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Melén, Erik; Koppelman, Gerard H; Vicedo-Cabrera, Ana Maria; Andersen, Zorana Jovanovic; Bunyavanich, Supinda

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Review

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

Erik Melén, Gerard H Koppelman, Ana Maria Vicedo-Cabrera, Zorana Jovanovic Andersen, Supinda Bunyavanich

Allergic diseases 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, and climate. We discuss the potential links between these changes and allergic diseases in children, and the clinical implications. Several exposures of relevance for allergic disease also correlate with epigenetic changes such as DNA methylation. We propose that epigenetics could be a promising tool by which exposures and hazards related to a changing environment can be captured. Epigenetics might also provide promising biomarkers and help to elucidate the mechanisms related to allergic disease initiation and progress.

Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden (Prof E Melén MD); **Department of Pediatric Pulmonology and Pediatric Allergology and Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, Beatrix Children's Hospital, University of Groningen, Groningen, Netherlands** (Prof G H Koppelman MD); **Institute of Social and Preventive Medicine and Oeschger Center for Climate Change Research, University of Bern, Bern, Switzerland** (A M Vicedo-Cabrera); **Department of Public Health, University of Copenhagen, Copenhagen, Denmark** (Prof Z J Andersen); **Division of Allergy and Immunology, Department of Pediatrics, and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof S Bunyavanich MD)

Correspondence to: Prof Erik Melén, Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm 11883, Sweden **erik.melen@ki.se**

Introduction

Allergic diseases include asthma, atopic dermatitis, food allergies, and allergic rhinitis, and these conditions affect millions of children and adolescents worldwide. It is widely acknowledged that lifestyle factors associated with modern, urban living conditions have contributed to the substantial increase in prevalence of these conditions in the second half of the 20th century.[1] Although the global increase in asthma prevalence seems to generally have levelled off in the past 10–20 years,[2] allergy to foods, some pollen types, and dust mites appears to have continued to increase in many regions. In addition, new allergies have emerged in many parts of the world. Although these trends can partly be explained by behavioural 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 also partly responsible for the new allergy profiles seen in patients.[3] For example, the extended pollen seasons associated with global warming have introduced new species to some ecoregion, 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 exacerbation of allergic symptoms.

Despite the strong effects of environment and lifestyle on allergies, heredity and genetics also have a major role in allergic diseases.[5] Asthma, rhinitis, and atopic dermatitis might coexist partly because of shared genetics involved in immune response processes, especially in childhood-onset disease.[6] Research has also explored the association between allergic disease and epigenetics,[7] which includes chemical DNA modifications (eg, methylation) that regulate gene expression and might 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 the consequences of allergen exposures for health and disease.

In this Review, we give an update on allergic diseases in children and adolescents and explore the role of current environmental exposures. A specific focus is given to factors stemming from global environmental changes, in particular climate change, and their relation to the increasing incidence of allergies and new allergies, to explore the link between exposure, epigenetics, and allergic disease (figure).

Key messages

- Allergic diseases affect millions of children and adolescents worldwide; in many regions between 5% and 30% of adolescents report rhinoconjunctivitis symptoms and up to 10% report food allergy
- Links between climate change and allergic diseases are of increasing concern; these links 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 with both environmental exposures and allergic diseases, although causality needs to be explored further
- Use of epigenetic signatures and omics profiles has the potential to detect and monitor aspects of environmental exposures of relevance for health and disease in children and adolescents

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

Epidemiology of food allergy

Food allergy is a common, chronic childhood condition estimated to affect up to 10% of children in many areas of the world.[9,10] The prevalence of food allergies
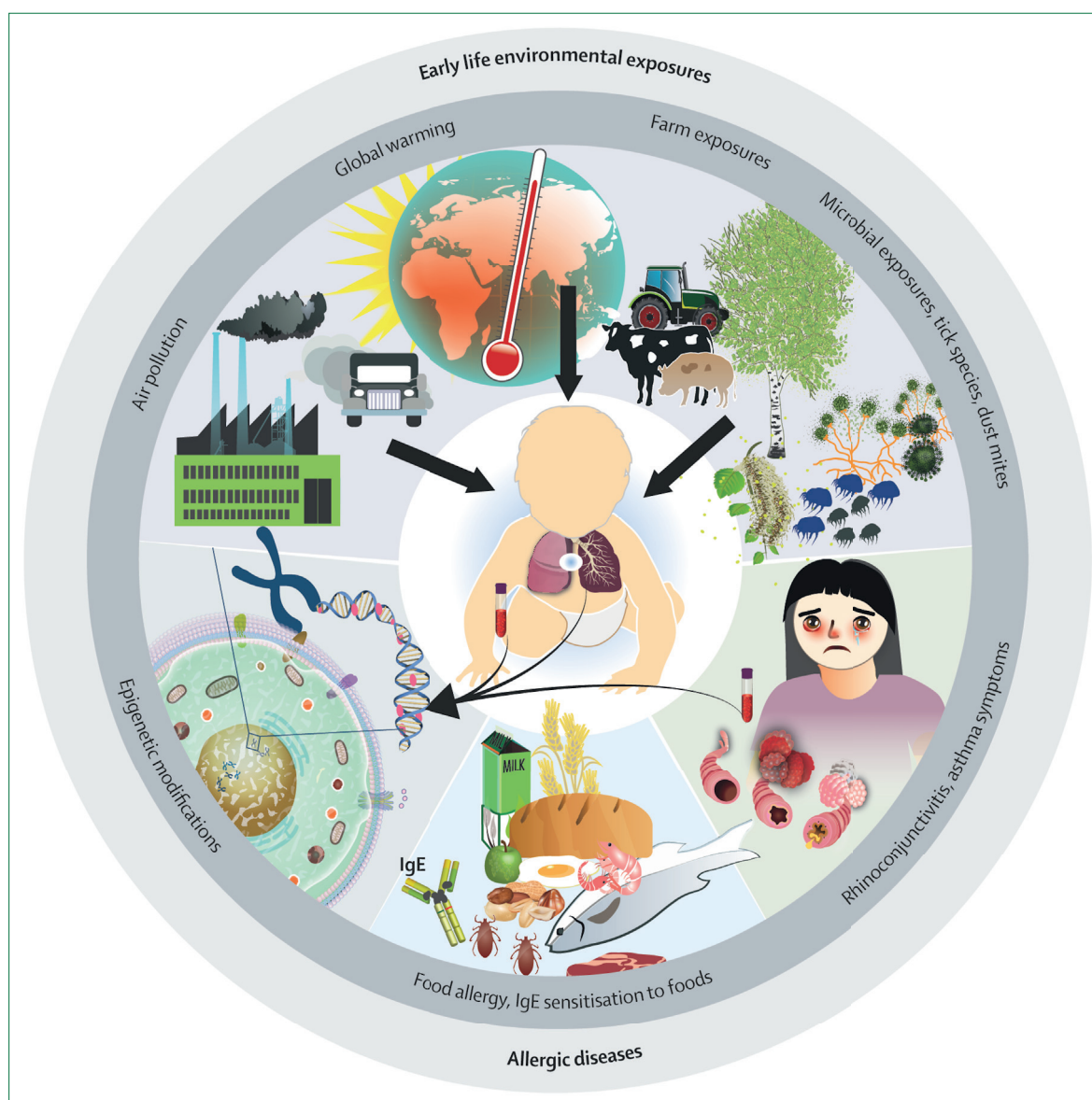
Figure: A schematic figure linking early life environmental exposures with epigenetic cellular modifications, food allergy, and rhinoconjunctivitis and asthma symptoms in children and adolescents

has been steadily increasing over the past two decades.[11] Although delayed introduction of food allergens in some communities might partly explain higher rates of food allergy in recent years, additional mechanistic explanations for this rising prevalence are needed.[12] Individuals with food allergies are at daily risk of potentially life-threatening hives, angio-oedema, respiratory difficulty, cardiovascular compromise, gastrointestinal distress, or anaphylaxis following ingestion of a food antigen to which they are sensitised.[13] In addition to the burden of the direct symptoms, food allergies impair quality of life, nutrition, emotional health, and lifestyle.[14] Peanut oral immunotherapy can reduce sensitivity to peanuts,[15] but there remains no

absolute cure for peanut allergy or any food allergy. For many, food allergy can persist into adulthood.

New food allergies

Mammalian meat allergy due to IgE specific for the carbohydrate allergen galactose-α-1,3-galactose (α-gal) was first reported in 2009 in the southeastern USA.[16] In susceptible individuals, repeated tick bites by the *Amblyomma americanum* (known as lone-star) tick and other tick species lead to sensitisation to α-gal, which is present in the gastrointestinal tract of the ticks. Because α-gal is also present in many mammalian meats, such sensitised individuals might experience allergic reactions upon ingestion of beef and other mammalian

meats. Although immediate reactions, which typically characterise IgE-mediated food allergy, can happen, many individuals with α-gal allergy have delayed allergic symptoms 3–6 h after ingestion. Meat allergy due to α-gal sensitisation has now been reported in many disparate parts of the world, including South Africa, Australia, Germany, Japan, Spain, Sweden, and the USA.[10] Most research suggests that meat allergy predominantly affects adults, although reports in recent years have highlighted the occurrence of α-gal sensitisation and associated meat allergy in children and adolescents.[17,18] Apart from repeated tick bites, polysensitisation (to other allergens) during childhood, and male sex, appear to be individual risk factors for later α-gal sensitisation.[19] Detailed studies of tick populations are scarce; however, climate change is thought to be contributing to changes in the distribution and ecology of these ticks, which, in turn, is altering the areas where human populations are susceptible to developing α-gal-mediated meat allergy.[20]

Concerns about the environmental and climate effects 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 (eg, age, with other exposures, or immunological maturation) of exposures to plant proteins could be affecting the rates of detection of allergies to these foods, although this has not been directly investigated yet. Many people who are allergic to pollen might also have 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 substantially from 0·2% in 1997 to 1·1% in 2008.[21] A 2015 systematic review of tree nut allergy prevalence indicated a prevalence as high as 4·9% in some parts of the world, with regional variation in the rates and subtypes of allergies to particular tree nuts.[22]

In summary, food allergy prevalence has been increasing since the 2000s and affect up to 10% of children and adolescents. Climate change might affect the distribution and prevalence of some food allergies.

Allergies to airborne allergens

Sensitisation to airborne allergens is seldom seen in infants during the first year of life but typically starts to appear from age 3–4 years. Often, sensitisation to a single allergen (monosensitisation) is followed by IgE responses to multiple allergens (polysensitisation), and sensitisation early in life is one of the strongest predictors for later development of allergic disease.[23] The key sensitising allergens associated with allergic disease depend on regional and geographical factors, lifestyle, and genetics. In northern and central European countries, the dominant sensitising factors are house dust mites, birch tree pollen, timothy grass pollens, and pets. In southern Europe and the USA, ragweed, other weed (eg, the Parietaria plant genus), and tree pollens (eg, olive, cypress in Europe; birch, cedar, and oak in the USA) dominate. Whereas, globally, dust mite, cockroach, and mould remain a source of major airborne allergens.[24–28] Sensitisation rates and allergy to airborne allergens, including grass pollen, tree pollen, and dust mites, appear to have increased globally in the 21st century. For example, studies conducted in northern Sweden show increased sensitisation rates in children aged 11–12 years in 2010 compared with 2000 (37% positive for allergen-specific IgE in 2010 vs 28% in 2000).[29] Similar trends were reported in the Netherlands between 1994 (41% overall sensitisation to airborne or food allergens) and 2014 (49% sensitisation), which was mainly explained by increasing aeroallergen sensitisation among children aged 4–11 years.[30] In China, national surveys have reported increased allergy prevalence in children between 2008 and 2018 for tree pollens (3% sensitisation to black poplar in 2008 vs 6% in 2018) and dust mite allergens (32% vs 65%).[28] Similar increasing trends were reported in South Korea between 2009 and 2018.[31] The International Study on Asthma and Allergies in Childhood reported a global increasing trend in the prevalence of rhinoconjunctivitis caused by airborne allergens (typically presenting as sneezing or a runny or blocked nose and itchy, watery eyes), between the mid-1990s and early 2000s.[32] Data collected in 2021 by the Global Asthma Network (GAN) indicate current prevalence rates ranging from 5% to 30% at age 13–14 years.[33] The GAN data also suggest that symptoms of rhinoconjunctivitis among children and adolescents might no longer be increasing globally, although substantial variations within regions and countries were observed. For example, the prevalence of rhinitis symptoms (but not asthma) increased significantly since 2000 in an adolescent population in one of the GAN countries, Ecuador.[34]

In summary, sensitisation to airborne allergens appears to have continued to increase globally in the 21st century, whereas symptoms of rhinoconjunctivitis among children (aged 6–14 years) might no longer be on the rise globally. Yet, up to a third of adolescents might be affected in some countries. Local and regional investigations of both allergy symptoms and sensitising allergens therefore remain high priority, 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 than adults to hazardous airborne substances and environmental exposures, possibly because of their developing organs and tissues. Children have higher ventilation per min in relation to body size and are often more physically active

than adults, which leads to higher exposure to potential allergens and environmental hazards overall. Vulnerable periods of exposure, for example in utero or early in life, might be relevant for some exposures. However, exposure over the entirety of childhood (eg, air pollution), and prenatal exposure, might negatively influence lung development.[35] Simulations show that per kg body mass, compared with an adult, an infant receives a nearly 4-times greater deposited dose of resuspended particles in the respiratory tract.[36] Children and adolescents also typically cannot choose their living conditions or influence modifiable exposure to any large extent and have to rely on caregivers (and society) for a healthy upbringing environment.

Since the last century, humanity has experienced unprecedented socioeconomic developments, with substantial improvements in living conditions and life expectancy. However, these developments have been accompanied with profound environmental changes and deleterious impacts affecting natural systems in terms of biodiversity loss, air pollution, and climate change.[37] Environmental hazards stemming from these global processes have been identified as relevant public health threats with a substantial health burden, which is highly relevant in a modern urban environment.[38] In studies in rural farm settings around the world, a diversity of exposures is a common finding for the reduction of allergy risks, and these studies have robustly shown reduced allergy risks for children who are raised on a farm.[39] Such diversity in exposure also translates into microbiome biodiversity (ie, of the gut, airway, and skin) associated with immune tolerance. In particular, microbial exposures in infancy seem to be important predictors for later health and disease throughout the lifecourse.[40]

The health effects of climate change are substantial and widespread. Direct effects include increases in mortality and morbidity due to extreme weather events, such as heatwaves, droughts, windstorms, flooding, and wildfires. More indirect effects derive from vector-borne diseases, changes in the microbiome, food or waterborne diseases, or socioeconomic effects 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 mould production that induces allergic manifestations.[4,43] In particular, the increase in moisture and dampness in buildings affected by water intrusion during extreme rain storms and flooding events worsens indoor environments, supporting the growth of house dust mites and moulds that are key allergen sources.[44] Modelling 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. These studies have also found that climate change has introduced the spread of pollen species to new areas, and caused warmer or milder weather in many areas.[45,46]

Air pollutants can also interact with airborne allergens and enhance the risk of allergic sensitisation and exacerbation of symptoms in sensitised individuals, especially under conditions in which periods of drought promote the resuspension of dust particles and increase exposure to this type of air pollution. The increasing occurrence of heatwaves can also adversely affect children with asthma or allergic rhinitis, as breathing hot air can aggravate airways and trigger symptoms.[3] Furthermore, dehydration could exacerbate ongoing asthma attacks. Increasing temperature in areas with humid air also poses challenges to people with asthma or allergies, as hot and humid air is heavy and harder to breathe, and also because moist air can trap lung irritants such as pollen, mould, and indoor dust mites. Additionally, heatwaves and drought conditions increase wildfire risk, contributing to massive exposures to smoke emissions in local communities, which contain particulate matter and other combustion products—pollutants that have known adverse effects on respiratory health.

Climate change and air pollution are inextricably linked. Although the main greenhouse gases (ie, carbon monoxide and methane) are not particularly directly harmful for health, they are emitted together with air pollutants originating from burning fossil fuels (eg, coal, oil, or wood), which are directly harmful to health, with children with asthma and allergy representing some of the most vulnerable groups. Particulate matter and nitrogen dioxide are emitted in fossil fuel combustions, one of the main sources of greenhouse gas emissions. A bulk of epidemiological studies has linked air pollution exposure with the 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 sensitisation,[49] associations are generally not strong[50] and are even less clear for clinical symptoms (ie, rhinoconjunctivitis).[47] However, the increased exposure to allergens due to climate change along with the exposure to air pollutants, which act synergistically and intensify the allergic response, could lead to increased incidence of allergy in the future.[51]

Although socioeconomic factors often spur migration, climate change might become an increasingly common motivation for communities to move. The diets and lifestyles of families who move often shift due to the availability of different foods and the distinct culture and lifestyle norms of a given location. This migration and change of diet can in turn affect exposure to allergens and allergy development. For example, a large study of more than 57 000 children aged 5 years in Australia found that children born in Australia to Asian-born mothers were more likely to have parent-reported food allergy (odds ratio [OR] 2·33; 95% CI 1·96–2·77) compared with children born to non-Asian mothers in Australia.[52] By contrast, children born in Asia who then

migrated to Australia had lower risk of food allergy compared with Australian-born non-Asian children (OR 0·33, 95% CI 0·20–0·55). Another study found that Jewish children in Israel had one-tenth the prevalence of peanut allergy than Jewish children in the UK, even after accounting for relevant covariates such as social class and genetic background.[53] Therefore, we might see changing patterns of food allergy around the world with increasing climate-induced migration.

Epigenetics linking genes, environmental exposures, and allergies

Epigenetic mechanisms

Epigenetics refers to potentially heritable changes in the regulation of gene expression that occur without changing the genetic code. The most widely studied epigenetic mechanism in allergic disease is DNA methylation, which is the covalent binding of a methyl-group to a cytosine base, mostly positioned next to a guanine, forming a CpG site. Also studied are histone modifications, which are post-translational modifications of the histone proteins used to package DNA. These modifications, which include methylation, acetylation, phosphorylation, and ubiquitylation, act to open or close the chromatin, 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 is complex, and often has inter-related layers of regulation of gene expression, which enables cells with the same genetic code to express genes depending on location, time, and context. Genetic factors also regulate epigenetic markers.[54] Epigenetics might provide a mechanistic explanation to the developmental origins of health, in which early life exposures might programme to the development of lifelong chronic disease.[8] Therefore, epigenetic markers are highly cell specific, crucial in cell and organ development, and can characterise cellular responses in health and disease. Epigenetic studies in disease need to be interpreted considering the cell type and age, and changes might reflect the cause or consequence of disease. Many studies have examined the association of epigenomic variation in relation to environmental exposure, and diseases such as asthma or allergic rhinitis. Most studies have investigated DNA methylation, by use of DNA arrays that interrogate 450 K or 850 K 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 (table), with the most well described examples concerning tobacco smoking. Both maternal smoking during pregnancy and parental smoking during childhood are significantly associated with a wide range of negative health consequences for the fetus and the child, including intrauterine growth restriction, malformations, preterm birth, infant mortality, childhood asthma, allergy, lower respiratory tract infections, and neurocognitive impairment.[75,76] Tobacco-free environments for children therefore remain a highly prioritised item on the global paediatric agenda.

Numerous cellular and physiological perturbations are associated with smoking exposure, one of which is altered DNA methylation levels. In a hallmark EWAS in 2016,[55] researchers from the Pregnancy and Childhood Epigenetics (PACE) consortium showed methylation changes in thousands of genes across all chromosomes (eg, AHRR, MYO1G, GFI1, CNTNAP2, and CYPA1) in newborns (cord blood) whose mothers smoked during pregnancy. Many of the changes persisted throughout childhood to 16 years, and also correlated with peripheral blood gene expression. Furthermore, the identified genes were known to be linked to conditions such as 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.[56] Air pollution is another well established risk factor for adverse outcomes in children, and substantial efforts have been made to link air pollution to methylation changes. Although several significant findings have been identified in large-scale studies,[57] the strength of association and degree of methylation change (ie, in CpG bases and sites) in blood following exposure is more modest for air pollution compared with tobacco smoke exposure.[77] However, controlled experiments in adults show that allergen and diesel exhaust exposure might induce numerous methylation changes in both blood and bronchial epithelial cells, which suggests that widespread epigenetic changes probably occur if the timing, dose, and target organ are studied appropriately.[58,78] In relation to air pollution exposure, the role of nasal airway microRNAs is also gaining attention and shows associations with exposure and respiratory disease (eg, bronchiolitis and asthma).[60]

Of particular interest in paediatrics is the link between development, growth, and ageing in relation to epigenetics. As mentioned, epigenetic mechanisms have a key role during fetal development, and are a potent way in which cells can turn on or off gene expression. As such, both gestational age at birth and birthweight (reflecting primarily intrauterine growth) show strong correlations with methylation levels at birth and later during childhood.[63,64] Social and behavioural factors early in life such as nutrition, socioeconomic status, family situation, and stress also influence the epigenome, as examples of biological embedding (ie, the process by which early life experience alters biological processes to affect later health outcomes) with effects for health and disease potentially lasting into adulthood.[79,80] Maternal diet during pregnancy (ie, food intake or supplementation)

	Sample	Epigenetic mechanism	Tissue or cell type	Key finding
Environmental exposures				
Maternal smoking during pregnancy[55]	Children	DNA methylation	Cord blood and peripheral blood	Changes in thousands of CpG sites; many changes persisted throughout childhood; correlation of maternal smoking during pregnancy with gene expression
Tobacco exposure[56]	Children	DNA methylation	Peripheral blood	Methylation profiles can be used as biomarkers for tobacco exposure
Prenatal and childhood air pollution exposure[57–59]	Children and adolescents	DNA methylation	Cord blood and peripheral blood	Several differentially methylated CpG sites and regions associated with prenatal and childhood air pollution exposure; interactome hotspots identified
Air pollution exposure[60]	Adults	microRNA	Cell lines and epithelial cells	Exposure associated with inflammation-related microRNA expression.
Maternal diet during pregnancy[61,62]	Children	Histone acetylation and DNA methylation	Placenta and cord blood	Olive oil and fish intake were associated with acetylation of immune regulatory genes (placenta); folic acid intake with methylation (cord blood)
Gestational age, birthweight, and ageing[63–65]	Children and neonates	DNA methylation	Cord blood and peripheral blood	Strong correlations between gestational age and weight at birth with methylation levels that track with age
Allergic disease				
Asthma[66,67]	Children	DNA methylation	Cord blood and peripheral blood	Some associations between cord blood CpG sites and subsequent asthma; strong cross-sectional associations of whole blood CpG sites and asthma during childhood; CpGs link to eosinophil, T-cells, and natural killer cell activity
Any allergic disease (such as asthma, rhinitis, or eczema)[68]	Children	DNA methylation	Peripheral blood	Evidence for partly shared epigenetic signatures of asthma, rhinitis, and eczema
Atopy or IgE sensitisation[69]	Adolescents	DNA methylation	Nasal epithelial cells	Strong associations between IgE and DNA methylation potentially useful for diagnostics
Asthma or rhinitis[70]	Adolescents	DNA methylation	Nasal epithelial cells	Association of CpG sites with replication of findings for rhinitis and for asthma or rhinitis (not asthma alone); potential link for both allergies with pet exposure
Cow's milk allergy[71]	Children	DNA methylation	Peripheral blood	Associations between methylation at Th1 and Th2 genes and cow's milk allergy
Peanut allergy[72]	Children	DNA methylation	Peripheral blood	Immunotherapy associated with methylation differences in regulatory T cells
Peanut allergy[73]	Children	DNA methylation	Peripheral blood	DNA methylation was associated with reaction severity with evidence for causal mediation
Food allergy[74] (ie, egg, peanut, cow's milk, or shrimp)	Children	DNA methylation	Peripheral blood	DNA methylation signature was a predictor of oral food challenge outcomes

Th=T helper cell.

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

can additionally influence epigenetics, as shown both in the placenta (histone acetylation)[61] and offspring cord blood (DNA methylation).[62] Children's age can be tracked with methylation analyses, suggesting that the rate of methylation is the result of developmental and growth processes, and cumulative exposures and life events.[65]

Epigenetics in allergic diseases

The largest childhood EWAS on asthma to date was performed by the PACE consortium, in a meta-analysis of the prospective association of newborn cord blood DNA methylation and asthma in childhood, and the cross-sectional relation of blood DNA methylation and childhood asthma (table).[66] This study reported the association of nine CpGs in cord blood with subsequent asthma in childhood, suggesting that cord blood DNA methylation could act as a predictive biomarker. Additionally, 179 CpGs were cross-sectionally associated

with childhood (aged 7–17 years) asthma. Many of these CpGs were also differentially methylated within eosinophils, showing that changes in blood DNA methylation might be preferentially driven by eosinophils. These results confirmed previous findings from the MeDALL study,[67] which indicated that profiles of blood DNA methylation associated with childhood asthma are significantly associated with transcriptomic signatures of eosinophils, T-cells, and natural killer cells. When the MeDALL study extended their scope to the presence of any allergic disease (ie, asthma, rhinitis, or eczema), blood CpG profiles were shared between these three diseases.[68] Therefore, blood DNA methylation profiles in allergy probably reflect the activation and presence of inflammatory cells in peripheral blood.

Studies from 2019[69] and 2020[70] investigated the epigenetics of nasal brushed cells in allergy, which provide an accessible way to study respiratory epithelial cells and

mucosal immune cells. In adolescent and young adult participants (aged 9–20 years) from Puerto Rico, nasal DNA methylation was signficantly associated with atopy (ie, IgE sensitisation), with 8864 differential methylated CpG sites related to atopy.[69] A diagnostic panel was subsequently made that could accurately diagnose atopy, using the top 30 CpG sites, in two different replication populations: African American children from the USA and European White children from the Netherlands. This study provided the first proof of concept of the diagnostic utility of DNA methylation in allergy across different ethnicities.[69] Another study[70] of asthma and rhinitis showed strong shared DNA methylation signatures (ie, the same CpGs) in nasal cells and correlated these with both epithelial and immune cell changes. The differential methylation of CpG sites was also related to whether or not participants had been exposed to pets, providing a first link to exposure, allergy, and DNA methylation.

Epigenomic studies[71–74,81] in food allergy have also been done. An EWAS of whole-blood methylation in 106 US children with cow's milk allergy and 76 control children who were non-atopic in the USA identified 568 hypomethylated and seven hypermethylated loci.[71] These differentially methylated loci were linked to genes involved in T-helper 1 cell (Th1) and Th2 cell balance, including *IL1RL1*, *IL5RA*, *IL4*, *CCL18*, and *STAT4*, which suggests mechanistic involvement of methylation in the modulation of Th1 and Th2 cell balance in cow's milk allergy. In a genome-wide DNA methylation study of 43 individuals with a peanut allergy, 23 of whom were receiving peanut oral immunotherapy and 20 of whom were avoiding peanut, investigators detected demethylation of *FOXP3* CpG sites in antigen-induced regulatory T-cells, which significantly differed between the treated and control groups.[72]

As epigenetic changes are thought to exert regulatory effects by altering gene expression, a 2020 study integrated epigenomics and transcriptomics to assess the mechanism underlying reaction severity in peanut allergy.[73] The study used double-blind placebo-controlled food challenges to determine reaction severity in 40 children who were allergic to peanut. Blood samples were collected from all children at baseline, during reaction, and following reaction. These samples were used by investigators to assay, identify, and replicate peripheral blood gene transcripts, peripheral blood CD4-positive lymphocyte CpG loci, and the interactions between them 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 CpG sites and reaction severity, supporting the idea that methylation serves as an anchor upon which gene expression modulates the severity of peanut allergy reaction.

The peripheral blood epigenome has also been searched for biomarkers of clinical reactivity to food allergens. In one study,[74] genome-wide DNA methylation profiles were generated from peripheral blood mononuclear cells collected from 71 infants aged 11–15 months who underwent either peanut or egg food challenge. The infants were classified into three groups: sensitised infants without allergic reaction to peanut or egg (n=29 peanut; n=29 egg) and the non-allergic control group (n=13). Using a supervised learning approach, the investigators identified 96 CpG sites for which the levels of methylation, when interpreted together, could predict food allergy status in an independent replication cohort (N=48) 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 Disease 2019 initiative,[82] we highlight the importance of preventive interventions targeting both children and adolescents to avoid chronic adult disease. In this Review, we have focused primarily on two clinical entities: food allergy and allergies related to airborne allergen exposures. These allergic conditions are each linked with our changing environment—food allergy primarily in the context of new allergies, such as red meat allergy linked to tick bites, and altered eating and lifestyle habits following travel and migration; and airborne allergies in the context of plant species and exposures new to a region, extended pollen seasons, and environmental hazards stemming from global warming processes. From a clinical and public health point of view, this situation should urge researchers to continue monitoring these trends in disease prevalence and environmental exposure. Monitoring should be done by firstly, making use of diagnostics for new allergies, such as α-gal sensitisation when meat allergy is suspected; secondly, by evaluating if climate-friendly strategies (eg, shifts towards sustainable diets) would affect the prevalence of present allergies or the emergence of new allergies; thirdly, by monitoring relevant allergen sources and levels outside traditional exposure periods, and including new species for a given region or area; and finally, by evaluating the potential environmental hazards linked to climate change, such as air pollutants, mould, and mite allergen exposure at the individual patient level.

This Review also highlighted the role of epigenetic changes in relation to both environmental exposures and allergic diseases. Several environmental exposures of relevance to allergic disease in children have been proven to correlate with levels of epigenetic modification (table). As such, epigenetics is a promising tool by which environmental exposures and hazards can be captured, best exemplified to date by studies of tobacco smoke exposure, and mechanisms related to disease initiation

and progress can be elucidated. Nasal epithelial methylation profiles in rhinitis and asthma, and peripheral blood profiles in food allergy are the best examples of disease mechanisms currently. Methylation levels strongly reflect cell type and cell activation in allergy, which needs to be considered 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. Such an approach has conceptual promise, as shown in studies that used an exposome analysis framework;[38,83] however, to our knowledge, there are no studies to date linking exposure changes from climate change with epigenetic profiles. Studies are ongoing that promise to expand our knowledge platform in this research field. Two of these studies[59,73] used multiomics analyses that incorporate, for example, environmental exposure, DNA methylation, and gene expression data. Another study[84] assessed multiexposure models across the life course and interactions with epithelial barriers and the microbiome, which are exemplified by the exposome concept that can be explained as the measure of all exposures of an individual related to health and disease. Two more ongoing studies[85,86] are investigating artificial intelligence applications and computational science in allergy.

This Review also highlights future research areas that would benefit from further investigation. These areas include: assessment of DNA methylation levels (and other omics biomarkers) in newborns, for example at annual intervals to monitor the effects of changing environments; a focus on populations residing in regions most affected by climate change; a research framework to address disease causality from genes to exposure; epigenetics and allergic disease; and, finally, the implementation of omics biomarkers in clinical settings.

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