Allergies to food and airborne allergens in children and adolescents: role of epigenetics in a changing environment

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Lancet Child & Adolescent Health, 2022
https://www.sciencedirect.com/science/article/abs/pii/S2352464222002152?via%3Dihub
PMID: 35985346
DOI: 10.1016/S2352-4642(22)00215-2

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Key words
Air pollution, Allergen, Allergy, Asthma, Climate change, Methylation

Summary (129/150 words)

Allergic diseases today affect millions of children and adolescents worldwide. In this review, we focus on allergies to food and airborne allergens, and provide examples of prevalence trends during a time when climate change is of increasing concern. Profound environmental changes have affected natural systems in terms of biodiversity loss, air pollution levels and climate change. We discuss potential links between these changes and allergic diseases in children, as well as clinical implications. Several exposures of relevance for allergic disease also correlate with epigenetic changes such as DNA-methylation levels. We propose that epigenetics may offer a promising tool by which exposures and hazards related to a changing environment may be captured. Epigenetics may also provide promising biomarkers and help elucidation of mechanisms related to allergic disease initiation and progress.

Key messages

- Allergic diseases affect millions of children and adolescents worldwide; between 5 and 30% of adolescents report rhino-conjunctivitis symptoms and up to 10 % report food allergy.
- Links between climate change and allergic diseases are of increasing concern, and these include: extended and altered pollen seasons, spread of allergens to new areas along with changing and warmer climate, air pollution exposures changes, increasing exposure to heat events, and altered biodiversity.
- These new climate change aspects of allergic diseases have clinical implications for prevention, diagnostics and treatment.
- Epigenetic changes, exemplified by DNA methylation, are associated both with environmental exposures and allergic diseases, although causality needs to be explored further.
- There is potential in the use of epigenetic signatures and omics profiles to detect and monitor aspects of environmental exposures of relevance for health and disease in children and adolescents.

Introduction

Allergic diseases include asthma, atopic dermatitis, food allergies and allergic rhinitis, and these conditions today affect millions of children and adolescents worldwide. It has been widely acknowledged that lifestyle factors associated with modern, urban living conditions have contributed to the significant increase in prevalence of these conditions in the second half of the 20th century.[1] While the increase in asthma prevalence seems to generally have leveled off globally in the last 10-20 years[2], allergy to foods and also certain pollens and dust mites appear to have continued to increase in many regions. In addition, "new" allergies have emerged in many parts of the world. While this can in part be explained by behavioral factors such as changing dietary habits, increasing interest in vegetarian and vegan diets, and global travel and trade, there are concerns that global environmental and climate change are partly responsible for new allergy profiles seen in our patients.[3] For example, global warming with extended pollen seasons has introduced new species for some ecoregions, which has been linked to increased allergies to inhalant allergens and worsening of symptoms.[4] In addition, climate change has been linked to an increased prevalence of thunderstorms, which are associated with peak levels of airborne pollen allergens and exacerbations of allergic symptoms.

Despite the strong impacts of environment and lifestyle on allergies, heredity and genetics also play a major role in allergic diseases.[5] Asthma, rhinitis and atopic dermatitis may co-exist partly because of shared genetics involved in immune response processes, especially in childhood-onset disease.[6] Much effort has also been given to explore the association between allergic disease and epigenetics[7], that include chemical DNA modifications (e.g. methylation) that regulate gene expression and may be induced by environmental exposures. Given that particular exposures such as tobacco smoking have been strongly linked to DNA-methylation profiles at birth and during childhood, epigenetics has been suggested to serve as "environmental biomarkers" linking our genes with exposure and disease.[8] In a changing environment, such epigenetic markers could give important insights about consequences for health and disease.

In this narrative review, our ambition is to give a state-of-the-art update on allergic diseases in children and adolescents and to explore the role of environmental exposures as of today. A special focus will be given to factors stemming from global environmental changes, in particular climate change, in relation to increasing incidence of allergies, "new" allergies, and the link between exposure, epigenetics and allergic disease (*Figure 1*).

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "allergy" AND "climate change" AND "epigenetics" from 1995 until February, 2022. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Time trends of allergies to food and airborne allergens in children and adolescents

Food allergy affects a substantial and growing proportion of children and adolescents

Food allergy (FA) is a common, chronic childhood condition estimated to affect up to 10% of children in many areas of the world.[9,10] FA prevalence has been steadily increasing over the past two decades.[11] While delayed introduction of food allergens in some communities may in part explain higher rates of FA in recent years, additional mechanistic explanations for its rising prevalence are still needed.[12] Individuals with FA are at daily risk for potentially life-threatening hives, angioedema, respiratory difficulty, cardiovascular compromise, gastrointestinal distress, and/or anaphylaxis following ingestion of a food antigen to which they are sensitized.[13] In addition to burden from its direct symptoms, FA impairs quality of life, nutrition, emotional health, and lifestyle.[14] Peanut oral immunotherapy can reduce sensitivity to peanut[15], but there remains no cure for peanut allergy or any FA. For many, FA can persist through adulthood.

New food allergies

Mammalian meat allergy due to IgE specific for the carbohydrate allergen galactose-alpha-1,3-galactose (alpha-gal) was first reported about 10 years ago in the southeastern United States.[16] In susceptible individuals, repeated tick bites by the *Amblyoomma americanum* (aka "lone-star") tick and other tick species lead to sensitization to alpha-gal, a carbohydrate present in the gastrointestinal tract of ticks. Because alpha-gal is also present in many mammalian meats, such sensitized individuals may experience allergic reactions upon ingestion of beef and other mammalian meats. While immediate reactions that typically characterize IgE-mediated food allergy can result, many individuals with alpha-gal allergy experience delayed allergic symptoms 3-6 hours after ingestion. Meat allergy due to alpha-gal sensitization has now been reported in many disparate parts of the world, including the United States, Australia, Spain, Germany, Japan, Sweden, and Africa.[10] Research to date suggests that meat allergy predominantly affect adults, although recent studies highlight the occurrence of alpha-gal sensitization and associated meat allergy also in children and adolescents.[17,18] Apart from repeated tick bites,

polysensitization (to other allergens) during childhood and male sex appear to be risk factors for later alpha-gal sensitization.[19] While detailed studies of tick populations are limited, it is thought that climate change is contributing to changes in the distribution and ecology of these ticks, which is in turn altering the areas where human populations are susceptible to developing alpha-gal-mediated meat allergy.[20]

Concerns about the environmental and climate impacts of animal agriculture have led some families to adopt vegetarian and vegan diets. These diets often rely heavily on plant-based protein sources, such as legumes and tree nuts. Plant protein-based milks such as almond, pea, and cashew milk have become increasingly available in many high-income areas of the world. Changes in the quantities and timing of exposures to plant proteins could be affecting rates of detected allergies to these foods, although this has not been directly investigated as yet. Many pollen allergic patients may also experience pollen food allergy syndrome due to cross-reactivity between pollen allergens and foods such as raw fruit, vegetables, and nuts. Studies of self-reported tree nut allergy in children show that the prevalence of tree nut allergy increased significantly from 0.2% in 1997 to 1.1% in 2008.[21] More recent assessments of tree nut allergy prevalence indicate prevalence as high as 4.9% in some parts of the world, with regional variation in rates and of allergies to particular tree nuts.[22]

In summary, FA prevalence has been increasing over the past two decades and affect up to 10% of children and adolescents. Climate change may affect the distribution and prevalence of some food allergies.

Allergies to airborne allergens

Sensitization to airborne allergens is seldomly seen in infants during the first year of life but typically starts to appear in the pre-school ages. Often, sensitization to a single allergen (monosensitization) is followed by IgE responses to multiple allergens (polysensitization), and sensitization early in life is one of the strongest predictors for later development of allergic disease.[23] The key sensitizing allergens associated with allergic disease depend on regional and geographical factors (as well as lifestyle and genetics). In Northern and Central European countries, sensitization to house dust mites, birch and Timothy grass pollens, as well as pets, are dominating, in Southern Europe and the US, ragweed, other weed (e.g. parietaria) and tree (e.g. olive, cypress in Europe; birch, cedar and oak in the US) pollens whereas globally, dust mite, cockroach and mold spores remain major airborne allergens.[24-28] Sensitization rates and allergy to airborne allergens, including grass pollen, tree pollen or dust mites appear to have increased globally in recent years. For example, studies conducted in Northern Sweden in 2010 show increased sensitization rates in school-children compared to 10 years earlier (37% positive

specific IgE at age 11-12 years vs 28%).[29] Similar trends were reported in the Netherlands between 1994 (41% overall sensitization to airborne and/or food allergens) to 2014 (49% sensitization), which was mainly explained by increasing aeroallergen sensitization among 4- to 11-year-olds.[30] Also in China, increasing prevalence in children are reported for tree pollens (2,9% sensitization to black poplar in 2008 vs 5,6% in 2018) as well as for dust mite allergens (32% vs 65%).[28] Similar increasing trends are being reported from South Korea between 2009 to 2018.[31] When it comes to reported rhino-conjunctivitis to airborne allergens (e.g. sneezing or runny or blocked nose, and itchy-watery eyes), increasing global trends were reported from the very large ISAAC (The International Study on Asthma and Allergies in Children) study between mid 1990s and early 2000.[32] Data collected very recently (2021) by the Global Asthma Network (GAN) reports current prevalence rates ranging from 5 to 30% (at age 13-14 years), but data also suggest that symptoms of rhino-conjunctivitis among children and adolescents may no longer be on the increase globally, although substantial variations within regions and countries were observed.[33] For example, the prevalence of rhinitis symptoms (but not asthma) in the last two decades increased significantly in an adolescent population in one of the GAN countries, Ecuador.[34]

In summary, sensitization to airborne allergens appear to have increased globally in recent years whereas symptoms of rhino-conjunctivitis among schoolchildren may no longer be on the increase globally. Yet, up to one-third of adolescents may be affected in certain countries. Local and regional investigations of both allergy symptoms and sensitizing allergens remain therefore a highly prioritized action, in particular in the context of a changing environment.

Climate change, environmental exposures, and allergies to food and airborne allergens

Children are known to be more susceptible to hazardous airborne substances and environmental exposures compared to adults, possibly because of their growing organs and tissues. Children have higher ventilation per minute in relation to body size and often higher physical activity compared to adults, which leads to relatively higher exposure. Vulnerable time periods of exposure, for example in utero or early in life, may be relevant for some exposures. However, using air pollution - lung function association data as example, exposure over the entire childhood age range, as well as prenatal exposure, may negatively influence development.[35] Simulations show that per kg body mass, an infant will receive a nearly four times greater respiratory tract deposited dose of resuspended particles compared to an adult.[36] It should also be noted that children and adolescents typically cannot choose their living conditions or influence modifiable exposure to any large extent and have to rely on caregivers (and the society) taking responsibility for a healthy upbringing environment.

During the last decades, humanity has experienced an unprecedented development with substantial improvements in living conditions and life expectancy. However, this has been accompanied with profound environmental changes and deleterious impacts affecting natural systems in terms of biodiversity loss, air pollution levels and climate change.[37] Environmental hazards stemming from these global processes have been identified as relevant public health threats with substantial health burden, which is highly relevant also in a modern urban environment.[38] Diversity of exposures has proven to be a central theme in farm studies round the world that very robustly have shown lower allergy risks for children being raised on a farm.[39] Such diversity in exposure also translates into microbiome biodiversity (gut, airway, skin) associated with immune tolerance. In particular, microbial exposures in infancy seem to be important predictors for later health and disease.[40]

Health impacts of climate change are substantial and widespread, ranging from increase in mortality and morbidity due to extreme weather events, such as heat waves, drought, windstorms, flooding, wildfires, to more indirect effects derived from vector borne diseases, changes in our microbiome, food or waterborne diseases or socioeconomic impacts such as increased poverty, malnutrition, and migration.[41,42] Climate change potentially influences the development and severity of allergic asthma and rhinitis by influencing pollen and mold production that induce allergic manifestations.[4,43] In particular, the increase in moisture and dampness in the buildings associated with water intrusion during extreme rain storms and flooding events, worsens indoor environments, leading to increased dampness and humidity and supporting the growth of house dust mites and molds that constitute important sources of allergens.[44] Modeling studies have found that climate change has modified the duration of pollen seasons, times of pollen release, amount of pollen produced, and in some cases, pollen composition and allergenicity, as well as introduced spread of new pollen species to new areas, along with climate change and warmer/milder weather in many areas.[45,46] Air pollutants can also interact with airborne allergens and enhance the risk of allergic sensitization and exacerbation of symptoms in sensitized individuals, especially under conditions where drought spells promote resuspension of dust particles and increase exposure to this type of air pollution. Increasing occurrence of heat waves may also adversely affect children with asthma or allergic rhinitis, as breathing hot air can aggravate airways and trigger symptoms.[3]. Furthermore, dehydration could deteriorate ongoing asthma attacks. Increasing temperatures in areas with humid air also pose challenges to asthma and allergy patients, as hot and humid air is “heavy” and harder to breathe, and also, because moist air may trap lung irritants such as pollen, mold and indoor dust mites. Heat wave and drought conditions contribute to increased wildfire risk, contributing to massive exposures to smoke emissions in local communities, consisting of particulate matter and other combustion products, pollutants that have known adverse effects of respiratory health.

Climate change and air pollution are considered the two sides of the same coin. Although the main greenhouse gasses (i.e., carbon monoxide, methane) are not particularly directly harmful for health, these are emitted together with air pollutants originating from burning fossil fuels (coal, oil, wood, etc.), which are directly harmful to health, with children with asthma and allergy representing some of the most vulnerable groups. In particular, particulate matter or nitrogen dioxide are emitted in fossil fuel combustions, one of the main sources of greenhouse gas emissions. There is a bulk of epidemiological studies linking air pollution exposure with development of asthma[47], asthma exacerbations[48] and lung function impairment in children.[35] Although early life exposure to high levels of air pollutants has been associated with increased risk of pollen sensitization[49], associations are generally not very strong[50] and appear even less clear for clinical symptoms, i.e. rhino-conjunctivities.[47] However, it is expected that the increased exposure to allergens due to climate change, along with the exposure to air pollutants that act synergistically intensifying the allergic response, could lead to in-creased incidence of allergy in the future.[51]

While socioeconomic factors often spur migration, it is anticipated that climate change may become an increasingly common motivation for communities to move. The diets and lifestyles of families who move often shift due to differently available foods and the distinct culture and lifestyle norms of a given location. This can in turn impact exposure to allergens and allergy development. For example, a large study of over 57,000 five-year-old children in Australia found that children born in Australia to Asian-born mothers were more likely to have parent-reported food allergy (OR 2.33, 95%CI 1.96-2.77) compared to non-Asian children.[52] In contrast, children born in Asia who then migrated to Australia have lower risk of FA compared to Australian-born non-Asian children (OR 0.33, 95%CI 0.20-0.55). Similarly, it was previously observed that Jewish children in Israel have 10-fold less peanut allergy than Jewish children in the United Kingdom, even after accounting for relevant covariates such as social class and genetic background.[53] Thus, we may see changing patterns of FA around the world with increasing climate-induced migration.

Epigenetics linking genes, environmental exposures and allergies

Epigenetics refers to potentially heritable changes in regulation of gene expression that occur without changing the genetic code. The most widely studied epigenetic mechanism in allergic disease is DNA-methylation, which refers to the covalent binding of a methyl-group to a cytosine base, mostly positioned next to a guanine, forming a CpG site. Next, histone modifications are post-translational modifications of histone proteins, which are used to package DNA. These modifications, which include methylation,

acetylation, phosphorylation and ubiquitylation, act to open or close the chromatin, leading to either enabling or repressing gene transcription. Finally, different classes of regulatory RNAs have been described, including small and long non-coding RNAs, that regulate gene transcription. Epigenetics can be seen as complex, often interrelated layers of regulation of gene expression, which enables cells with the same genetic code to express genes in a location, time and context-dependent fashion. Also genetic factors regulate epigenetic markers.[54] Epigenetics may provide a mechanistic explanation to developmental origins of health, where early life exposures may program an individual to lifelong chronic disease.[8] Therefore, epigenetic markers are highly cell specific, crucial in cell and organ development, and can characterize cellular responses in health and disease. Epigenetic studies in disease need to be interpreted in light of the cell type, age, and may reflect cause or consequence of disease. Over the past years, many studies have examined the association of epigenomic variation in relation to environmental exposure, and diseases like asthma, allergic rhinitis. Most studies investigated DNA-methylation, using DNA-arrays that interrogate 450K or 850K DNA-methylation sites across the genome, so-called epigenome wide association studies (EWAS).

Epigenetics and environmental exposures

Several environmental exposures have been found to influence epigenetic changes (as summarized in Table 1), and well-described examples concerns tobacco smoking. Both maternal smoking during pregnancy and parental smoking during childhood are strongly associated with a wide range of negative health consequences for the fetus and the child; from intrauterine growth restriction, malformations, preterm birth and infant mortality, to childhood asthma, allergy, lower respiratory tract infections and neurocognitive impairment, to list a few conditions.[55,56] Tobacco-free environments for children therefore remain a very prioritized item the global pediatric agenda.

There are numerous cellular and physiologic perturbations associated with smoking exposure, one of which being altered DNA methylation levels. In a hallmark EWAS paper from 2016, researchers from the PACE consortium could demonstrate methylation changes in thousands of genes across all chromosomes (e.g. *AHRR, MYO1G, GFI1, CNTNAP2* and *CYPA1*) in newborns (cord blood) whose mothers smoked during pregnancy.[57] Many of the changes persisted through childhood, and did also correlate with peripheral blood gene expression levels. Further, identified genes were known to be linked to diseases like asthma, cancer, neuropsychiatric diseases and birth defects. These findings have been widely replicated and the correlations with exposure are so strong that methylation profiles can be used as biomarkers for tobacco smoke exposure in children.[58] Air pollution is another well-established risk factor for adverse outcomes in children, and substantial efforts have been made to link air pollution also to methylation changes. While several

significant findings have been identified in large-scale studies[59], it should be acknowledged that the strength of association and level of methylation change in blood following exposure, is much more modest for air pollution compared to tobacco smoking exposure.[60] However, controlled experiments in adults show that allergen and diesel exhaust exposure may induce numerous methylation changes in both blood and bronchial epithelial cells, which suggest that widespread epigenetic changes probably occur if the timing, dose and target organ are studied appropriately.[61,62] In relation to air pollution exposure, the role of nasal airway microRNAs has also gained attention lately and shows intriguing associations with exposure as well as respiratory disease (bronchiolitis and asthma).[63]

Of particular interest in a pediatric setting is the link between development, growth, aging with epigenetics. As mentioned above, epigenetic mechanisms are profound during fetal development, and is a very potent mechanism by which cells can turn on or off gene expression. As such, both gestational age at birth and birth weight (reflecting primarily intrauterine growth) show strong correlations with methylation levels at birth and later during childhood.[64,65] Also social and behavioral factors early in life such as nutrition, socio-economic status, family situation and stress influence the epigenome, as examples of "biological embedding" with potentially long-lasting health effects for health and disease.[66,67] Maternal diet during pregnancy (food intake or supplementation) may additionally influence epigenetics, as shown both in the placenta (histone acetylation[68]) and offspring cord blood (DNA methylation[69]). Interestingly, children's age can be tracked using methylation analyses, suggesting that methylation levels are the result of developmental and growth processes, as well as cumulative exposures and life events.[70]

Epigenetics in allergic diseases

The largest childhood EWAS on asthma to date has been performed by the PACE consortium meta-analyzing the prospective association of newborn cord-blood DNA-methylation and asthma in childhood, as well as the cross-sectional relation of blood DNA-methylation and childhood (Table 1).[71] This study reported the association of 9 CpGs in cord blood with subsequent asthma in childhood, opening the possibility that cord-blood DNA-methylation could act as a predictive biomarker. Next, 179 CpGs were cross-sectionally associated with childhood asthma. Many of these CpGs were also differentially methylated within eosinophils, showing that blood DNA-methylation changes may be preferentially driven by eosinophils. This confirmed previous findings from the MeDALL study, which indicated that childhood asthma associated blood DNA-methylation profiles are strongly related to transcriptomic signatures of eosinophils, T-cells and NK-cells.[72] When the MeDALL study extended their scope to the presence of any allergic disease (either asthma, rhinitis or eczema), blood CpG profiles of allergy were shared between these

three diseases.[73] Thus, blood DNA-methylation profiles in allergy likely reflect activation and presence of inflammatory cells in peripheral blood.

Recent studies investigated the epigenetics of nasal brushed cells in allergy, that provide an accessible way to study respiratory epithelial cells as well as mucosal immune cells. In adolescent and young adult subjects from Puerto Rico, nasal DNA-methylation was strongly associated with atopy (i.e. IgE sensitization); with 8864 differential methylated CpG sites related to atopy.[74] When using the top 30 CpG sites, a diagnostic panel was made that could accurately diagnose atopy in two different replication populations: African American children from the US and European white children from the Netherlands. This provided the first proof of concept of the diagnostic utility of DNA-methylation in allergy across different ethnicities. A study of asthma and rhinitis showed strong shared DNA-methylation signatures in nasal cells, and correlated these to both epithelial and immune cell changes. Of interest, exposure to pets related to CpG sites differentially methylated in allergy, providing a first link to exposure, allergy and DNA-methylation.[75]

Epigenomic studies in food allergy have also been undertaken.[76] An EWAS of whole blood methylation in 106 US children with cow's milk allergy and 76 non-atopic controls identified 568 hypomethylated and 7 hypermethylated loci.[77] These differentially methylated loci were linked to genes involved in Th1 and Th2 balance such as *IL1RL1, IL5RA, IL4, CCL18,* and *STAT4*, suggesting mechanistic involvement of methylation in modulating Th1/Th2 balance in cow's milk allergy. In a genome-wide DNA methylation study of 43 peanut allergic individuals, 23 of whom were receiving peanut oral immunotherapy (OIT) and 20 of whom were avoiding peanut, investigators detected demethylation of forkhead box protein 3 (*FOXP3*) CpG sites in antigen-induced regulatory T cells that significantly differed between the treated and control groups.[78]

As epigenetic changes are thought to exert effects by altering gene expression, a recent study integrated epigenomics and transcriptomics to advance mechanistic understanding of reaction severity in peanut allergy.[79] Forty peanut allergic children underwent double-blind placebo-controlled food challenges to rigorously determine reaction severity. Blood samples were collected at baseline, during reaction, and following reaction from all children, enabling the investigators to assay, identify, and replicate peripheral blood gene transcripts, peripheral blood CD4+ lymphocyte CpG loci, and their interactions that mediate reaction severity. Interaction networks revealed that neutrophil-mediated immunity was a key process in severe allergic reactions, with NFKBIA and ARG1 serving as hubs. Gene expression of *PHACTR1* and *ZNF121* was found to causally mediate the association between methylation at corresponding CpGs and

reaction severity, supporting that methylation serves as an anchor upon which gene expression modulates peanut allergy reaction severity.

The peripheral blood epigenome has also been searched for biomarkers of clinical reactivity to food allergens. In one study, genome-wide DNA methylation profiles were generated from PBMCs collected from 71 infants age 11-15 months who underwent either a peanut or an egg food challenge.[80] The infants were classified into three groups: sensitized infants without allergic reaction to peanut or egg (N = 29 in both groups) and non-allergic controls (N = 13). Using a supervised learning approach, the investigators identified 96 CpG sites whose methylation levels, when interpreted together, could predict FA status in an independent replication cohort with 79.2% accuracy.

Clinical implications and future research directions

Allergic diseases continue to be major health challenges for millions of children and adolescents worldwide. In agreement with the Global Burden of Diseases initiative, we would like to highlight the importance of preventive interventions targeting both children and adolescents to avoid chronic adult disease.[81] In this review, we have focused primarily on two clinical entities, FA (food allergies) and allergies related to airborne allergen exposures. These allergic conditions are each linked and intertwined with our changing environment; FA primarily in the context of "new allergies", such as red meat allergy linked to tick bites, changing eating and lifestyle habits following travel and migration, and airborne allergies in the context of "new" plant species and exposures, extended pollen-seasons and environmental hazards stemming from global warming processes. From a clinical and public health point of view, this situation urges us to continue monitoring these trends in disease prevalence and environmental exposure by a) making use of diagnostics for "new allergies" such as alpha-gal sensitization when meat allergy is suspected b) evaluating if climate-friendly strategies (e.g., shift towards sustainable diets) would impact the prevalence of present allergies or emergence of new allergies c) monitoring relevant allergen sources and levels also outside traditional exposure periods, and to include "new" species for a given region or area and d) evaluating potential environmental hazards linked to climate change, such as air pollutants and mold, mite allergen exposure at the individual patient level

We have in this review also highlighted epigenetic changes in relation to both environmental exposures and allergic diseases. Several environmental exposures of relevance for allergic disease in children have been proven to correlate with epigenetic levels. As such, epigenetics offers a promising tool by which environmental exposures and hazards may be captured, to date best exemplified by tobacco smoke, and mechanisms related to disease initiation and progress may be elucidated. Nasal epithelial methylation

profiles in rhinitis and asthma, and peripheral blood profiles in FA provide the best examples currently. It should be reinforced that methylation levels most strongly reflect cell type and cell activation in allergy, which needs to be taken into account in any study or clinical application.

We see great potential in the use of epigenetic signatures and omics profiles to detect and monitor aspects of environmental exposures of relevance for health and disease in children and adolescents. While there is conceptual promise with such an approach, including studies using an exposome analysis framework[38,82], there are to our knowledge no studies to date linking exposure changes from climate change with epigenetic profiles. Currently, there are however ongoing, promising work that will expand our knowledge platform in this research field, including a) the use of multi-omics analyses that incorporates for example, environmental exposure, methylation and gene expression data.[79,83] b) multi-exposure models across the life-course and interactions with epithelial barriers and our microbiome, exemplified by the exposome concept "the measure of all the exposures of an individual related to health and disease"[84] c) artificial intelligence applications and data-driven science in allergy[85,86]

Our review also highlights future research areas that would benefit from further investigation, including assessment of methylation levels (and other omics biomarkers) in newborns for example at yearly interval to monitor impact of changing environments, a particular focus on populations residing in regions with the highest pressure from climate change effects, a research framework to address disease causality from genes to exposure, epigenetics and allergic disease and finally, implementation of omics biomarkers in clinical settings (Panel A).

Authors' contributions

Conceptualisation: EM.

Literature search: EM, GHK, AMVC, ZJA, SB.

Figures: EM.

Data interpretation: EM, GHK, AMVC, ZJA, SB.

Writing: original draft: EM, GHK, AMVC, ZJA, SB.

Writing: review and editing: EM, GHK, AMVC, ZJA, SB.

Acknowledgements

The authors would like to thank Fuad Bahram and FB Scientific Art Design for assistance with figures. EM is supported by grants from the H2020 research program (ERC: TRIBAL, No 757919 and the EXPANSE project, No 874627), The Swedish Research Council, The Swedish Heart-Lung Foundation and Region Stockholm. SB is supported by R01 AI118833, R01 AI147028, U01 AI160082, and U19 AI136053 from the US National Institutes of Health. GHK is supported by grants from ZON-MW (VICI grant), Netherlands Lung Foundation, H2020 research program (Prominent), GSK, Vertex and TEVA the Netherlands. ZJA is supported by the Novo Nordisk Foundation Challenge Programme (#NNF17OC0027812). The funders had no active role in this manuscript.

Conflict of interest

EM reports consultant or advisory board fees from ALK, AstraZeneca, Chiesi, Novartis and Sanofi outside the submitted work. SB has no financial conflicts of interest. GHK reports participation in advisory boards to GSK and PURE-IMS (money to institution). AMVC has no financial conflicts of interest. ZJA has no financial conflicts of interest.

Table 1. Summary of key epigenetics findings in relation to environmental exposure and allergic disease.

Environmental exposures				
Exposure	Epigenetic mechanism	Tissue / cell type	Key finding	Reference
Maternal smoking during pregnancy	DNA-Methylation	Cord blood, peripheral blood, children	Changes in thousands of CpGs. Many changes persisted through childhood. Correlation with gene expression.	[57]
Tobacco exposure	DNA-Methylation	Peripheral blood, children	Methylation profiles can be used as biomarkers for tobacco exposure.	[58]
Prenatal and childhood air pollution exposure	DNA-Methylation	Cord blood, peripheral blood, children, adolescents	Several differentially methylated CpGs and regions associated. Interactome hotspots identified.	[59,62,83]
Air pollution exposure	microRNA	Cell lines, epithelial cells, adults	Exposure associated with inflammation-related microRNA expression.	[63]
Maternal diet during pregnancy	Histone acetylation, methylation	Placenta, cord blood	Olive oil / fish intake associated with acetylation of immune regulatory genes (placenta); folic acid intake with methylation (cord blood).	[68,69]
Gestational age, birth weight and ageing	DNA-Methylation	Cord blood, peripheral blood, children	Strong correlations between gestational age / weight at birth with methylation levels that track with age.	[64,65,70]
Allergic disease				
Asthma	DNA-Methylation	Cord blood, peripheral blood, children	Some associations between cord blood CpGs and subsequent asthma; strong cross-	[71,72]

			sectional associations of whole blood CpGs and asthma during childhood .Link to eosinophil, T-cells and NK cell activity.	
Any allergic disease (either asthma, rhinitis or eczema)	DNA-Methylation	Peripheral blood, children	Evidence for partly shared epigenetic signatures of asthma, rhinitis and eczema.	[73]
Atopy / IgE sensitization	DNA-Methylation	Nasal epithelial cells, adolescents	Strong associations potentially useful for diagnostics.	[74]
Asthma, rhinitis	DNA-Methylation	Nasal epithelial cells, adolescents	Association with replication for rhinitis as well as for asthma or rhinitis. Potential link with pet exposure.	[75]
Food allergy (cow's milk)	DNA-Methylation	Peripheral blood, children	Associations between methylation at Th1 and Th2 genes and cow's milk allergy.	[77]
Food allergy (peanut)	DNA-Methylation	Peripheral blood, children	Immunotherapy associated with methylation differences in regulatory T cells.	[78]
Food allergy (peanut)	DNA-Methylation	Peripheral blood, children	DNA methylation associated with reaction severity with evidence for causal mediation.	[79]
Food allergy	DNA-Methylation	Peripheral blood, children	DNA methylation signature as predictor of oral food challenge outcomes.	[80]

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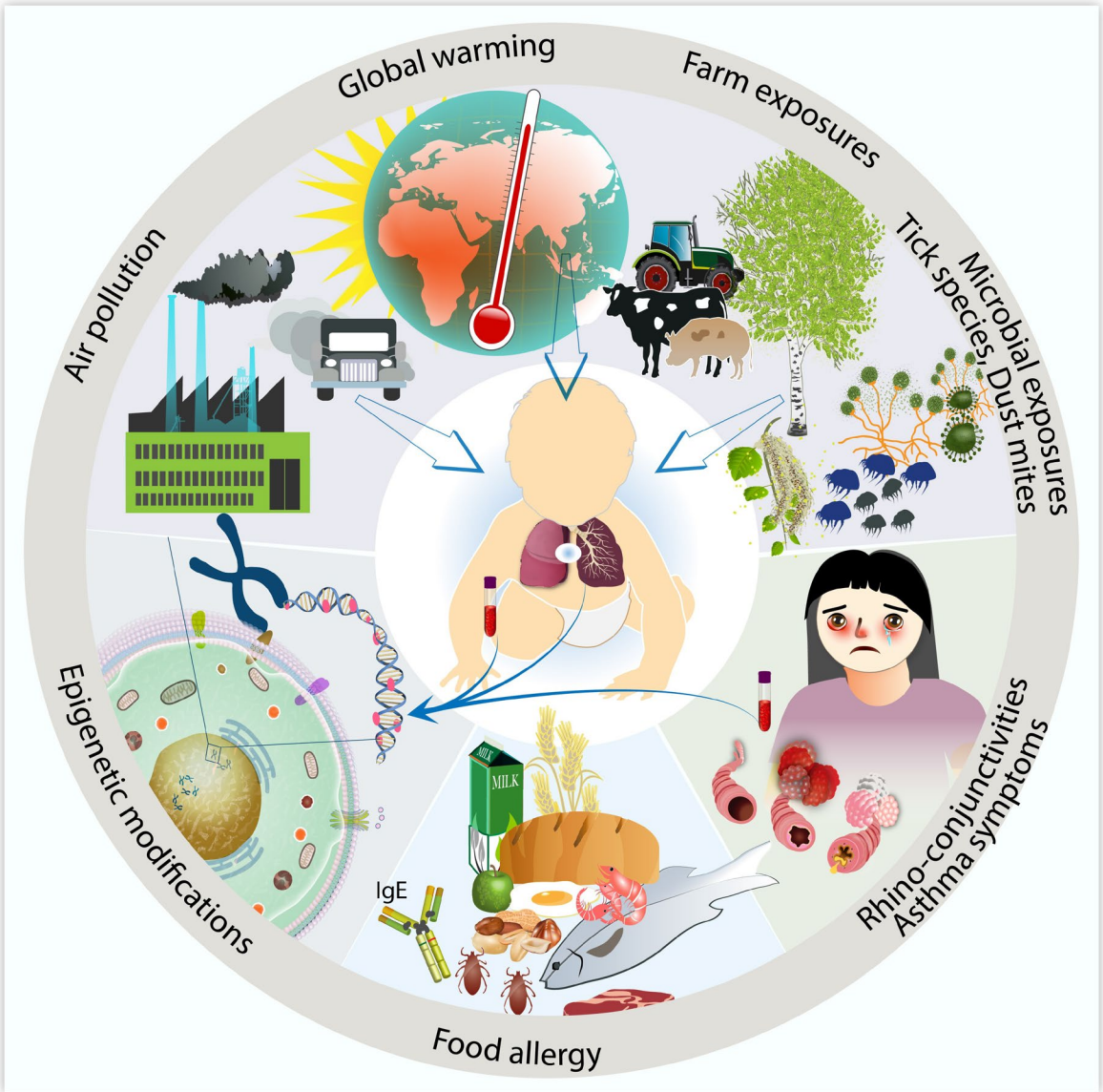
Figure legends

Figure 1. A schematic figure linking early-life environmental exposures (upper part), exemplified with air pollution from industries and traffic, global warming, farm exposures, pollen allergens, dust mite and microbial exposures, with epigenetic cellular modifications (left bottom corner) and allergic disease represented by food allergy / IgE sensitization to foods (bottom) and rhino-conjunctivities and asthma symptoms in children and adolescents (right bottom corner). FB Scientific Art Design.



Panel A: Priority research areas and activities

1) Assessment of methylation levels (and other omics biomarkers) in newborns to monitor impact of changing environments
2) A particular research focus on populations residing in regions with the highest pressure from climate change effects
3) A research framework to address disease causality from genes to exposure, epigenetics and allergic disease
4) Implementation of omics biomarkers in clinical settings