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Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma

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Abstract

Exposome research can improve the understanding of the mechanistic connections between exposures and health to help mitigate adverse health outcomes across the life span. The exposomic approach provides a risk profile instead of single predictors and thus is particularly applicable to allergic diseases and asthma. Under the PRACTALL collaboration between the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma, and Immunology (AAAAI), we evaluated the current concepts and the unmet needs on the role of the exposome in allergic diseases and asthma.

KEYWORDS
allergic diseases, asthma, biomarkers, environment, exposome, PRACTALL

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; AEP, aggregate exposure pathway; AGEs, advanced glycation end products; AhR, aryl hydrocarbon receptor; AOP, adverse outcome pathway; BDT, biomedical data translator; BPA, bisphenol A; CDHR3, cadherin-related family member 3; CysLT, cysteinyl leukotrienes; DHA, docosahexaenoic acid; DHEA, dehydroepiandrosterone; EAACI, European Academy of Allergy and Clinical Immunology; EBC, exhaled breath condensate; eCO, exhaled carbon monoxide; EPA, eicosapentaenoic acid; EWAS, exposome-wide association studies; FeNO, fraction of nitric oxide in exhaled air; GIS, geographic information system; GPS, global positioning system; GWAS, genome-wide association studies; HDL, high-density lipoprotein; HELIX, Human Early-Life Exposome; NCATS, National Center for Advancing Translational Sciences; NHANES, National Health and Nutrition Examination Survey; NOS, nitric oxide synthase; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; PUFA, polyunsaturated fatty acid; SES, socioeconomic status; SNPs, single nucleotide polymorphisms; TSLP, thymic stromal lymphopoietin; TWAS, transcriptome-wide association studies; YKL-40, chitinase-3-like-1 protein.

PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology.

1 | INTRODUCTION

This consensus document summarizes the current knowledge on the role of the exposome in allergic diseases and asthma under the auspices of the PRACTALL collaboration platform. PRACTALL is an initiative of the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) aiming to harmonize the European and the American approach to improve the allergy practice and science.

This PRACTALL document addresses several key questions:

1. How is the exposome altering the biology to promote allergies/asthma?
2. What is the relevance of the exposome for allergy and asthma evolution?
3. What is the relevance of gaps, priority research needs and opportunities?
4. What is the relevance of the exposome data to clinical practice and to policy advocates?

2 | FRAMING THE ISSUE

2.1 | The domains of the exposome relevant to allergic diseases and asthma

The exposome comprises a person's entire environmental exposures that a person experiences, from conception throughout its life course. The concept was introduced in 2005 as the environmental counterpart of the genome to underscore the importance of the total environment to human health and to bring research efforts in line with those on the human genome.[1] This definition was expanded later by incorporating behavioral risk factors, the body's response to environmental influences (resilience or allostatic load), and the endogenous metabolic processes that modulate exposure.[2,3] Wild differentiated between the "eco-exposome" as the point of contact between an external environmental stressor, the biological receptor of an individual, and the "endo-exposome" as the inward effects arising from exposure on those receptors.[3] Vriejheid described a general external environment (climate, urban environment, green spaces, traffic, and social capital), a specific internal environment (smoking, diet, physical activity, water, and consumed products), and an internal environment measured through -omic (e.g, genomic, transcriptomic, and proteomic) tools.[4]

The exposome and biology are highly interactive: Changes in biology due to the environment modulate vulnerability to subsequent exposures. The balance between the biological effects of exposure (binding to macromolecules, structural changes, enzyme function disruption, damage through reactive oxygen or nitrogen species) and the specific biological responses (ubiquitination, autophagy, proteolysis, DNA repair, antioxidant systems, and so on) represents the biological impact of the exposure. The level of resilience is key for maintaining health and the cumulative cost of the correction process (allostatic load), and it is an important footprint of the exposome. Linking exposure to the specific biological responses in exposome research could improve understanding of the mechanistic connections between exposures and health to help mitigate adverse health outcomes across the life span. Moreover, the exposomic approach is particularly applicable to study chronic diseases such as allergic diseases and asthma since it provides a risk profile instead of single predictors.

2.2 | The exposome versus genome, transcriptome, proteome, epigenome, and metabolome in driving the disease phenotype and endotype

Each of the exposome domains induces a multitude of –omic responses. As an example, air pollution exposure interacts with the genome to perturb biological events in asthma pathways.[5] Novel insights into how these responses occur following individual and combined exposures, and their associated health impacts, continue to emerge. Genetic polymorphisms also interact with many other environmental stressors to generate asthma phenotypes such as decreased lung function, adult-onset asthma, or the severe asthma phenotype.[5-9] Air pollution also induces transcriptomic, epigenomic, and metabolomic responses.[10-12]

A few recent studies interrogated the transcriptomic effects (i.e, whether genes are turned on and off) of environmental exposures. Searching for genes differentially expressed under different exposures over multiple experiments is the basis for the transcriptome-wide association studies (TWAS). In another recent study, ex vivo peripheral blood mononuclear cell transcriptomic responses from asthmatic children to rhinovirus infection provided a personalized framework for predicting asthma exacerbations with 74% accuracy.[13] Proteomic studies are emerging as well. A proteomic signal in breast-milk featuring protease inhibitors and apolipoproteins distinguished between allergic and nonallergic mothers.[14] Nasal protein profiles from brush samples were compared between healthy adults and adults with asthma occupationally to protein allergens, isocyanates, or welding fumes. Hierarchical clustering revealed greater differences in asthma related to welding fumes when compared to protein allergen and isocyanate-related asthma.[15] Proteomic analysis of bronchoalveolar lavage fluid in patients with asthma revealed that approximately 150 distinct proteins were significantly upregulated after exposure to allergens. These proteins were linked to inflammation, eosinophilia, airway remodeling, tissue damage and repair, mucus production, and plasma infiltration.[16]

The exposome represented by presumed seasonal exposures was related to epigenetic associations, adult blood DNA methylation that was enriched for genes important to development, the cell cycle, and apoptosis. DNA methylation in a smaller subset of CpG sites was nominally associated with adult allergic outcomes.[17] Environmental exposures have also been shown to combine with genetic and epigenetic components to influence asthma outcomes: Particulate matter 2.5 μm ($PM_{2.5}$) exposure over 7 days, one common DNA sequence variation, and CpG methylation levels jointly affected airway inflammation (i.e, FeNO levels) in the Children's Health Study cohort.[18]

The importance of the infant microbiome and its associated metabolome on the risk of developing allergic diseases is gaining greater recognition.[19,20] Exposure of healthy volunteers to air pollution for 5 h induced metabolic features in the blood, some of which were associated with reductions in lung function.[21]

In summary, while the discovery of -omic patterns has great potential to inform on the impact of the exposome on asthma endotypes and phenotypes, this field is relatively young and with an unclear future impact in the field of respiratory care. Ongoing initiatives, such as the Human Early-Life Exposome (HELIX) project of six existing European birth cohort studies, will compare prenatal and postnatal chemical and physical exposures to transcriptomic, proteomic, epigenomic, and metabolomic molecular profiles.[4] Future studies may consider improving the interacting -omic measures, such as the "Interactome," which uses a more multi-axial systems approach to identify the relevant networks that underlie asthma and allergic disease.[22] Combined genomic, transcriptomic, epigenomic, and metabolomic analyses of the regulation of asthma control generated lipidomic data that were integrated with a conditional Gaussian Bayesian network using the strongest predictors (mRNA, CpG sites, and SNPs) identified. Remarkably, four single nucleotide polymorphisms (SNPs) and two metabolites strongly predicted asthma control.[23]

2.3 | Development of the exposome through biomarkers

The ability to characterize environmental exposures through biomonitoring is key to exposome research efforts. To understand the complexity of exposures faced throughout the life span, both traditional and nontraditional biomonitoring methods should be used.[24,25] Exposomic approaches differ from traditional biomonitoring methods in that they can include all exposures of potential health significance, whether from endogenous or exogenous sources. Issues of sample availability and quality, identification of unknown analytes, the capture of nonpersistent chemicals, integration of methods, and statistical assessment of increasingly complex data sets remain challenges that must continue to be addressed. Exposome-Explorer (http://exposome-explorer.iarc.fr) is the first database dedicated to biomarkers of exposure to environmental risk factors with detailed information on the nature of biomarkers, their concentrations in various human biospecimens, the study population and the analytical techniques used for measurement, correlations with external exposure measurements, and data on biological reproducibility over time.[26] The Exposome-Explorer makes it easy to compare the performance between biomarkers and their fields of application and is particularly useful for epidemiologists and clinicians wishing to select panels of biomarkers that can be used in biomonitoring studies or in exposome-wide association studies (EWAS).

One of the main aims in prevention is to predict individual risk related to the early environment to potentially allow for intervention prior to disease onset. Biomonitoring during critical time windows of susceptibility (Figure 1) and during different phases of disease from inception to chronicity [27] also has the potential to validate new tools for risk assessment and to estimate the burden of environmental disease. Exposomics and Helix are two large consortia funded by the European Commission focusing on: (a) "reduction of uncertainty" paradigm; (b) the role of multiple environmental contaminants in disease risk, on the basis of improved exposure assessment; (c) novel chemical risks identified via untargeted -omics ("hazard identification"); and (d) the burden of disease attributable to environmental agents (how the latter changes with improved exposure assessment and risk estimation for selected exposures and diseases). HELIX has a special focus on children. Combined, they are expected to reach a refined model for exposure risk assessment that would have an impact on environmental policies.

As shown in Table 1, numerous biomarkers of environmental exposures have been identified that may quantify or predict the individual risk of disease. These biomarkers can be classified as biomarkers of exposure, intermediate biomarkers of early effect (biomarkers of susceptibility), or biomarkers of response/disease (Figure 2). Furthermore, biomarkers of exposure relevant to allergic diseases and asthma can be grouped according to the stressor (Figure 3).

Biomarkers may be combined with predictive models for individual exposure and questionnaire data to obtain greater accuracy in environmental exposures. For example, cotinine biomarkers validate questionnaire responses on environmental tobacco smoke, and indoor air pollution biomarkers (e.g, PAH-DNA adducts) validate questions on cooking and heating sources in the home.

2.4 | The complex network—the building environment, allergens, infections, occupational exposure, and school environment

Both increased urbanization and the increased amount of time spent indoors (residences, workplaces, public buildings, etc.) to almost

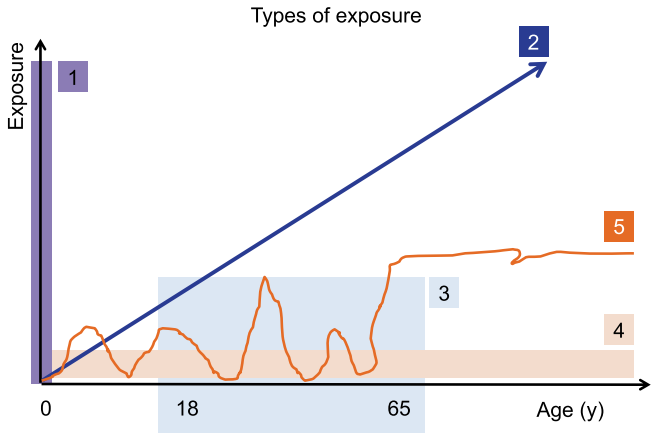

FIGURE 1 Several types of exposure occurring through lifetime are relevant for the impact of the environment for allergic diseases and asthma. 1. Early life exposure. Environmental stressors in early life are major contributors to allergic diseases and asthma. 2. Linear incremental exposure (eg ageing effect) 3. Occupational exposure 4. Chronic low level exposure 5. Multiple-hit exposure: a combination of intermittent and persistent exposure with variable dose and length of exposure (weight gain/loss, diet, exercise, pollution, microbiome, habitat change, etc)

TABLE 1 Biomarkers of exposure, susceptibility, and allergic responses

Biomarker	Source tissue	Linked exposure (s)	Linked pathway	Susceptibility measured
Cotinine	Blood, saliva, urine	Cigarette smoke (primary and secondary)	Increased nicotine and xenobiotic metabolism	Decreased lung function; asthma exacerbations
Polycyclic aromatic hydrocarbon (PAH) DNA adducts	White blood cell DNA	Polycyclic aromatic hydrocarbon (PAH); diesel exhaust	DNA damage	Increased FeNO
PAH metabolites	Sera, urine	PAH	Altered aryl hydrocarbon receptor (AhR) signaling	Mouse, cat-specific IgE
Exhaled carbon monoxide (eCO)	Exhaled gas	Cigarette smoke	Airway inflammation; oxidative stress	Asthma; allergic rhinitis
Bisphenol A (BPA) levels	Urine	BPA	Endocrine disruption	Increased FeNO
Phthalate metabolites	Sera, urine	Phthalates	Endocrine disruption	Increased FeNO; asthma symptoms
Leukotriene E4, bromotyrosine	Urine	Particulate matter; cigarette smoke (secondary)	Enhanced CysLT metabolism	Asthma symptoms; increased FeNO
DNA methylation	Blood; nasal epithelium, bronchoalveolar lavage	Air pollution/diesel; allergens	Epigenetic regulation	Asthma
Cortisol	Saliva, urine, blood	Stress; NO_2	Hypothalamic-pituitary-adrenal axis; activation of sympathetic nervous system	Asthma exacerbation; decreased FeNO
Other -omics	Blood	Many	Environment x gene regulation	Asthma
Fraction of nitric oxide in exhaled air (FeNO)	Exhaled gas	Allergen, viruses, BPA, phthalates	Steroid responsiveness	Accelerated lung function decline; asthma exacerbations
Periostin	Sera; airway (bronchial and nasal) epithelium	[a]	Allergic immune responses	Increased asthma severity, lung function decline; eosinophilic airway inflammation
IgE	Sera	Allergens	Allergic sensitization	Allergy; asthma
Eosinophils	Blood, sputum	Allergens	Allergic inflammation	Eosin; asthma phenotype; asthma control
8-isoprostane, pH, hydrogen peroxide	Exhaled breath condensate	Air pollution	Oxidative stress	Allergy; asthma exacerbations; increased asthma severity
Thymic stromal lymphopoietin (TSLP)	Airway epithelium	Allergens?	Allergic sensitization	Severe asthma
YKL-40	Sera; airway	Mold?	Airway inflammation	Asthma severity; Asthma control
Nuclear magnetic resonance spectroscopy (NMR) metabolites	Urine; exhaled breath condensate (EBC)	[a]		Asthma
Allostatic load	Cumulative score for blood pressure, cholesterol, HDL, fasting glucose, waist-to-hip ratio, cortisol, DHEA	[a]	Resilience	Asthma

[a]Some biomarkers under investigation have been linked to certain susceptibility measures, but not yet to exposure(s) or pathways.

80%-90% point to the need to characterize the built environment exposome and the factors that shape it.[28] Within the built environment, exposure to external physical factors, chemicals, or biological agents, including indoor allergens, pathogens, insects, and their associated biochemicals, impacts the risk of developing allergic diseases and asthma, and hampers the control of the disease. Highly diverse and complex microbial communities, known as microbiomes, inhabit all areas of the built environment, including food, tap water, indoor air, and various surfaces. These microbial constituents are continually being ingested, inhaled, and colonized the skin and mucous membranes. The physical, chemical, and microbial components of the exposome are highly interrelated. For example, inhalation of house dust is accompanied by exposure to microorganisms and allergens. Free chlorine, a strong oxidizing chemical routinely added to water systems to kill pathogens and limit microbial growth, also produces a range of unwanted disinfection by-products which might alter the integrity of epithelial barriers. Thus, a holistic and comprehensive understanding of the exposome in the built environment is needed to design a framework for informing design and control of buildings in a manner that promotes human health and well-being.

Net effects of the environment on the development of allergic diseases and asthma are likely to depend on the sum of (or interaction between) numerous exposures. For example, the traditional farming environment is associated with lower rates of childhood allergic diseases and asthma.[29] Studies in western Europe indicate that there are several specific exposures that may mediate these beneficial effects, including consumption of raw farm milk, contact with animals, a rich microbial environment, and contact with grains and silage.[30] In urban environments with high rates of poverty, environmental exposures and effects on allergy and asthma are quite complex. On the one hand, increased exposure to microbes and high levels of certain allergens (cockroaches, mice, and cats) are inversely associated with allergic sensitization, wheezing, and asthma. These observations are similar to the effects of some farm exposures.[31,32] On the other hand, exposure to high rates of stress, tobacco smoke, and outdoor pollutants, prenatally or in early life, promotes allergies and/or asthma. The hygiene hypothesis was initially proposed as an explanation for the alarming rise in allergy prevalence in the last century stipulating that the lack of infections associated with a Western lifestyle leads to a reduction in type 1 immune responses. During the last few years, tolerance to allergens has become central in the hygiene hypothesis in the last years. Loss of adequate microbial stimulation due to a Western lifestyle and immunostimulatory environmental signals during early life or passed on by the mother are key elements supporting the observed rise in type 2 allergic diseases.[33]

Allergic sensitization can also modify the effects of respiratory virus infections. For example, children who are highly sensitized to allergens are at increased risk of rhinovirus wheezing illnesses.[34] Notably, treatment with omalizumab led to several beneficial effects including increased virus-induced interferon responses and reducing the frequency of viral detection and viral illnesses.[35,36] Pollutants such as NO_2 also increase the risk of virus-induced wheezing in children.[37]

The effects of respiratory virus infections also depend on host genetics. In addition to the aforementioned examples with air pollution, polymorphisms in the 17q21 region are associated with higher risks of wheezing with rhinoviruses and also greatly increase the risk of developing asthma, following a rhinovirus wheezing episode.[38] Interestingly, in children with these same variants, farm exposures decrease the risk of subsequent asthma. The same genotype can confer genetic risk and also allows for protection in the farm environment.[39] In addition, children with polymorphisms in cadherin-related family member 3 (CDHR3), the receptor for rhinovirus C, are more likely to develop rhinovirus C infections and illnesses, and ultimately childhood asthma.[40-42]

The occupational environment is an important source of health hazards, including lung diseases.[43] With the continuous introduction

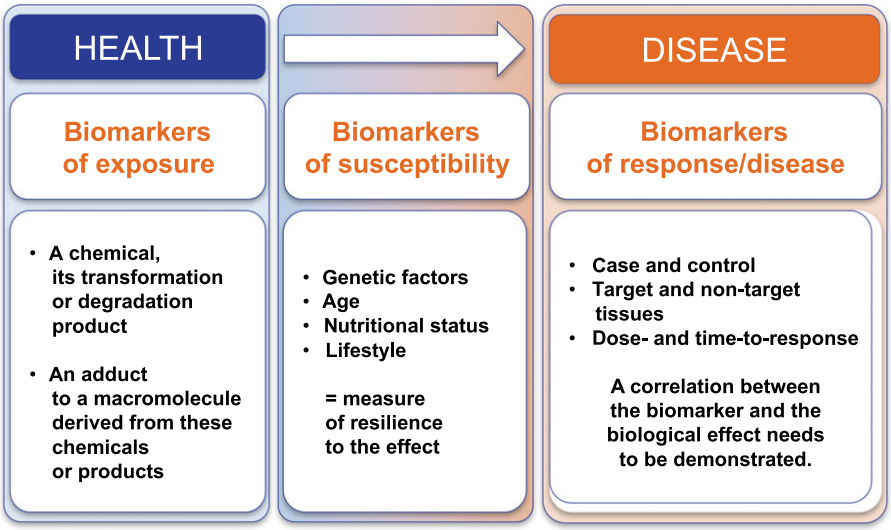

FIGURE 2 Development of the exposure through biomarkers

of new agents and technologies in the workplace, new occupational threats and diseases are being described,[44] some of which can be particularly difficult to ascertain.[45] The occupational exposome describes the entire workplace exposures that interact with the genome and other environmental factors that may provide important clues for the understanding of chronic work-related diseases. The identification of new hazardous agents and the validation of environmental and biological indicators of exposure and effect are important goals in surveillance of work-related diseases and in prevention of new health hazards. Faisandier et al., have proposed a theoretical framework of the occupational exposome using a network-based approach for characterizing occupational health problems linked by similar workplace exposures.[46] This model can allow the assessment and characterization of relevant disease-exposure associations in the form of a relational network. The occupational exposome can be analyzed at the level of an isolated disease or at the level of several diseases, considering different dimensions of the workplace exposure, such as job title, hazards, activity, and so on.[46] The characterization and a better understanding of the occupational exposome can be of great value to unveil the pathogenic mechanisms of chemical-induced adverse effects and should open the way to implementation of effective preventive strategies.[47]

Children spend 6-10 h per day in school, which is a substantial proportion of their time away from home. The school/daycare environment may therefore be viewed as a child's required occupation. The school environment represents a distinct set of exposures. Schools are also typically centrally located within a community and may be in closer proximity to heavy traffic routes and industrial exposures than residential areas.[48,49] The school is also a hub for pick-up, drop-off, and idling cars and buses, potentially contributing to a site-specific increase in ambient pollution. These factors make schools a unique microenvironment of indoor exposures and an area of investigation relating school and home exposures to allergens, molds, pollutants, and other microbial exposures.[50-55]

The implementation of public smoking bans and clean air policies has led to a reduction in the hospitalization for asthma, and these policies should be reinforced in as many countries as possible.[56] School-specific targeted intervention work is ongoing.[51,57]

2.5 | Diet, lifestyle, social and psychological factors, city planning, and social determinants of health

Diet is becoming increasingly recognized as an external exposure relevant to allergy and asthma, although the specific risk determinants are not well understood. However, in one large study from the NutriNet-Santé cohort, the association between the overall quality of diet evaluated by three dietary scores and the asthma symptom score and control was investigated in 34 766 participants. Roughly 25% of participants reported at least one asthma symptom. A negative association between a healthier diet and the asthma symptom score indicative of poorly controlled asthma was observed in men (odds ratio [OR] 0.39) and, with borderline significance, in women (OR 0.73). Healthier diet behaviors were associated with fewer asthma symptoms and better asthma control.[58] In the pooled analysis of the Dutch Maastricht Essential Fatty Acid Birth and the Greek RHEA Mother-Child cohorts, higher eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations and a higher n-3:n-6 fatty acid ratio at birth were associated with lower risk of childhood wheeze and asthma. Dietary interventions resulting in a marked increase in the n-3:n-6 polyunsaturated fatty acid (PUFA) ratio, and mainly in n-3 long-chain PUFA intake in late gestation, may reduce the risk of asthma symptoms in mid-childhood.[59]

Other dietary exposures have been linked to allergy and asthma through their induction of relevant biomarkers or pathways (Table 1). For example, a single McDonald's meal promotes oxidative stress and increases the expression of inflammatory genes.[60] Advanced glycation end products (AGEs) are highly oxidant compounds formed through the nonenzymatic reaction between reducing sugars and free amino acids, and they are found at high levels in fast foods.[61] Thus, a single meal high in AGE can boost oxidative stress and various markers of metabolism.[62] Furthermore, the effects of such meals on allostatic load may be more pronounced in those who are physically inactive. On the other hand, a single healthy meal incorporated into standard Westernized dietary practices each day (e.g., lunch based on traditional Mediterranean or Japanese diet) can reduce markers of allostatic loads.[63,64]

However, many questions remain to be solved concerning the extent to which the allostatic load can be modulated by the background diet in the context of concomitant intervention of stress, the immune system, microbiota, socioeconomic status (SES), and numerous other factors.[65] Several studies have shown that antioxidant tissue levels of antioxidants that would buffer the effects of the allostatic load are lower in persons with individual and neighborhood SES disadvantage.[66,67] Neighborhood disadvantage is associated with lower microbial diversity as well.[68] The diet can undoubtedly influence the microbial ecosystem, and at the same time, the biophysiological response to the diet will be influenced by the gastrointestinal microbial ecosystem.[69] Levels of blood antioxidants and omega-3 fatty acids may also be a product of the intestinal microbial diversity dependent upon the consumption of essential fats and deeply colored, fiber-rich plant foods.[70,71]

The exposome also encompasses a wider set of psychological, social, and behavioral variables that include stress, subjective well-being, personality traits, resilience, social connectedness, and social support. Constructs such as stress and social isolation may seem hard to pin down, but there are well-validated instruments for measuring them from social science and psychology. The ability to measure these constructs electronically—via smartphones (e.g, Ecological Momentary Assessment), social media (e.g, tweets reflecting mood), and electronic health records opens the door for their widespread inclusion in exposome research.

Many factors that influence our health operate at the societal rather than individual level: cultural background, SES, access to health care, and high-quality education, coined by Jacquez and Sabel as “behavome”.[72] Geo-coding via geographic information system

(GIS), as discussed later, can capture some of these societal factors, opening up additional possibilities of linking neighborhoods and communities to disease outcomes.

Urban green spaces are a key element in the planning of today's cities because they favor the interaction between citizens and the environment, as well as promoting human health. Urban landscape elements, particularly trees, have the potential to affect airflow, air quality, and the production of aeroallergens. Improved air quality and respiratory health are among the anticipated economic and social benefits of the urban forest. More vegetation within a 100-m or 250-m buffer around the home was associated with lower personal exposure to particulate matter ≤2.5 μm ($PM_{2.5}$).[73]

Lack of planning in the design of urban spaces with low species biodiversity at planting, overabundance of species acting as pollen sources, exotic species prompting new allergies in the population, botanical sexism, the presence of invasive species, inappropriate garden management and maintenance activities, cross-reactivity between phylogenetically related species and the interaction between pollen, its microbiome, and air pollutants are major causes triggering pollen allergy.[74-76] In recent decades, city planning strategies have favored pollen-producing male bushes, trees, and plants. These "litter-free" male plants are chosen to avoid having to clean up the seeds and fruit produced by pollen-collecting female plants. This practice known as botanical sexism drives up pollen counts in urban areas, which subsequently affects allergy symptoms. Given that many modern cities currently fall below the ideal tree canopy level (40% of the city area), there is an opportunity to plant more female trees and shrubs, while also considering the overall allergy potential of particular species. Insect pests infesting landscape trees and shrubs produce insect dander and sticky secretions ("honeydew") that trap airborne mold. The result is a tree or shrub that is highly allergenic. Songbirds are the best defense against these pests, and thus, planting fruiting plants specifically to attract and feed the wild native songbirds is recommended. A long-range plan for eradication of dominant weeds is also helpful. Regulations on keeping grass lawns mowed in order to avoid getting too tall and releasing allergenic pollen should also be enforced as a public health issue. In addition, a thick, healthy, regularly mowed lawn makes an excellent trap for pollen that comes from nearby trees or shrubs. Female clones of grasses such as buffalograss should be encouraged since they use very little water, require less fertilization, and they produce no pollen. There is a clear need for guidelines regarding the design and planning of urban green spaces with a low allergy impact. Active consultation with botanists and allergists for city planning should be advocated.

3 | THE EXPOSOMICS

Currently, there is no standard or systematic way to measure the influence of environmental exposures on health. Documenting exposure is highly challenging: Different classes of offending agents (physical, chemical, biological, and psychosocial) from various sources (water, air, soil, food, consumer products, and medicines) encountered in various places (home, school, work, neighborhood, community, travel, etc.) or in different life stages (fetal, child, adolescent, adult, and elderly) engage contact with our body through different entry gates (lung, skin, and gut) and target different biological pathways in different organs. Documenting exposure is relatively easy for high-dose chronic exposure. However, for low dose chronic exposure proper documentation is hampered by the sensitivity of the assay, for intermittent exposure by the frequency of testing while for transient exposure the system should be in place at the time of exposure or the evaluation relies on the measurement of the footprint (the biologic response or allostasis).

There are two current approaches in the exposomic research: the bottom-up (targeted) approach building from known exposures and connections to the molecular initiating event generating the disease; and the top-down (untargeted) approach starting in an unbiased fashion from the disease and the initial molecular event aiming to discover novel exposures and connections.[77,78] The targeted approach relies on biomonitoring levels of known analytes (chemical, biological) in a sample, environmental monitoring, and questionnaires. The untargeted approach relies on -omic tools searching for patterns and peaks followed by validation. The semi-targeted (hybrid) approach uses computational biology to expand the list of targets and then develops biomonitoring methods.

While exposure to outdoor air pollution, pollen, temperature, noise, water and soil contaminants, ultraviolet radiation, and green space is generally measured and/or modeled on a population level, exposure to food contaminants, consumed products, indoor pollutants and aeroallergens, and physical activity is evaluated at an individual level. Individual assessment may be used to build or validate environmental models. Environmental exposure and dose estimates can be linked with -omic data to obtain biomarkers of exposure or diseases and to determine mechanistic pathways underlying the environmental endotypes.

The ideal exposure measurement evaluates multiple sample types (biological, questionnaires, etc.) across relevant matrices using various analytical methods and integrates -omic tools in a dose and time-to-response studies using experimental model systems to gain detailed mechanistic information.

The evaluation of the exposure needs to follow the same approach used to assess genetic relationships in the genome-wide association studies (GWAS). The GWAS approach controls for multiplicity; it is comprehensive, transparent, and unbiased and allows validation of novel findings. The linkage with disease risks opens the way to EWAS. By taking a data-driven, agnostic, unbiased approach, EWAS leads to more reproducible hypotheses.[79] The goal of EWAS is to sort through the thousands of environmental stressors to which people are exposed during life and identify those few exposures that may be the causes of disease. Epidemiologists can then follow up with focused studies to establish causality. Research into the relationships between external exposures and global profiles of molecular features (as measured by -omics) constitutes a novel advance toward the development of "next-generation exposure assessment."

Genes are turned on and off as the function of exposure. If causal, exposure must influence biology via gene expression.[80] Searching

for genes differentially expressed under different exposures over multiple experiments is the basis for the TWAS.

3.1 | Standardized measurement platforms and measurement harmonization

Exposomics relies on sensors and big data. However, more data are not equivalent to better information: We need the right data and furthermore to determine their relevance. Many challenges need to be overcome: selection of relevant sensor data sources, modeling a high temporal-spatial grid, characterizing uncertainty, and data integration to support ease of use. The four "V"s of measurement platforms that exposomic research needs to find a solution for are Variety (no standards—heterogeneous), Velocity (multiple data gathered per second), Volume (data accumulated over long times and from multiple sources), and Veracity (significant uncertainty, variability, and gaps—noisy data).

Exposomic research lacks a comprehensive environmental health surveillance system. Barriers to build this system include available resources, communication strategies, data comparability and sharing, and political will. Anticipated benefits include high-quality data, informing public health, environmental decisions and benchmarking the success of public health interventions, improved risk assessments for environmental stressors, and new ways to prioritize environmental health research.

3.2 | Informatics and data analytics to support exposome-based approach for allergic diseases and asthma

Whereas genomic data consist of stable linear sequences, exposome data are heterogeneous, nonlinear variables that change over time and space. Dense webs of correlation among environmental variables make it hard to tease out causation. Exposome researchers can rely on the bioinformatics tools developed for GWAS, but to fully develop the exposomic approach, exposure to new tools for storing, integrating, and analyzing the data is needed.

Exposure assessment in exposome studies involves large amounts of data collected at multiple scales and life stages. Major challenges include how to integrate and interpret data in a meaningful way, how to account for shared exposures, how to integrate data across multiple spatial and temporal scales and methodological approaches, and how to adjust for measurement errors.

The aggregate exposure pathway (AEP) framework, a conceptual framework that complements the adverse outcome pathway (AOP) concept, organizes exposure and data from source to dose and to outcome.[81,82] In the dynamic adverse outcome pathway model proposed for systems toxicology, quantitative system-wide molecular changes in the context of an exposure are measured, and a causal chain of molecular events linking exposures with quantifiable outcomes in the target organs (histology, imaging, and functional tests) is proposed. Mathematical models are then built to describe these processes in a quantitative manner. The integrated data analysis leads to the identification of how biological networks are perturbed by the exposure and enables the development of predictive mathematical models of toxicological processes. Together, the two frameworks complete the view of the exposure-outcome continuum to enable knowledge integration and a better understanding of the health impacts of exposure. In addition, the AEP framework supports exposure modeling and forecasting by organizing exposure data within individual units of prediction.

Few studies have attempted to comprehensively quantify correlations among multiple exposures. In an analysis of 81 environmental exposures assessed during pregnancy via a range of biomonitoring, geospatial modeling, remote sensing, and questionnaire approaches, Robinson et al reported a weak correlation among exposures overall but a stronger correlation among exposures within the same family, suggesting that adjustment for potential confounding between families of exposure may be permitted in future epidemiological studies of the exposome.[83] The authors also note that correlations may be inflated for exposures assessed using a similar methodological approach, for example, the same analytical platform or modeling input variables, possibly obscuring true exposure variability. Considering the interdependencies of the exposome, Patel and Manrai constructed an "exposure correlation globe" to identify and display correlated clusters of exposures by extending unsupervised learning approaches originally developed for use with genomic data to 81 937 environmental exposures collected as part of four consecutive NHANESs.[84] The correlation globe provides a complex view of exposure: Looking for the hubs of the network, one can deduct what factors are correlated with others the most. The results of these and related models will provide a better understanding of the estimated effect and on how to appropriately identify and adjust for potential confounding.

Statistical methods need to solve problems from technology-related biases (errors occurring across scales of measurement with different precision and analyte, use of multiple measurement tools with different sampling strategies), bidirectionality, reciprocal relationships, intraindividual variability, idiographic effects, and feedback loops. Additional research focused on capturing time-varying effects is also required.

There are both opportunities and challenges in creating a search engine supporting the exposomic approach. High-throughput methods are systematic, are reproducible, and allow control for multiple hypotheses, and the results support scientific prioritization. The challenge derives from the big data yielded by the high-throughput methods since there is the risk of big bias and it is not easy to disentangle the dense correlational web. The researcher might end with fragmented and small associations. Other challenges are confounding factors, reverse causality, and the influence of time and life course.

In addition, there is a need for expansion of the data resources to increase the analytic power to query the biological role of EWAS discoveries.

3.3 | Precision medicine and big data approach

The precision medicine approach relies in part on the integration of patient-centric molecular, environmental, and clinical "big" data into targeted management pathways.

Few methods exist to ensure that big data resources motivated by precision medicine are being used reproducibly. Relevant challenges include integrative analyses of heterogeneous measurement platforms (genomic, clinical, quantified self, and exposure data), the trade-off in making personalized decisions using more targeted but potentially much noisier subsets of data, and the unprecedented scale of asynchronous observational and population-level inquiry (i.e, many investigators separately mining shared/publicly available data). Another challenge for the implementation of precision medicine involves novel methods for assessing data quality. Software that enables analysts to transparently document analysis protocols can help ensure reproducibility.[85-87]

The Biomedical Data Translator (BDT) program, sponsored by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health, is exploring novel approaches to interrogate big data for precision medicine applications in ways that can be very powerful in assessing the impact of the exposome on human health. This project involves 13 teams of data scientists, specific content experts, physicians, and other scientists from NCATS and 17 universities and research centers working in a coordinated fashion to develop a data integration and translation tool. This project focuses on developing application programming interfaces that can interrogate a number of disparate knowledge sources that describe and/or impact human biology.

At present, 40 distinct knowledge sources have been included in this project, which includes data on environmental exposures available from the US Environmental Protection Agency, data on socioeconomic data (income level, access to health insurance, and transportation) available from the US Census, electronic health record data, accessed with appropriate regulatory oversight (clinical measures, diagnostic assessments and tests, diagnoses, interventions, and drug exposures), and data from a number of open data sources. These open source data include exome or genome pedigrees, experimental and mechanistic data on molecular biology and biological pathways, systems biology, and chemical structures and drug targets.

As the BDT data protocols and procedures evolve, there will be a number of ways to expand access to environmental and other novel data sets with those outlined above to allow for queries focused on the impact of exposome elements on allergic and immunological diseases. For example, there are emerging data that demonstrate that exposure to ambient air pollutants modifies the gut microbiome.[88,89] While the microbiome is beyond the scope of this review (and the focus of the previous PRACTALL), it is noteworthy that there are emerging data to suggest that ambient environmental particulate matter impacts airway and gut microbiome, as well as microbiome influences on pollen biology. Additionally, there are data that indicate that biodiversity (including microbial diversity) is associated with improved human health and that indoor biomass pollution impacts human microbiome.[90] As microbiome data sets become available to BDT-type approaches, there will be richer approaches to assess exposome effects on human health.

4 | EXPOSOME VISION AND CHALLENGES

In addition to the application of biomarkers and of integrated big data approaches for multi-analyte exposure assessment, the translation from exposure biology to exposomics needs integration of temporal-spatial variation in the exposome, including over the life course. This includes tools for measuring the individual external exposome over the life course and research that translates exposome data to improved public health policy.

4.1 | Addressing the dynamic, life course nature of the exposome

The impacts of environmental exposures on health effects over the life course are dynamic (Figure 1). Emerging data have identified several key time windows of susceptibility on asthma and allergic outcomes. One is the prenatal time period, as Hsu et al., demonstrated using satellite-based spatiotemporal measures to model daily $PM_{2.5}$ exposures throughout pregnancy on physician diagnosis of asthma by age 6 years, mid-pregnancy at 16-25 weeks' gestation, especially for boys.[91] When $PM_{2.5}$ measures are combined with maternal stress exposure, the prenatal time window of susceptibility may narrow to 19-23 weeks.[92] When NO_3^- measures are combined with high maternal stress, pregnancy remains a key period.[93]

Lagged exposure-response associations have also been observed. For example, 7-day lag periods with 10 $\mu g/m^3$ increase in PM and hospitalizations for asthma were detected in Seoul, S. Korea, especially among elderly participants.[94] Differential effects related to the sequence of exposures and the timing of exposures were elegantly demonstrated in experiments by Clifford et al. Here, initial priming effects on DNA methylation in bronchial brushings of airway epithelial cells of experimentally exposed diesel observed at 48 h were amplified 4 weeks later following a second exposure with the allergen. Interestingly, when the sequences were reversed, a different pattern of CpG methylation became evident.[95]

Addressing the dynamic, life course nature of the exposome can be done using birth cohorts specifically addressing the exposome with prospective follow-up or extend across multiple generations or by longitudinal studies with repeat measures of multiple exposures (e.g, Helix, ECHO). Integrating data from several cohorts that together mimic all life stages is evaluated by EXPOSOMICS by pooling together data collected from birth cohorts (RHEA and PICCOLI+), childhood cohorts (INMA and ALSPAC), adolescence (PISCINA), early adulthood (SAPALDIA and EPIC-SCAPE), adulthood (OXFORD-ST), and mid- and late life (MCC and EPICURO).

4.2 | Tools for measuring personal environmental exposures

Major scientific and technological advances currently support the assessment of the exposure: geographic information system (GIS); remote sensing; global positioning system (GPS) and geolocation technologies; portable and personal sensing, including smartphone-based sensors and assessments; and self-reported questionnaire assessments, which increasingly rely on Internet-based platforms.

Many instruments are currently available to measure personal exposure to specific exposome domains. These can be divided into personal or wearable monitors, and stationary monitors that record fixed measurements from the location where they are placed. For example, small, mobile monitors that capture air pollutants are becoming increasingly available, even commercially. While the sensor technologies may differ across instruments, personal monitors advantageously capture spatiotemporal trends with high resolution and reliable validity, especially for fine particles, gasses such as O_3, NO_2, CO, and volatile organic compounds.[96,97] They also permit assessments of the relationships between the intensity of environmental exposures that may change with individual activities or inhalation rates, such as those related to sleep, exercise or type of exercise, and commuting to work or school,[98] and can be filtered into real-time computer navigation systems for further coverage.[99] Accelerometers count steps and sleep times; heart rate monitors may gauge exercise intensity.

New smartphone-linked diaries and imaging provide additional tools for capturing the exposome. In addition to facilitating the capture of how air pollution exposure changes with individual activities and by GPS-derived location, they may help ascertain diet and use of consumer products. Smartphone cameras snap photographs of food to provide a more accurate account of dietary intake. All these data can then be overlaid with GPS data to learn about context, such as which locations are most conducive to exercise. Using GPS-enabled smartphones, spatial-temporal paths (also called "space-time cubes") can be intersected with spatial-temporal maps of environmental hazards (e.g, the hazard map) or even the density of fast food restaurants to quantify individual exposures.

Residential air monitors, placed on one's school, office, or even moved from location to location at certain intervals, may capture indoor exposures missed by general methods such as GIS. Residential monitors also readily capture outdoor pollutants that penetrate inside related to high air exchange rates, such as black carbon/soot and trace elements. Particular attention needs to be paid toward features of the location, such as whether the sensor faces a street, alley, or green space, as well as floor height.[99,100] For both personal and residential monitors, consideration of quality assurances and controls and processing of the data is important. Other considerations may relate to the effects of season, limits of battery power, reproducibility, and normalization of background noise.[97] Moreover, residential dust can be a reservoir for allergens and microbial products that are relevant to the onset of allergic diseases and their prevention.[101]

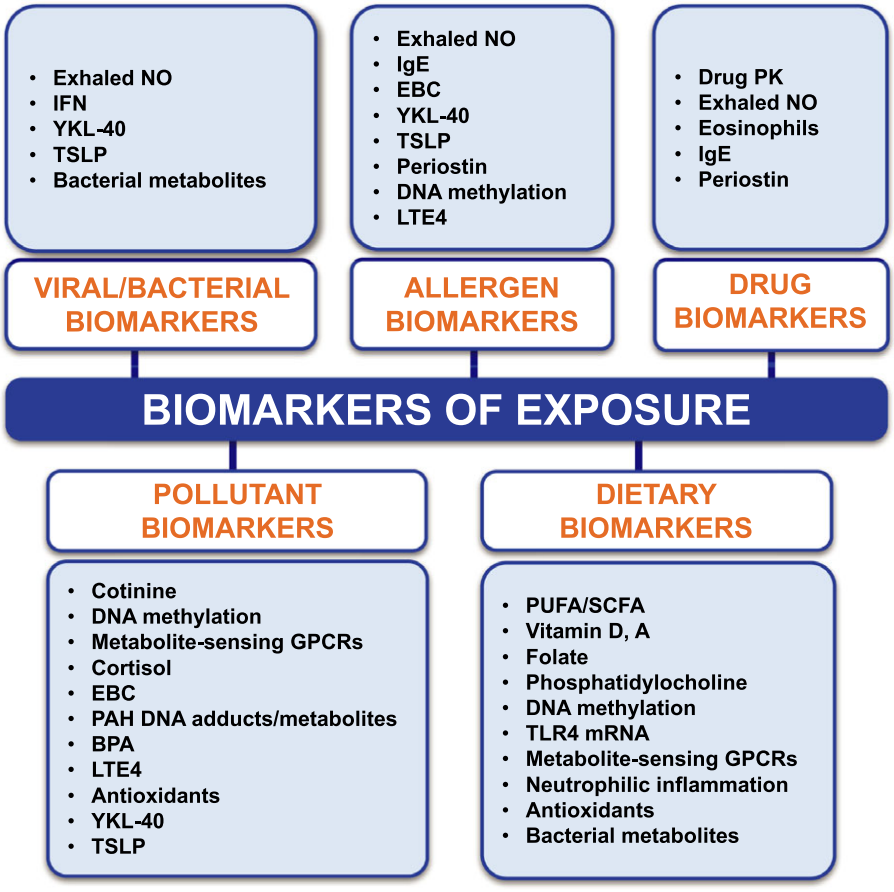

FIGURE 3 Biomarkers of exposure can be classified according to the environmental stressor. The best exposomics biomarker is related as many exposures as possible

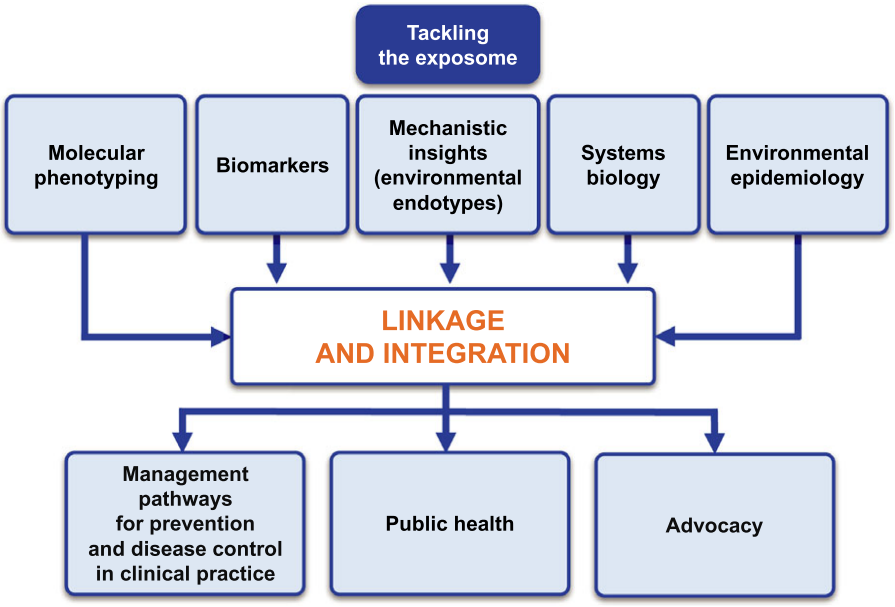

FIGURE 4 The holistic approach of the exposome to the environmental causes of allergic diseases and asthma leads to better understanding of disease mechanisms driving the environmental endotypes and phenotypes and supports the development of management pathways for prevention and disease control in clinical practice and the advocacy effort to improve public health

GIS has transformed environmental health research by integrating databases that connect different attribute data by geographic location. Data on external environmental exposures obtained from remote sensing, geolocation technologies, or sophisticated modeling outputs can be combined with health attribute data obtained via personal sensing or other approaches. GIS integrates topologic geometry, which can manipulate geographic information, with automated cartography, enabling users to compile digital or hard-copy maps. GIS can quantify buffer distance between an exposure source and a human receptor and may be used to characterize proximity to roadways, factories, and green spaces. GIS can also display and analyze mobility of people as they travel through the external environment.

Remote sensing technologies are useful for external exposure assessment in areas where ground-based monitoring is not available. There is an expanding list of environmental exposures that can be measured via remote sensing such as $PM_{2.5}$ and NO_2 concentrations, green spaces, temperature, and the built environment.[102] A major advantage of remote sensing is that it has virtual global coverage, useful for large population studies.

Future challenges in portable and personal sensing include measuring longer-term exposures and health outcomes, reducing cost, improving operability for application in larger population-based studies—in particular to avoid problems in compliance, potential sampling bias, and behavioral change due to wearing of the monitors—improving reliability and quality of data, measuring a greater number of exposures, and integrating and interpreting data from diverse sources. Unfortunately, most personal environmental sensors remain too bulky and costly to deploy on the thousands of participants needed for EWAS-type studies. Further research to validate the expanding number of available software applications and improve personal devices with additional features such as more miniaturization is also required. Although assessment of the exposome is based largely on objective assessments due to economic reasons, population-based studies will still rely on questionnaires and surveys as inexpensive and effective ways to capture self-reported, personal characteristics and historic exposures from a large population. Information from questionnaires on residential and occupational history can still be linked to the growing number of geospatial data sources to create integrated metrics of exposure to environmental contaminants, such as air pollution. Technological improvements regarding how questionnaires are administered (e.g, smartphones, social media, and social networks) allow quick integration of reported data into the analytical data sets.

4.3 | The relevance of the exposome data to clinical practice and to policy advocates

Bit by bit, progress in describing human exposure is made. However, several gaps need innovative solutions such as integrating all the layers of exposomic data and linking them to genome data to estimate the gene-environment interactions. The exposome community needs to adopt the "big science" approach similar to the Human Genome Project by investing in improving measurement technologies, establishing a data repository for exposures that allow data sharing and agree on standards, such as for variable names, meta-data, and security.

Exposomic research must also evaluate the practical considerations related to operational parameters, training, and funding, including balancing costs versus the necessary accuracy for technological deployment in large-scale studies. Adequate training to current and future researchers and research users is urgently needed to facilitate transdisciplinary collaborations on both targeted and broad-spectrum external exposure applications.

The new 2012-2017 Strategic Plan for the National Institute of Environmental Health Sciences (NIEHS) combines fundamental and exposure research with detailed focus on health disparities and global environmental health. Training and education, communication,

and implementation as a support for the implementation science are further prioritized.

There are also funding implications, such as the need for larger exposome-related research grants and transdisciplinary research centers, though this challenge does not preclude the use or leveraging of existing resources, including incentives for multisector (public and private sectors) initiatives to integrate the exposome into ongoing work. The ideal exposome should fulfill the following criteria:

- Measures a wide spectrum of exposures
- Quantifies relevant biological exposure at the target site
- Not influenced by simultaneous measurement of other exposures
- Stable
- Sensitive to changes over time
- Provides a measure of both recent and remote exposure

For the utility of the exposomic approach for allergic diseases and asthma, there are still several open questions

- What is the population of interest ("the model")?
- What is the nature (duration, frequency, timing) and magnitude (concentration and dose) of relevant exposures?
- Which associations are relevant for a particular allergic disease?
- What are the mechanisms driving the environmental endotypes ?
- Which approach is best: population-level value vs personalized medicine approach?

Several research priorities can be advocated:

- Follow the concept of integrative exposomics [102,103]
- Develop bioinformatics approaches that link exposures with biological responses and disease outcomes. The exposome will be represented as multifactorial variables. This will require sophisticated informatics approaches
- Complex unifying models based on language standards for exposures
- Guidelines for sample collection standards for use with emerging and anticipated technologies
- Develop criteria for selecting the best assay(s) to assess the biological response for the research question of interest. These criteria should be updated periodically to address emerging tools and technologies.

5 | CONCLUDING REMARKS

The exposome concept offers a new and exciting paradigm for the improvement and integration of currently scattered and uncertain data on the impact of the environmental component on allergic disease inception and evolution. The designs/models of environmental exposure should be assessed in longitudinal cohort studies of asthma and allergic diseases and the assessment strategy adapted to the population and cohort studies. Several challenges need to be overcome such as how to prioritize and select the best tools and outcomes and to standardize the timing and duration of measures. In addition, it needs to be established if the exposure profile is suitable for population and cohort studies.

Although many priority research needs and challenges related to measurement harmonization remain, it is important to begin the exposomic studies. While still formative, these studies assess the feasibility of many new methods of exposure assessment, discovery analysis, and data integration. Large-scale initiatives test the validity of exposure assessment in ways that smaller studies cannot. Switching from the "one-exposure-one-health-effect" approach to a more holistic approach (Figure 4) to assess the environmental impact on health and disease is essential to improve our understanding of the predictors and risk and protective factors of complex, multifactorial, chronic diseases, like asthma and allergic diseases. These developments will ultimately lead to better prevention strategies.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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