and bacteria proliferation.

CONSIDERING INTERACTIONS TO IMPLEMENT THE EXPOSOMIC APPROACH

Interactions between aeroallergens and meteorological factors at a molecular level, and the immune system

Although studies on the effects of increased temperature and CO₂ on distribution, phenology, and pollen production indicate some consistent trends for most plants producing allergenic pollen, data about the effects on allergen content of pollen (the so-called “molecular aerobiology”)⁶⁶ are still in their infancy. The milestone in this field is the European Union-funded Health Impacts of Airborne Allergen Information Network (HIALINE) project that aimed at measuring the daily amount of pollen and the allergen content of pollen from grass (Phl p 5), olive trees

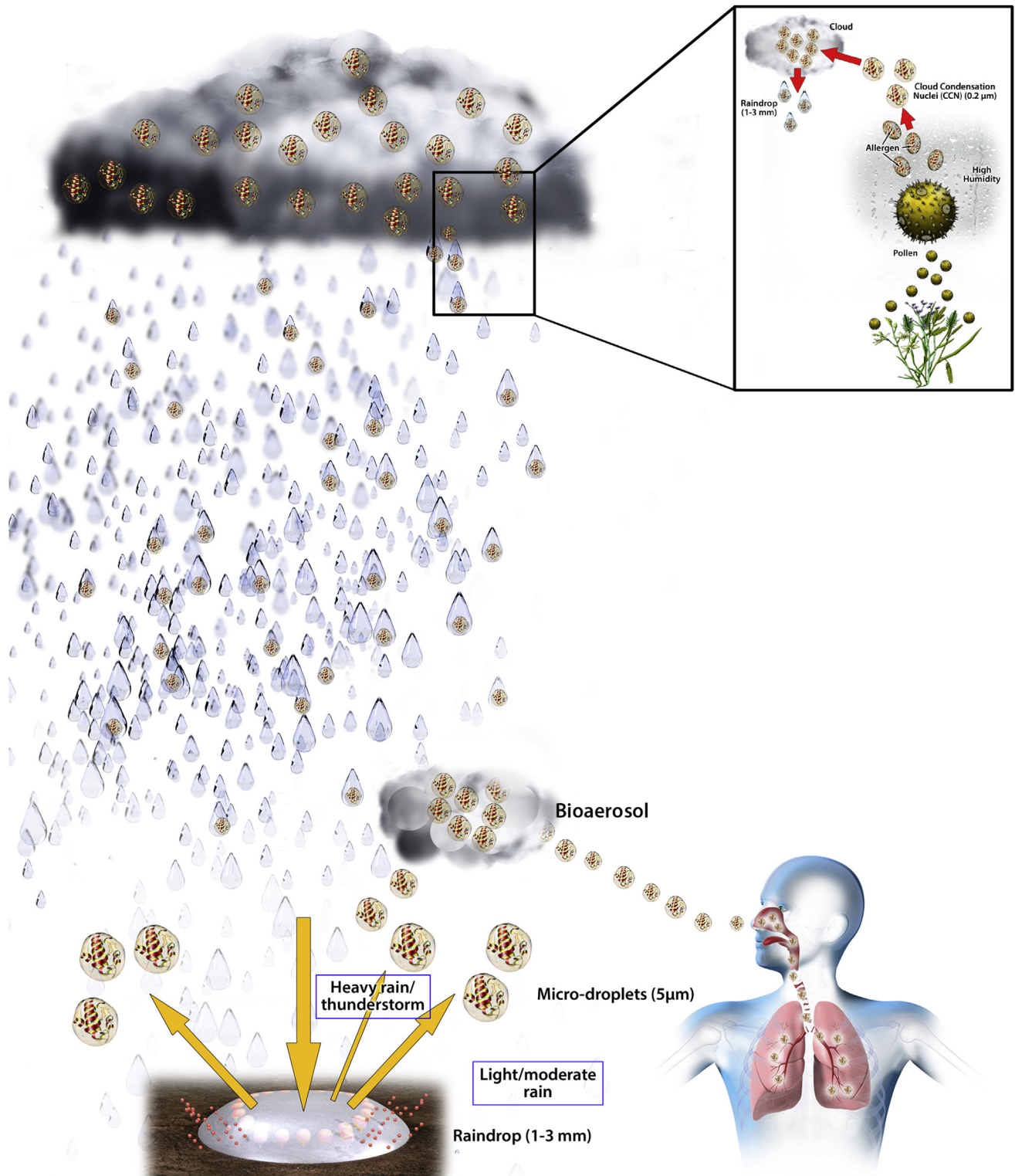


FIG 3. Hypothesis of the interactions between aeroallergens and different types of humidity and rain and of their effect on allergen “respirability.” In detail, pollen flies and encounters a high-humidity zone, where it breaks into smaller particles that contain allergens. SPPs (sub-pollen particles) “attract” humidity and form droplets, which aggregate and, together with other drops and droplets, form a cloud. Then raindrops fall and hit the ground; in case of heavy rain, thunderstorms, or both, the effect is so strong that water jets containing very small particles (possibly containing allergens) are sprayed into the air, thus contributing to bioaerosol formation. The very small size of particles allows penetration into the deeper airways, thus inducing asthma attacks. If rain is light or “normal,” particles escape in a larger size, possibly containing a larger amount of allergen,⁷⁵ but are less able to enter the deeper airways.

TABLE II. Effects of air pollutants and temperature on allergenicity and onset of pollen season based on studies published in the last 4 years

	Pollen/mold	CO ₂	O ₃	NO ₂	Temperature
Allergenicity*	Birch		↑	↑	
	Ragweed	↑	↔	↑	
	Hornbeam			↑	
	Oak			↑	
	Plan tree		↔	↑	
	<i>Aspergillus fumigatus</i>			↑	
Earlier start	Grass	↑			↑
	Birch				↑
	Oak				↑
	Olive tree				↑

↑, Increase; ↔, no changes.

*Allergen content and/or IgE recognition of exposed samples by patients' sera.

(Ole e 1), and birch (Bet v 1) simultaneously (www.hialine.eu). Results from 10 monitoring stations across Europe showed that the same amount of pollen releases variable amounts of Phl p 5 and that the allergen content of pollen (potency) varies per location and year and over the course of the pollen season.⁶⁷ The key role played by environmental factors is shown by a recent experimental study on ragweed pollen collected in 3 countries: France, Italy, and Canada.⁶⁸ Plants grown under standard (ie, exposed to seasonal changes in temperature, relative humidity, and light) conditions produced pollen with a higher Amb a 1 content variability than those grown in controlled conditions, regardless of the geographic area of origin. Moreover, the variability was clearly plant specific. Of note, expression of transcripts (transcriptome) encoding allergenic ragweed proteins (*A. artemisiifolia*) increased under increased CO₂ levels and drought stress in a greenhouse experimental design.⁶⁹

Other than the way the aeroallergen comes in contact with the immune system, the size and carrier of the allergen are crucial for the mechanisms of sensitization and exacerbation of allergic diseases. Recent findings raised new hypotheses on the effects of humidity and rain on allergen bioavailability in respiratory allergy. Despite their low frequency and relatively small effect on public health, thunderstorm-related asthma epidemics represent an *in vivo* model for understanding the effects of rain and humidity on pollen's ability to elicit asthma symptoms, even in patients without previous asthma manifestations. One of the hypotheses explaining the enhanced clinical effect of aeroallergen during such extreme weather events is the mechanical (effect of raindrops) and/or osmotic rupture of pollen, which produces sub-micronic fragments able to enter the deeper airways.⁶⁶ Recent data coming from different scientific fields might contribute to complete this puzzle. In the HIALINE project, Buters et al⁶⁷ found that the group 5 allergens were detectable among airborne coarse PM (between 2.5 μm and 10 μm in diameter) and not associated with pollen grains that are larger and that allergen concentration increased with humidity. The role of pollen and, more recently, subpollen particles as cloud condensation nuclei (defined as small particles on which water vapor condenses)⁷⁰ is widely recognized. When the pollen flies and encounters high relative humidity conditions, it ruptures and releases small fragments into cloud droplets, which eventually coalesce into raindrops.⁷¹ As soon as the raindrops hit the ground, the effect generates water jets, which break up into aerosol, as shown in a recent study based on high-speed imaging.⁷² Taken together,

these data indicate that small (approximately 5 μm) microdroplets can carry allergens, providing an explanation of thunderstorm-related asthma^{73,74} and of the mechanisms of pollen-induced asthma (Fig 3).⁷⁵

Interactions between chemical air pollutants, aeroallergens, and the host

With the first descriptions of PM attached on the surface of birch pollen collected in urban areas compared with that from a rural environment, an impressive amount of data have been produced about the effects of air pollution on pollen allergenicity, although only a few of them are recent.⁷⁶ Advances in sampling and measurement methods and molecular analysis, including both genomic and proteomic mass spectrometry, have paved the way for studies on the effects of the environment on airborne allergenic molecules. Air pollutants can modify allergenic proteins, thus affecting their interactions with the immune system. They do this in 2 ways: through variation in protein stability, which can change the duration of "exposure" to the immune system and antigen presentation process, and through cross-linking of allergenic proteins, which can in turn enhance cross-linking with FcεRI on epitopes and adjuvants, thus creating new ones or modifying existing ones.⁷⁷

Increased allergenicity was observed in ragweed,⁷⁸ birch,^{75,79} and hornbeam and *Ostrya* species pollen⁸⁰ when exposed to NO₂ (Table II). NO₂ seems the key factor inducing a 2- to 5-fold increased concentration of the allergen Asp f 1 in the conidia of *Aspergillus fumigatus* compared with the control for short exposure times of up to 12 hours in a polluted urban area and in an experimental setting.⁸¹ Exposure to O₃ showed an increase in NADPH oxidase activity (and reactive oxygen species production) in ragweed pollen in one study⁸² and no substantial changes in a more recent study⁸³; the clinical effect was not clear because in both studies no changes of Amb a 1 content were observed. However, the allergenicity of ragweed pollen, which was collected along high-traffic roads, showed a positive correlation with NO₂ concentrations but no correlation with O₃ levels.⁸³ Conversely, birch pollen taken from trees in more O₃-polluted areas of Munich showed an enhanced allergenicity and immune stimulatory potential.⁸⁴ A recent study on Pla a 1 and Pla a 2, the major allergens of *Platanus acerifolia*, concludes that O₃ and NO₂ can interact in a different manner with each specific pollen allergen, increasing or decreasing its allergenicity.⁸⁵ It has also become evident that extremely small nanomaterials and Asian sand dust particles can enhance allergic inflammation.⁸⁶

Mechanisms underlying the association between air pollutants, aeroallergens, and respiratory allergy are still to be understood, although they are becoming clearer at the cellular and molecular levels. In addition to the well-established epidemiologic relationship, experimental data have emerged on the effect of air pollutants and allergens.⁸⁷⁻⁹¹ Various studies showed that O₃, NO₂, and diesel exhaust particles are able to increase the permeability of the bronchial epithelium and to reduce the clearance of inhalable allergens and irritants, facilitating their access to the submucosa, where they interact with both resident and recruited cells.⁸⁸ Carlsten's research team contributed to our knowledge with a series of experiments on the effects of coexposure to diesel exhaust and allergen on the airways.^{89,90} In atopic patients they found that coexposure has differential effects on Clara cell

secretory protein 16, surfactant protein D, and myeloperoxidase and that surfactant protein D and myeloperoxidase levels in bronchoalveolar lavage fluid are responsive to allergen, whereas Clara cell secretory protein 16 is more responsive to diesel exhaust particle exposure.⁸⁹ In a case-crossover study on bronchial epithelial cells (the first cells exposed to inhalants) of atopic subjects, allergens were able to modulate gene and microRNA expression, even 48 hours after a transient exposure, whereas no effects were detected when diesel exhaust was added.⁸⁷ Finally, diesel exhaust augmented the allergen-induced increase in airway eosinophilic inflammation in 18 blinded atopic volunteers randomly exposed to filtered air or 300 mg of PM_{2.5}/m³ of diesel exhaust.⁹⁰

In a recent study, release of IL-8 and IL-6 from nasal epithelial mucosal cells was significantly increased when cells were exposed to NO₂ and subsequently to Der p 1, whereas exposure to NO₂ only induced a concentration-dependent increase in IL-6 but not IL-8.⁹¹ Of note, NO₂ concentrations reflected levels usually measured in urban areas. In addition, air pollutants in conjunction with climate factors differentially affected eczema prevalence and severity, some with apparent harmful effects.⁵¹

THE BIODIVERSITY HYPOTHESIS AND ROLE OF THE MICROBIOME

Because known risk factors cannot explain the increase in the prevalence of allergic diseases worldwide, research has shifted toward other possible causes. Among these, biodiversity loss and climate change resulting from human activity have recently been evoked.⁹² Altered composition of the gut and skin microbiota is characteristic of various inflammatory conditions, including asthma and allergies.^{93,94} Animal studies support the hypothesis that aberrations in the gut and skin microbiome might represent a mediator in allergy development.^{27,95} Exposure to gut microbial diversity confers protection against allergic sensitization and allergy.⁹⁵ Colonization with *Staphylococcus aureus* below the epidermis was associated with AD development, suggesting a potentially functional role for these organisms in the regulation of skin barrier and response to environmental allergens.^{26,27} There is a strong epidemiologic relationship between both the gut and skin microbiome and AD.^{26,27} However, the mechanisms connecting these 2 entities are still unknown. Upper and lower airway microbiota also need to be considered due to their reduced biodiversity and community composition (more proteobacteria, including *Haemophilus*) in asthmatics.⁹³

Recent studies also indicated a beneficial relationship between green spaces and greenness and allergies through increased exposure to a greater number and diversity of microbes.⁹⁶ Green spaces are critical habitats to support biodiversity overall in urban zones but are crucially inadequate in today's cities. The world's urban population is expected to surpass six billion by 2045. Much of the expected urban growth will take place in countries of the developing regions, particularly Africa. Therefore managing urban areas has become one of the most important development challenges of the 21st century. Questions that need to be addressed to advance the ecology of urban green spaces for biodiversity conservation and restoration are presently under debate.⁹⁷ However, the green environment is also a source of allergens that can exacerbate allergic responses both in themselves and through interactions with air pollutants.⁹⁸

ADAPTATION AND MITIGATION ACTIONS TO CONTROL EXTERNAL EXPOSOME

One of the major global challenges is the reduction in GHG emissions, some of which are also air pollutants. Both large- and small-scale interventions are needed to slow down the increase in GHG emissions, and both institutions and individuals are responsible.

Another objective involves controlling urban settings. Urbanization is on an upward trend, with 66% of the global population expected to be living in cities by 2050.⁹⁹ Because extreme temperature events and air pollution are projected to increase in the next decades under the current climate change scenarios, a considerable part of the planetary population will be at high risk. Urban green areas can improve air quality by reducing the concentration of air pollutants, such as PM,¹⁰⁰ mitigating the effects of heat waves and reducing the so-called urban heat island effect.¹⁰¹ However, green areas should be designed taking the allergic population into account. To date, there are no tools for city planners and architects to design "allergy safe" green spaces except for general guidelines and aerobiological studies.¹⁰² To overcome these limitations, an index was recently proposed.¹⁰³

The increase in frequency of thunderstorms in some geographic areas because of climate change will potentially heighten the importance of thunderstorm-related asthma exacerbations.¹¹ Therefore weather forecasts should be implemented with specific advice for patients with respiratory allergy.

Presently, there is growing recognition within the scientific and policy communities that efforts to address climate change should focus not only on substantially reducing major greenhouse emissions like CO₂ but also on near-term actions to reduce levels of those climate pollutants that remain in the atmosphere for much shorter periods of time.¹⁰⁴ With atmospheric lifetimes on the order of a few days to a few decades, the primary short-lived climate pollutants are methane, black carbon, and certain hydrofluorocarbons. Short-lived climate pollutants are responsible for 30% to 40% of global warming to date. Actions to reduce their emissions could reduce by half the amount of warming that would occur over the next few decades. On another level, actions aimed at reducing personal annual emissions are now under the spotlight because they can contribute significantly to global emissions and can be implemented more rapidly than national and international policies and energy transformations.¹⁰⁵ Four major individual actions were recently proposed on the basis of their high effect on GHG emissions in developed countries: having fewer children (the so-called "having fewer children") has by far the highest effect, although this is debated, followed by living car-free, avoiding airplane travel, and eating a plant-based diet.¹⁰⁶

In practice, to decrease the effects of environmental factors affecting allergic diseases, we can encourage policies to promote access to nonpolluting sources of energy, reduce private traffic in towns and improve public transport, decrease the use of fossil fuels and control vehicle emissions, and plant nonallergenic trees in cities. In addition, weather forecasts must be updated to include advice for patients with respiratory allergy, with alerts for extreme events, including thunderstorms.

CONCLUSION

Substantial evidence indicates that a wide range of environmental risk factors and interactions contribute to allergic diseases, showing the relevance of considering the external exposome in the

etiopathogenesis of these diseases. This should improve the comprehension of these conditions and open the way to adapted prevention strategies accounting for lifestyle and socioeconomic factors.

RESEARCH NEEDS

Research to understand the effect of the external exposome is as crucial as strategies and policies to reduce emissions of GHGs and air pollution. The scientific community is responsible for both investigating the macromechanisms and micromechanisms of the effects of environmental changes on human health and tracking the indicators of effect, adaptation, and mitigation, as in the case of “the Lancet Countdown” initiative.¹⁰⁷

Present and future environmental research on macromechanisms is bound to large multidisciplinary projects funded by public bodies and institutions. In Europe, 2 research projects focus on the effect of the exposome on asthma and allergies, namely Health and Environment-wide Associations based on Large population Surveys (HEALS; www.heals-eu.eu), of which one of the authors (Dr Annesi-Maesano) is principal investigator, and HELIX (The Human Early-Life Exposome). The former project, HEALS, uses monozygotic data to disentangle the role of the exposome after controlling for the genetic background. Such a project should be able to access and manage large amounts of data provided by environmental monitoring networks and by *ad hoc* objective assessments of individual exposures (eg, real-time remote sensors of air pollution exposures at the individual level)¹⁰⁸ to implement the exposome approach to explain asthma development. To estimate the effect of the exposome on allergic diseases, statistical methods able to examine the simultaneous effects of mixture of exposure at different periods and locations have to be implemented. Therefore appropriate and continuous technical and financial support of these projects and networks is of paramount importance for the surveillance of global changes and as input for modeling future scenarios.

The micromechanisms at work in the relationship between weather variables, air pollutants, aeroallergens, and the airways mucosa require further study. In particular, there is a need for standardized and validated experimental models for assessing the allergenicity of pollens exposed to different types and concentrations of chemical air pollutants with respect to a reference pollen preparation, as proposed recently by Schiavoni et al.⁸⁸ There are still gaps in our knowledge about the variability of allergen content of aeroallergens and its relationship with weather and climate. Studies on more allergens from the same biological source and on different sources of allergens (ie, pollen and molds) are needed because technology is now able to meet this goal. How allergens act in concomitance with other environmental factors throughout the entire lifespan also must be addressed. Birth cohorts from different geographic areas, together with a common and standardized set of allergens for IgE testing now seem crucial for a more in-depth understanding about the role of exposure to allergens in the development of respiratory allergy. Finally, it is necessary to better investigate the development of allergic diseases for integration of both the external and the internal exposome, as assessed by using omics studies.

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Key concepts

- The concept of the external exposome contributes greatly to comprehension of the development of allergic diseases. It must be implemented by using appropriate tools to accurately assess individual exposures throughout the lifespan (eg, with real-time remote sensors in the case of air pollution).
- Socioeconomic factors and lifestyles are crucial to building the external exposome and identifying at-risk individuals.
- External and internal exposomes must be linked by using appropriate statistical methods.
- Climate changes interact with and affect air pollution and biocontaminant levels, including allergens (climate change affects the timing, dispersion, quantity, and quality of aeroallergens) that in turn increase the frequency and severity of allergy and affect the clinical expression of allergic disease.
- A growing body of evidence shows that components of air pollution interact with airborne allergens and enhance the risk of atopic sensitization and exacerbation and development of symptoms in sensitized subjects.
- The molecular approach for allergy diagnosis and assessment of allergen exposure paves the way for a dramatic improvement in the understanding of the role of allergens in the development and exacerbation of respiratory allergy.
- Thunderstorm asthma represents a natural model of interactions between host- and environment-related factors.

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