Received: 29 January 2019 | Revised: 27 May 2019 | Accepted: 5 June 2019

DOI: 10.1111/all.13946

REVIEW

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

The exposome in atopic dermatitis

Nicholas Stefanovic[1] | Carsten Flohr[2] | Alan D. Irvine[3,4]

[1]School of Medicine, Trinity College Dublin, Dublin, Ireland

[2]Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust and King's College London, London, UK

[3]Department of Paediatric Dermatology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland

[4]National Children's Research Centre, Crumlin and Clinical Medicine, Trinity College Dublin, Dublin, Ireland

Correspondence
Nicholas Stefanovic, School of Medicine, Trinity College Dublin, Ireland.
Email: stefanon@tcd.ie

Alan D. Irvine, Department of Paediatric Dermatology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland.
Email: irvinea@tcd.ie

Funding information
CF holds a UK National Institute for Health Research (NIHR) Senior Career Development Fellowship (CDF-2014-07-037). CF is also supported by the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust, London, UK. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

Abstract

Atopic dermatitis (AD) is a complex inflammatory disorder with multiple interactions between genetic, immune and external factors. The sum of external factors that an individual is exposed to throughout their lifetime is termed the exposome. The exposome spans multiple domains from population to molecular levels and, in combination with genetic factors, holds the key to understanding the phenotypic diversity seen in AD patients. Exposomal domains are categorized into nonspecific (human and natural factors affecting populations), specific (eg humidity, ultraviolet radiation, diet, pollution, allergens, water hardness) and internal (cutaneous and gut microbiota and host cell interaction) exposures. The skin, as the organ that most directly interacts with and adapts to the external environment, is a prime target for exploration of exposomal influences on disease. Given the well-recognized physical environmental influences on AD, this condition could be much better understood through insightful exposomal research. In this narrative review, we examine each domain in turn, highlighting current understanding of the mechanisms by which exposomal influences modulate AD pathogenesis at distinct points in time. We highlight current approaches to exposome modification in AD and other allergic disease and propose future directions for exposome characterization and modification using novel research techniques.

KEYWORDS

allergy, atopic dermatitis, exposome, microbiome

1 | INTRODUCTION

Atopic dermatitis (AD) (syn. atopic eczema) is a chronic inflammatory skin condition, affecting up to 20% of children and 5%-10% of adults.[1,2] Current understanding of AD pathogenesis points towards a sophisticated interplay between genetic and environmental factors. The pathogenesis of AD may start in many cases with a genetically predetermined skin barrier defect, which manifests itself as dry skin. This inherent skin barrier deficit leads to an overexpression of pro-inflammatory cytokines and subsequently the activation of innate lymphocyte subsets and antigen-presenting cells (T_H2 and T_H22). IL-4 and IL-13 in particular drive eosinophil and mast cell recruitment and IL-31 secretion, a key cytokine involved in itch sensation.[3] Transcutaneous sensitization to environmental allergens and bacterial infections, in particular *Staphylococcus aureus*, further contributes to the barrier disruption and eczematous skin inflammation. While a genetic barrier defect is present in many, this is not a prerequisite and many pathological pathways can lead to AD. There remains a marked variation in age of onset, severity of disease, tendency to develop further atopic comorbidities (food allergies, allergic rhinitis, asthma) and response to treatment, which is inadequately explained by genetic susceptibility alone. It is thought that the sum

of environmental influences plays a significant role to explain this phenotypic variation encompassed by the term "atopic dermatitis", perhaps best considered as an overarching term that includes several distinct clinicopathological entities, or endotypes, which are not yet fully characterized.

The concept of the sum of environmental influences is termed "the exposome."[4] This term includes exposures throughout an individual's life from conception to death, spanning the domains of environment, diet, behaviour and endogenous processes specific to the individual's internal biological milieu. Defining the pertinent exposome of a disease enables the identification of common pathways downstream of distinct environmental exposures. In this regard, an exposomal approach merges epidemiological enquiry of the environment as a distinct influence on AD with current knowledge of the cellular and molecular pathways at play. Consequently, this permits quantification of the biological response and potential modification of environmental factors to influence disease course. Current literature on the external factors to the pathogenesis of AD identifies several environmental contributors, including air pollutants (airborne particulate matter, tobacco smoke and organic compounds), allergens and microbiota (bacteria, viruses and fungi) among others.[5-7] A recent review by Cecchi et al[8] highlighted a working model of the external exposome with particular emphasis on asthma and the unique aetiopathogenesis of respiratory allergy, and several concepts in their review are informative for AD exposomal research.[8]

Given that AD is commonly the first manifestation of atopic multimorbidity followed by food and respiratory allergies, often termed the "atopic march," though this linear longitudinal pattern is only one potential disease trajectory,[9,10] AD is uniquely poised for exposomal research. An enhanced understanding of the factors comprising the AD exposome theoretically enables environmental intervention early in the disease process, thereby altering the disease course with the potential to halt the progression to other allergic diseases. Similarly, identifying an environmental factor common and contributory to a population affected by a disease might enable large-scale preventative approaches. In this narrative review, we provide an up to date summary of our current understanding of the AD exposome and its contribution to AD pathogenesis, with distinction between the external exposome common at the population level and the internal factors that are specific to individuals.

2 | THE EXTERNAL EXPOSOME AND ENVIRONMENTAL INFLUENCES

The model proposed by Cecchi et al for asthma suggests that the external exposome comprises disease-modifying factors that affect individuals from the outside.[8] They further stratify this into nonspecific factors affecting populations such as climate, migration and urbanization and quantifiable exposures that are specific to individuals, for example diet, pollution, allergens and drugs. Taking this template, study of the nonspecific external exposome in AD requires epidemiological inquiry in the first instance, to identify influences on AD pathogenesis that are common to populations—be they natural or man-made.

Geographical variation in AD prevalence has been well characterized, both internationally and within regions of individual countries. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase One reported increased prevalence of AD symptoms in countries with high gross national product, significant antibiotic prescribing, higher trans-fatty acid consumption and paracetamol usage, while vegetable consumption, smoking and immunization were inversely associated.[11] The data thus highlight that differences in lifestyle, in part due to economic development and associated population changes, may lead to increased AD prevalence at the population level. Data from ISAAC Phase Three support this, as disease burden in areas that were originally classed as areas of high prevalence (typically developed, urbanized regions) has not changed significantly over time. Increases in disease prevalence were primarily seen in low prevalence regions, typically low per capita income settings, further supporting the notion that lifestyle factors are driving changes in disease prevalence.[12] The plateauing effect in prevalence burden observed between ISAAC Phases One and Three could be due to the fact that those who are genetically predisposed to develop AD, for instance through inheritance of *FLG* skin barrier gene mutations, do so when they encounter further exposomal disease-initiating and disease-modifying exposures that were not present in the environment previously. It is worth noting that while *FLG* mutations represent the strongest genetic risk for AD development, the majority of AD patients do not carry such mutations, and only, approximately 40% of AD mutants develop AD. Despite this, *FLG* mutation carriers do exhibit a distinct phenotype that is associated with a progression towards atopic comorbidities, suggesting that they represent a particular cohort in whom an exposomal approach may be utilized to facilitate better disease control early on in the disease course in an effort to ameliorate such comorbidities.[13,14]

3 | THE EFFECT OF SPECIFIC EXTERNAL EXPOSURES ON AD

There have been multiple efforts to characterize the effects of specific external exposures (eg diet, water hardness, pollution and allergens) on AD development and progression. Akin to the nonspecific external exposome, these factors are likely to act in concert to drive the immune responses in AD skin. The inflammatory processes in AD likely involve perpetuating cycles of genetically predetermined barrier susceptibility, external exposures that contribute to barrier disruption (eg frequency of washing and detergent use), dysregulated skin barrier immunity and consequently increased itch sensation and scratch behaviour that leads to further deterioration in epidermal permeability and susceptibility to environmental insults.[15] An exposomal approach aims to elucidate common pathways downstream of individual-specific external exposures in order to modulate the above processes (Figure 1). It is also worth noting that psychological stress during pre- and postnatal life may modulate the disease

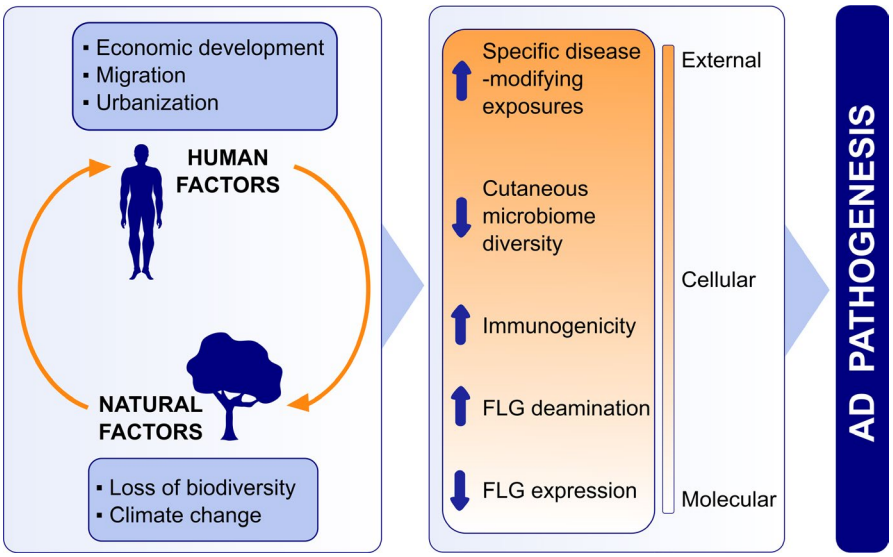

FIGURE 1 The effect of nonspecific external exposures on AD pathogenesis. The interplay between nonspecific external exposures from both human and natural domains exerts an effect on AD pathogenesis. Patterns of economic development, migration and urbanization act as both cause and consequence of climate change and loss of biodiversity. Consequently, this increases susceptible individuals' exposure to specific disease-modifying exposures, alters the microbiome and interacts with host genetic and immune factors to contribute to AD flares. AD,atopic dermatitis

course via neuroendocrine pathways and induction of a T_H2 phenotype; however, the effect of specific psychological factors (personality, anxiety, depression) on AD pathogenesis is beyond the scope of this review.[16,17]

3.1 | Ultraviolet radiation, temperature and humidity

Natural factors such as ultraviolet radiation (UVR), temperature and humidity also contribute to both AD flares and regional prevalence variation. An ecological analysis of ISAAC data demonstrated a positive linear correlation between country-level monthly minimum and mean UVR exposure and AD prevalence, particularly among 13- to 14-year-olds.[18] Lower AD prevalence is also associated with areas of high relative humidity, high temperatures and low use of central heating.[19,20] Recent data from Denmark highlight that the inverse of the above weather conditions is conducive to AD flares, using healthcare utilization as a surrogate marker for exacerbations.[21] The mechanism underpinning this is likely multifactorial, with filaggrin and filaggrin breakdown products (FBP) lying at the core. Low humidity may suppress filaggrin expression via an as-yet-unidentified mechanism,[22,23] while simultaneously driving deimination and breakdown of filaggrin to increase levels of natural moisturizing factor (NMF).[24] In the presence of UV light, trans-urocanic acid (an FBP) is converted to immunosuppressive cis-urocanic acid, thereby regulating the immune system in the context of AD flares.[25,26] Acting in synergy, the above mechanisms both suppress expression and deplete existing filaggrin to generate NMF under conditions of low humidity. Epidermal barrier integrity is thus disrupted, consequently facilitating an upregulated immune response.[27] Individuals with loss-of-function mutations in filaggrin (*FLG*) are disproportionately affected by the above cascade.[28] This illustrates the exposomal approach as it is a case of several environmental factors converging on a common pathway in AD pathogenesis.

3.2 | Environmental pollution

As illustrated, the prevalence of AD is increasing in areas of urbanization. Cross-sectional studies have confirmed an association with higher levels of traffic-related air pollution and AD prevalence in both urban and small-town settings.[29-32] There is some evidence for an association with maternal smoking during pregnancy and tobacco exposure postnatally.[33] Observational data support these epidemiological findings, as children exposed to airborne particulate matter, benzene, nitrogen compounds and tobacco smoke antenatally were shown to be at higher risk of developing AD.[34,35] High levels of outdoor airborne pollutants were shown to exacerbate symptoms of established AD in older children.[32,36] Similar effects were observed in relation to volatile organic compounds, a common indoor air pollutant associated with paint.[37] A recent review suggests that the mechanism by which the above associations contribute to AD pathogenesis involve both epigenetic changes in utero and damage of the stratum corneum through generation of reactive oxygen species.[7] The proposed pathway in relation to tobacco smoke exposure involves epigenetic immune priming and consequent T_H2 polarization, particularly during the third trimester.[38] Postnatally, further exposure to airborne pollutants leads to oxidative damage to the lipids and proteins of the stratum corneum, disrupting the epidermal barrier and facilitating a dysregulated immune response.[39,40] T_H2 cytokines then drive the characteristic inflammation and pruritus

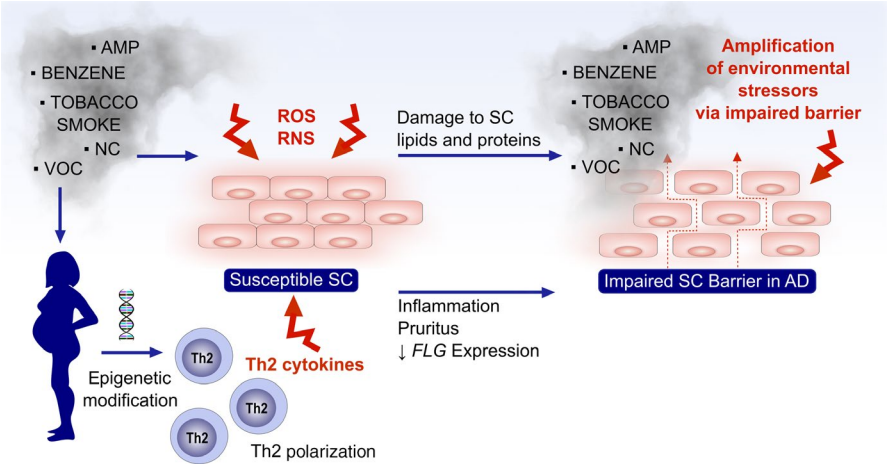

FIGURE 2 The role of airborne pollutants in AD pathogenesis. Airborne pollutants induce epigenetic modifications in utero, polarizing the immune response towards a TH2 phenotype, as well as directly damaging SC lipids and proteins. TH2 cytokines drive the characteristic inflammation and pruritus, as well as suppress *FLG* expression. The resulting itch-scratch cycle further impairs the barrier through mechanical damage, driving inflammation and enabling direct contact with airborne pollutants, leading to a perpetuating cycle. AD, atopic dermatitis; APM, airborne particulate matter; NC, nitrogen compounds; RNS, reactive nitrogen species; ROS, reactive oxygen species; SC, stratum corneum; VOC, volatile organic compounds

associated with AD and downregulate filaggrin expression, further compromising the structural integrity of the epidermal barrier.[41] The result is a perpetuating cycle of AD symptoms, whereby damage induced by scratching enables enhanced contact with airborne pollutants and the characteristic immune response. The effect of use of biomass fuel burners in the home—a significant source of air pollution in developing countries—has been analysed in ISAAC Phase Three, but was found not to have a statistically significant effect on the prevalence of AD, possibly due to the presence of confounding factors that lower AD prevalence in areas where biomass fuel cooking is prevalent.[42] The study highlighted a higher prevalence of AD in areas where electric heating is used in the home, further cementing the link between urbanization and AD prevalence. Further studies have linked using kerosene fuel for indoor cooking in the home as being an important risk factor for AD development.[43,44]

While research is needed to elucidate precisely the pathophysiological mechanisms by which air pollutants contribute to AD, evidence suggests that minimizing air pollution (eg by bake-out of volatile organic compounds and smoking cessation) during critical antenatal and early infancy periods could ameliorate the risks of developing and exacerbating (Figure 2) AD in individuals who are inherently susceptible from birth.[37,38]

3.3 | Water hardness

Cohort and cross-sectional studies have demonstrated an increased prevalence of AD in regions with hard domestic water, with no definitive relationship reported for chlorine.[45-47] Specific external exposures such as frequent detergent use and hard water may weaken the epidermal barrier via increasing skin surface pH and subsequent reduction in NMF and up-regulation in protease activity.[48] This results in a weakened barrier that facilitates sensitization to both environmental and food allergens. Most recently, it was shown that hard water exposure leads to greater cutaneous deposition of sodium lauryl sulfate (SLS), a surfactant present in many wash products. The deposits subsequently caused irritation and increased TEWL particularly in *FLG* mutation carriers.[49] The mechanism underpinning this may involve the reduction of profilaggrin expression induced by SLS.[50] Studied water softening techniques have included ion-exchange and commercially available baby cleansers, although only the former has shown to ameliorate the irritant effects of surfactant.[49,51] Further studies are currently underway to assess the impact of softening interventions on AD development and persistence at various time points on the pathogenesis pathway.

3.4 | The role of allergens and allergic sensitization

It has long been recognized that AD is associated with the so called "atopic march"- in which infant AD commonly (though not exclusively) precedes the development of food and later respiratory allergies.[52] It is now understood that this classical longitudinal progression is just one pathway to atopic multimorbidity and many possible sequences of disease phenotypes are possible.[53] Research to date has hypothesized that a key initiator and mediator of the atopic march is a defective skin barrier, mediating a T_H2-skewed immune response and a persistent pro-inflammatory state.[10] Once sensitized to an environmental allergen, further exposure can trigger AD flares and contribute to disease chronicity. For instance, when AD predominantly affects the head and neck area, significant aeroallergen sensitization (eg to house dust mite, tree or grass pollen) is often a key factor, leading to disease exacerbations during the pollen season.[54]

With regard to food allergens, a systematic review by Tsakok et al suggests that there is also a causal relationship between AD and subsequent food protein sensitization and allergy, thus supporting

the above hypothesis.[55] Emerging data from the Canadian Healthy Infant Longitudinal Development study analysed the patterns of allergen sensitization in 2629 infants at ages 1 and 3.[56] Infants with AD who were poly-sensitized to multiple food and aeroallergens by age 3 were at highest risk of developing allergic disease, compared to mono-sensitized infants or infants with AD but no evidence of sensitization. It is worth noting that infants who were sensitized to a food allergen at 1 year were more likely than nonsensitized infants to have the allergen excluded from their diet by year 3, despite no evidence of allergic disease. Between years 1 and 3, there was a decrease in sensitization rates for most common food allergens, highlighting that this sensitization was transient.

Early restoration or enhancement of the skin barrier is an important consideration in primary prevention of AD and the subsequent development of allergic comorbidities.[57] Emollient therapy from birth may be a feasible and cost-effective method of preventing AD development, with several ongoing trials in the area.[58-60] It is worth noting, however, *FLG* mutations as a relevant factor have not been studied specifically in the above trials, due to their small size and lack of subgroup analysis. The mechanism underpinning this is likely to involve decreased skin pH and an alteration in the skin microbiome, with *Streptoccus salivarius* populations reported to exert a protective effect.[61] The AD allergic exposome is thus best thought of as a combination of external influences that both precede the development of AD in susceptible infants, and subsequently drive an immune response that perpetuates AD. Interrogation of individual influences at a pathway level, supported by additional epidemiological insights, may enable derivation of an optimum combination of exposures to common allergens, at critical time points and at protective doses. Doing so may facilitate immune tolerance in infants with an impaired skin barrier and prevent allergic sensitization. This approach is also critical to elucidating the mechanisms underpinning allergic sensitization in infants with no primary skin barrier impairment (Figure 3).[62]

4 | THE ROLE OF THE MICROBIOME

4.1 | Cutaneous microbiome

A key facilitator of interactions between the external environment and the host is the skin microbiome—an entity that is both sensitive and susceptible to external influences.[63] The critical external influence that begins shaping the neonatal microbiome is the mode of delivery, with infants delivered vaginally possessing a skin microbiome rich in *Lactobacilli*, while the microbiome of those born via caesarean section is initially enriched in organisms colonizing the mother's skin.[64] The healthy skin microbiome is topographically diverse and is dominated by four phyla—*Actinobacteria*, *Firmicutes*, *Proteobacteria* and *Bacteroidetes*.[5] The functions of the cutaneous microbiome are diverse and are centred around bi-directional interactions with the epidermal barrier and systemic immunity.[63] Based on evidence from mouse models, the postnatal development of a diverse skin microbiome includes rapid colonization with commensal microbiota, such as *Staphyloccoccus*

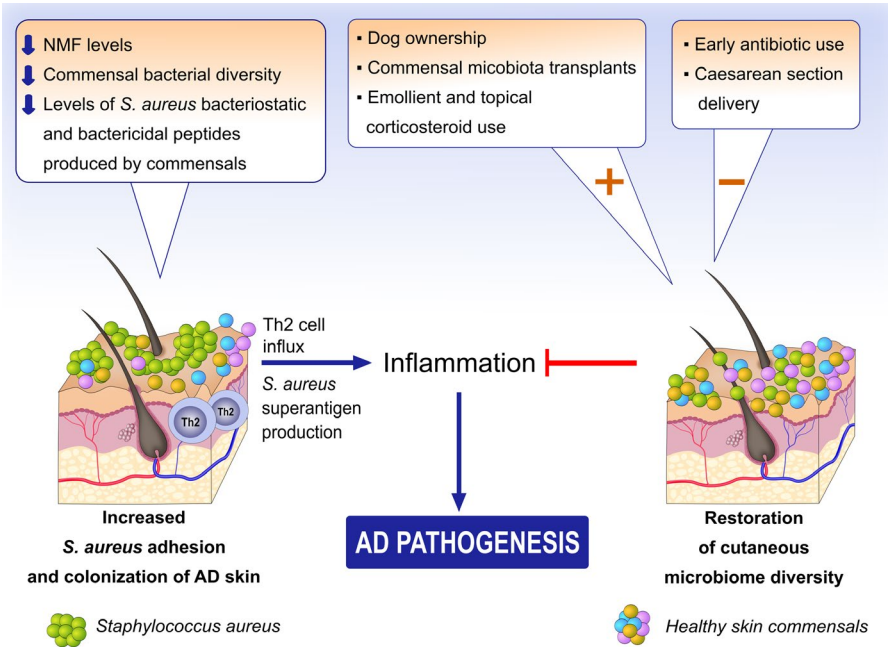

FIGURE 3 The role of the cutaneous microbiome and its interaction with the exposome. Both lesional and nonlesional AD skin facilitates enhanced *Staphylococcus aureus* adherence and displays reduced microbial diversity. *Staphylococcus aureus* superantigen production facilitates TH2 cell influx, driving the characteristic inflammatory response. An exposomal approach aims to restore the normal cutaneous biodiversity via identifying positive and negative influences on the skin microbiome, thus enabling a degree of definitive prevention and amelioration in AD. The listed exposures do remain partly hypothetical at present, as further studies investigating the extent of their effect on cutaneous microbiome diversity are sought. AD, atopic dermatitis

epidermidis. Tolerance to commensals is induced via rapid T_{reg} cell epidermal influx, and subsequently, there is considerable cross-talk between the cutaneous microbiome and the immune system to maintain a state of health.[65,66] As with allergic exposures, timing of commensal colonization is crucial. The potential for induction of tolerance to commensals is greatest in neonatal life, with decreased capacity for tolerance development as an individual ages.[67] These findings may provide a mechanistic explanation for the relationship between early life antibiotic exposure and the demonstrated risk of subsequent AD development.[68] Indeed, the microbiome may represent the interface between the epidermal barrier and external exposures.

Lesional and nonlesional skin from AD patients is dysbiotic with diminished *Streptococcus*, *Corynebacterium and Prophionibacterium* diversity and enhanced *Staphylococcus* colonization.[69] *Staphylococcus aureus* is a pathogen of particular significance, as it abundantly colonizes over 90% of patients with AD.[70] *Staphylococcus aureus* produces several surface and secreted virulence factors and superantigens, driving the production of specific IgE and a consequent influx of T_H2 cells and release of associated cytokines that perpetuate pruritus and further disrupt the epidermal barrier.[71] Adhesion is facilitated by bacterial clumping factor B, the expression of which is highly enhanced in skin expressing low levels of NMF, further suggesting an intimate link between dysfunctional filaggrin metabolism and dysbiosis as an exposomal influence in AD.[72,73] The aim of manipulating the AD microbiome is restoration of microbial diversity, as demonstrated during recovery following AD flares.[69] Coagulase-negative staphylococci, whose carriage is reduced in AD even at presymptomatic stages, produce peptides bactericidal to *S aureus* and inhibit biofilm formation.[74-76] Given the cutaneous microbiome's unique location at the skin surface, it is a prime target for manipulation via exposomal influences.

The cutaneous microbiome is significantly altered over time and is influenced by the physical, ambient and social environment surrounding an individual.[63] The challenge is thus to elucidate the precise influences that alter the microbiome to confer a protective and therapeutic microbial milieu in AD patients. Conventional AD treatments such as emollient use, bleach baths and topical steroids have been demonstrated to restore bacterial diversity to that more closely resembling healthy skin.[77,78] A more novel theory proposes that cutaneous microbiome diversity is increased following regular contact with nature. The theory proposes that pet owners, particularly dog owners, have a higher propensity to spend more time in outdoor natural environments, thereby altering their microbiome and benefitting from reduced psychological stress and the immunomodulatory effects thereof.[79] Indeed, dog ownership has consistently demonstrated to confer a protective effect against development of AD.[80]

4.2 | Gut microbiome and dietary influences

The gut and its microbiome also act as a distinct body surface, mediating interactions between external exposures (mainly diet and gut parasites) and the immune system. Four out of five prospective birth cohort studies reported an inverse relationship with faecal microbiota diversity in early life and subsequent development of AD.[81,82] In the above studies, infants who subsequently developed AD had higher prevalence of *Escherichia coli*, *Clostridium difficile* and obligate anaerobe species in their faecal samples within the first month of life. Early studies examining gut microbiome diversity have highlighted that patients with AD are likely to have lower levels of *Bifidobacterium* in their faecal samples, with more recent work demonstrating increased abundance of *Faecalibacterium prausnitzii* particularly under 1 year of age.[83-85] Emerging data highlight that *S aureus* may also play a role in the gut. Infants whose gut strains of *S aureus* did not express the *ebp* gene encoding for elastin binding protein and the SEIM superantigen were less likely to develop AD, although the mechanisms contributing to this remain to be elucidated.[86,87]

The role of the microbiome is expanded further when helminth parasites and their relationship to AD development are considered. Helminth infection may modulate immune responses by inducing an anti-helminthic T_H2 cytokine–dominated milieu, which may result in an allergic phenotype once the infection is removed.[88,89] Evidence in support of this comes for instance from a large placebo-controlled trial in a helminth-endemic region of Uganda, whereby treatment with albendazole during the third trimester of pregnancy was associated with an increased prevalence of AD in offspring up to 1 year.[48,90] In contrast, a randomized placebo-controlled trial of helminth eradication in a helminth-endemic area in Vietnam found no effect on the prevalence of AD in schoolchildren, when anti-helminthic treatment was administered to schoolchildren, highlighting that there may be a critical time window for immuno-modulation at the gut interface during the perinatal period.[91] A natural extension of this observation is the effect of oral antibiotics on AD. A systematic review of the literature reported that early life exposure increases the risk of developing AD, with an even stronger association seen with a higher number of courses of antibiotics; the effect is mediated through antibiotics' effect on the gut microbiome and consequent dysbiosis.[68,92,93] Recent data from the Danish National Birth Cohort reported an association between antenatal antibiotic exposure and AD in the first 18 months of life, but only in cases whereby antibiotic use occurred during both early and late gestation.[94]

Conversely, probiotic supplementation with lactobacilli and bifidobacteria during the last trimester of pregnancy and in early life appears protective. Once AD is established, however, such dietary supplementation confers no additional benefit in treatment.[95-97] The mechanism underpinning this likely involves the microbial gut-skin axis and immunomodulatory components produced by certain bacterial strains, as discussed below. The evidence for prebiotics (oligosaccharides) appears promising, although limited in follow-up duration. A meta-analysis of studies of prebiotics for prevention of AD reported a reduced prevalence among infants whose diets were supplemented with a fructooligosaccharide and galactooligosaccharide combination.[98] A single randomized controlled trial of prebiotics for treatment of paediatric AD failed to show a benefit; in contrast to this, synbiotics (a mixture of pre- and pro-biotics) have been shown to be effective as a treatment but not prevention strategy.[99,100]

The gut microbiome is sensitive to dietary modification, thus potentially linking diet with AD pathogenesis. Epidemiological data show an association between unpasteurized farm milk consumption

and a reduction in AD prevalence, although it is unclear whether this is due to an altered microbial composition or unprocessed milk constituents.[48,101-103] Breastmilk has been shown to possess a distinct microbiome, and the introduction of its microbial species diversifies the infant's own gut microbiome, a mechanism also likely applicable to unpasteurized farm milk.[104,105] For instance, data from the PROmotion of Breastfeeding Intervention Trial (PROBIT) highlight that being breastfed is not only associated with a reduced prevalence of AD in early life, but this effect extended into teenage years.[106-108] It must be noted, however, that neither prolonged nor exclusive breastfeeding were associated with reduced AD prevalence in the above studies. This was also supported by a meta-analysis of prospective observational studies as well as the Enquiring About Tolerance (EAT) study, which randomized three-month old infants to either the introduction of allergenic foods alongside breastfeeding or exclusive breastfeeding for six months.[109] No effect on AD prevalence was observed between the two groups.[110] Furthermore, breastfeeding may confer diverse immunomodulatory effects based on its IgA, soluble CD14 and cytokine (particularly TGF-β) composition— which varies highly across individual mothers. TGF-β has been shown to be elevated in unpasteurized farm milk and infants whose mothers consumed unpasteurized farm products during pregnancy or were exposed to a farm environment had an altered immunological and cytokine milieu compared to controls.[111-113] Thus, it is feasible that a crucial antenatal and early neonatal life periods exist, whereby breastfeeding confers an immunomodulatory effect, but this decreases as the child ages. With regard to formula feeding, hydrolysed whey and hydrolysed casein formula has been associated with a reduction in AD prevalence in susceptible infants, as well as a reduction in established AD severity, although the duration of formula feeding and exclusive formula feeding remains controversial.[114-116] Two studies of amino acid–based formula reported conflicting results, and no statistically significant effect was observed for soy-based formula.[114,117] Whey-based formula, particularly with added prebiotic oligosaccharides, alters the infant gut microbiome to resemble that of a breastfed infant, with abundant *Bifidobacteria*.[118,119] This lends support to the hypothesis that individual breastmilk constituents or their formula substitutes aid in the development of a healthy gut microbiome and confer a protective effect in AD. Evidence for dietary influences on AD risk beyond the neonatal period also comes from ecological observations, such as those in ISAAC Phase One, whereby a diet high in trans-fatty acids was associated with increased AD prevalence, while consumption of fish, fruits, vegetables and plant proteins was inversely associated with AD.[120] Further research is required into the precise biological impact of individual dietary components on the development of the gut microbiome, the maturation of the child's immune system in early life and the resulting impact on AD risk to inform potential exposomal manipulation strategies with the aim to prevent AD.

4.3 | The skin-gut interaction

We have highlighted that in AD patients, the gut and the skin represent two distinct topographical entities that facilitate dysbiotic microbiota. An essential consideration is the potential interaction between the two microbiomes with each other, with the immune system and the mechanism by which this contributes to AD. In their recent review, Lee et al postulate that a diverse gut microbiome impacts AD in a trifold manner.[121] Induction of immune tolerance by certain probiotic strains (particularly *Lactobacilli*) is mediated through a trifold mechanism; enhanced IL-10/TGF-β signalling and a subsequent expansion of the T_{reg} population, short-chain fatty acids (SCFA) produced by certain species exerting an anti-inflammatory effect and a neuroendocrine mechanism whereby mediators produced by the gut modulate itch sensation. SCFA produced in the gut by various species (*Akkermansia*, *Bifidobacteria*, *Facalibacterium*) have also been implicated in maintaining cutaneous microbiome diversity. Propionic acid produced by cutaneous *Propionibacterium acnes* has been demonstrated to inhibit *S aureus* growth, while butyrate further induces T_{reg} cells—two mechanisms that are known to be dysregulated in AD.[122,123] In addition, a diet rich in fat and low in fibre alters the microbiome to the extent that SCFA production in the gut is significantly impaired and immune homeostasis is consequently altered in favour of the pathogenic T_H2 phenotype.[124]

The T_H2-T_{reg} balance has been studied by Chatila and colleagues with regard to the gut microbiome and food allergy, although the cytokines at the core of the mechanism are also common to AD. Experimental evidence from murine models shows that gut bacterial dysbiosis can facilitate a re-programming of T_{reg} cells into T_H2 cells via reduced TGF-β signalling and enhanced IL-4 production by ILC2 cells in response to IL-33.[125,126] ILC2 cells have previously been shown to be expanded in AD lesional skin with increased production of IL-33 in response to epithelial barrier disruption, as seen in susceptible *FLG* mutant individuals.[127]

4.4 | Multi-level exposome manipulation as a preventative strategy

To alter the disease course, the AD exposome could be manipulated at multiple levels, from population to individual. Climate change, urbanization and loss of biodiversity are likely to impact the aetiopathogenesis of AD. The microbiome and proximity to nature (ie rural and farm environments), with consequently increased environmental and individual biodiversity, may be the key mediator linking the nonspecific exposome with the internal milieu.[128] A recent study of Finnish and Russian children residing in the same geographic region of Karelia, who are genetically homogenous but socio-economically distinct, found greater diversity of *Acinetobacter* in the Russian population, likely due to a nonwesternized lifestyle and frequent contact with natural surroundings.[129] This was highly correlated with lower prevalence of allergic diseases, including AD.[130] Concentric efforts of society to increase biodiversity and the number of microbial species in urban settings are thus required, with increasing green spaces providing a multifaceted benefit.[131] At an individual level, we may alter the exposome and indeed the microbiome by identifying beneficial practices, susceptible individuals and critical times for intervention. For instance, exposure of infants delivered by caesarean section to vaginal microbes, or indeed

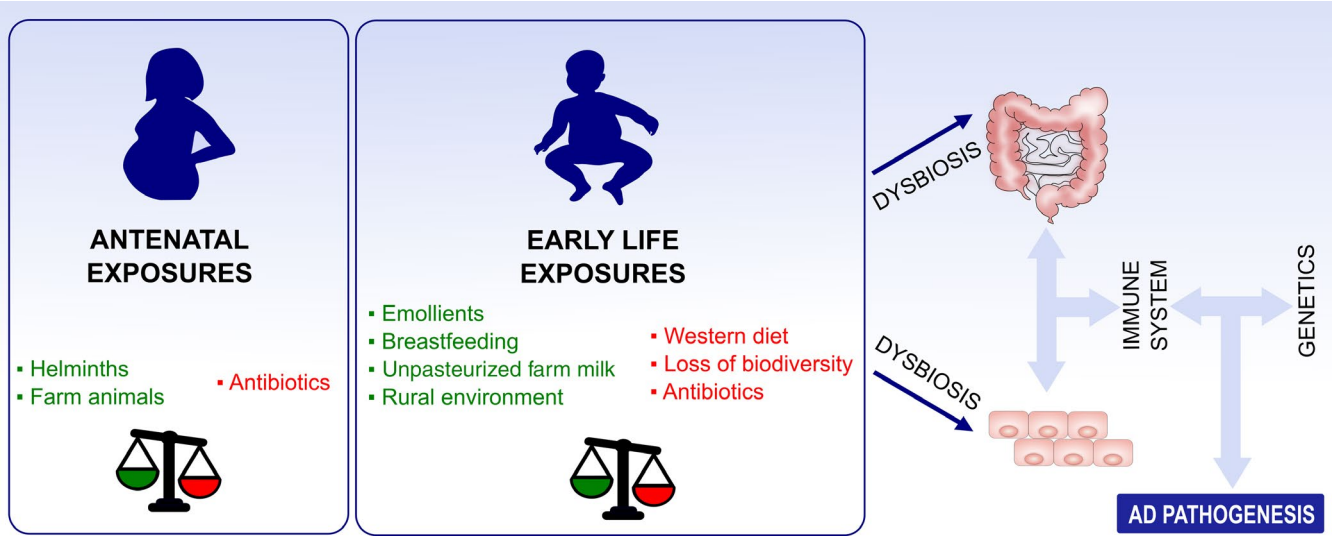

FIGURE 4 Individual exposures, their doses and timing influence the interplay between the host microbiota, host immunity and genetics. The host gut and skin microbiota are entities sensitive to external manipulation by environmental influences, particularly at certain times in an individual's lifespan, such as the third trimester of gestation and the early neonatal period. Given the intimate interaction of the two microbiomes with each other via the gut-skin axis and with the host's immune system, gut and skin dysbiosis are both likely to play a significant role in atopic dermatitis (AD) pathogenesis. The balance of detrimental and beneficial influences on the microbiome at critical time points determines the course of AD and allergy in the individual. The evidence regarding the above is varied in its robustness (strong evidence for breastfeeding, biodiversity, weak or emerging evidence for emollients, synbiotics and unpasteurized farm milk); however, it is the balance between a multitude of factors rather than individual factors in isolation that remain the pertinent factor in AD pathogenesis

direct transplantation of human skin microbiota to individuals with AD.[132,133] Similarly, early introduction of specific allergenic foods into the diet has not been associated with reduced AD prevalence.[110]

With regard to timing, the perinatal period is likely to be crucial. Maternal exposures, including diet and smoking, have a demonstrated effect on the foetal immune system, and the mechanism underpinning this may indeed involve the microbiome.[134] Longitudinal studies have demonstrated that a maternal diet rich in fish (and consequently anti-inflammatory n-3 polyunsaturated fatty acids) reduces the incidence of AD in the offspring.[135] It is likely that immunomodulatory dietary components have an immune priming role in the foetus, although this remains to be confirmed experimentally. What is known, however, is that the maternal microbiome influences the risk of atopy in the offspring, via transplacental passage of microbial metabolites and IgG.[136] Given the intimate link between diet and alterations in the gut microbiome, it is plausible that alterations in the maternal diet translate to an immune response in the foetus, with consequent implications for allergic disease (Figure 4).[137-140]

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

Conceptualizing the exposome provides researchers with a crucial link between epidemiology, immunology and cell biology with regard to aetiology and pathogenesis of specific diseases. In this review, we highlighted that with regard to AD numerous external influences impact on the delicate functional balance of the epidermis. Here, we identify several pathways by which our changing world may detrimentally and/or positively impact the skin of susceptible individuals with regard to the development of AD or of allergic diseases at large. Exposomal impacts need to be studied not only with regard to the nature of the exposure, but also its dose and timing. Akin to seasonal variation in AD flares being influenced by climate, specific external exposures and microbiomal shifts appear to be highly time-sensitive.

Achieving this goal of temporal analysis of individual influence will necessitate novel approaches and study methodology, such as longitudinal monitoring of individuals to capture specific exposures together and the use of artificial intelligence.[141] In the modern era, wearable sensors for recording and analysis of geotemporal exposomal niches have been developed and though still in their infancy, such technologies to facilitate the characterization of nonspecific, specific and microbiomal exposomes at the molecular and organism levels for individuals, as well as for distinct locations.[142,143] Emerging technologies and environment-wide association studies now facilitate monitoring of exposures, making exposure biomarker and consequently exposome analysis more feasible as computational power increases.[144] Conceptually, we can thus use personal wearable devices to record an individual's specific exposures, assess the level of exposure and effect on pathogenesis via biomonitoring. A particular challenge is the precise characterization of a nonspecific disease-modifying exposure, for example urbanization on the individual, although we may use surrogate markers of exposure common to the population on hand. We propose that by studying the pathways downstream of various doses of exposures at various times both pre- and postnatally an optimum set of

exposures may emerge, enabling a degree of definitive prevention or symptom amelioration in AD.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ORCID

Alan D. Irvine https://orcid.org/0000-0002-9048-2044

REFERENCES

1. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Prim*. 2018;4(1):1.
2. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy* 2018;73(6):1284-1293.
3. Tsakok T, Woolf R, Smith CH, Weidinger S, Flohr C. Atopic dermatitis: the skin barrier and beyond. *Br J Dermatol*. 2018;180(3):464-474.
4. Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. *Toxicol Sci*. 2014;137(1):1-2.
5. Powers CE, McShane DB, Gilligan PH, Burkhart CN, Morrell DS. Microbiome and pediatric atopic dermatitis. *J Dermatol*. 2015;42(12):1137-1142.
6. Fu T, Keiser E, Linos E, et al. Eczema and sensitization to common allergens in the United States: a multiethnic, population-based study. *Pediatr Dermatol*. 2014;31(1):21-26.
7. Ahn K. The role of air pollutants in atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(5):993-999.
8. Cecchi L, D'Amato G, Annesi-Maesano I. External exposome and allergic respiratory and skin diseases. *J Allergy Clin Immunol*. 2018;141(3):846-857.
9. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. *J Allergy Clin Immunol*. 2018;143(1):46-55.
10. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2014;69(1):17-27.
11. Asher MI, Stewart AW, Mallol J, et al. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? and eczema? Review of the ecological analyses of ISAAC Phase One. *Respir Res*. 2010;11(1). https://doi.org/10.1186/1465-9921-11-8
12. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC phase three. *J Allergy Clin Immunol*. 2009;124(6):1251-1258.
13. Marenholz I, Nickel R, Rü schendorf F, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march.
14. Irvine AD, McLean W, Leung D. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med*. 2011;365(14):1315-1327.
15. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol*. 2008;121(6):1337-1343.
16. Arndt J, Smith N, Tausk F. Stress and atopic dermatitis. *Curr Allergy Asthma Rep*. 2008;8(4):312-317.
17. Lin T-K, Zhong L, Santiago J. Association between stress and the HPA axis in the atopic dermatitis. *Int J Mol Sci*. 2017;18(10):2131.
18. Fuertes E, Flohr C, Silverberg JI, Standl M, Strachan DP. Global associations between UVR exposure and current eczema prevalence in children from ISAAC phase three. *J Invest Dermatol*. 2017;137(6):1248-1256.
19. Silverberg JI, Hanifin JM. Relative humidity, dew point, indoor heating and ultraviolet index are associated with the prevalence of eczema. *J Invest Dermatol*. 2012;132:S44.
20. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol*. 2013;133(7):1752-1759.
21. Hamann CR, Andersen Y, Engebretsen KA, et al. The effects of season and weather on healthcare utilization among patients with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2018;32(10):1745-1753.
22. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol*. 1986;115(1):84-92.
23. Katagiri C, Sato J, Nomura J, Denda M. Changes in environmental humidity affect the water-holding property of the stratum corneum and its free amino acid content, and the expression of filaggrin in the epidermis of hairless mice. *J Dermatol Sci*. 2003;31(1):29-35.
24. Cau L, Pendaries V, Lhuillier E, et al. Lowering relative humidity level increases epidermal protein deimination and drives human filaggrin breakdown. *J Dermatol Sci*. 2017;86(2):106-113.
25. Langan SM, Irvine AD. Childhood eczema and the importance of the physical environment. *J Invest Dermatol*. 2013;133(7):1706-1709.
26. Rieko K-K, Motonobu N. Effect of cis-urocanic acid on atopic dermatitis in NC/Nga mice. *J Dermatol Sci*. 2016;84(1):e65-e66.
27. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):792-799.
28. McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol*. 2013;131(2):280-291.
29. Krämer U, Sugiri D, Ranft U, et al. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. *J Dermatol Sci*. 2009;56(2):99-105.
30. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med*. 2008;177(12):1331-1337.
31. Annesi-Maesano I, Moreau D, Caillaud D, et al. Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. *Respir Med*. 2007;101(8):1721-1729.
32. Lee YL, Su HJ, Sheu HM, Yu HS, Guo YL. Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children. *J Invest Dermatol*. 2008;128(10):2412-2420.
33. Jedrychowski W, Perera F, Maugeri U, et al. Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. *Int Arch Allergy Immunol*. 2011;155(3):275-281.
34. Penard-Morand C, Raherison C, Charpin D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J*. 2010;36(1):33-40.
35. Yi O, Kwon H-J, Kim HO, et al. Effect of environmental tobacco smoke on atopic dermatitis among children in Korea. *Environ Res*. 2012;113:40-45.
36. Kim J, Kim E-H, Oh I, et al. Symptoms of atopic dermatitis are influenced by outdoor air pollution. *J Allergy Clin Immunol*. 2013;132(2):495-498.
37. Kim E-H, Kim S, Lee JH, et al. Indoor air pollution aggravates symptoms of atopic dermatitis in children. *PLoS ONE* 2015;10(3):e0119501.
38. Shinohara M, Matsumoto K. Fetal tobacco smoke exposure in the third trimester of pregnancy is associated with atopic eczema/dermatitis syndrome in infancy. *Pediatr Allergy Immunol Pulmonol*. 2017;30(3):155-162.

39. Niwa Y, Sumi H, Kawahira K, Terashima T, Nakamura T, Akamatsu H. Protein oxidative damage in the stratum corneum: evidence for a link between environmental oxidants and the changing prevalence and nature of atopic dermatitis in Japan. *Br J Dermatol*. 2003;149(2):248-254.
40. Sticozzi C, Belmonte G, Pecorelli A, et al. Cigarette smoke affects keratinocytes SRB1 expression and localization via H2O2 production and HNE protein adducts formation. *PLoS ONE* 2012;7(3):e33592
41. Brandt EB, Sivaprasad U. Th2 cytokines and atopic dermatitis. *J Clin Cell Immunol*. 2011;2(3). https://doi.org/10.4172/2155-9899.1000110
42. Vicedo-Cabrera AM, García-Marcos L, Llopis-González A, et al. Atopic dermatitis and indoor use of energy sources in cooking and heating appliances. *BMC Public Health* 2012;12:890.
43. Venn AJ, Yemaneberhan H, Bekele Z, Lewis SA, Parry E, Britton J. Increased risk of allergy associated with the use of kerosene fuel in the home. *Am J Respir Crit Care Med*. 2001;164(9):1660-1664.
44. Yemaneberhan H, Flohr C, Lewis SA, et al. Prevalence and associated factors of atopic dermatitis symptoms in rural and urban Ethiopia. *Clin Exp Allergy*. 2004;34(5):779-785.
45. McNally NJ, Williams HC, Phillips DR, et al. Atopic eczema and domestic water hardness. *Lancet* 1998;352(9127):527-531.
46. Perkin MR, Craven J, Logan K, et al. Association between domestic water hardness, chlorine, and atopic dermatitis risk in early life: a population-based cross-sectional study. *J Allergy Clin Immunol*. 2016;138(2):509-516.
47. Engebretsen KA, Bager P, Wohlfahrt J, et al. Prevalence of atopic dermatitis in infants by domestic water hardness and season of birth: cohort study. *J Allergy Clin Immunol*. 2017;139(5):1568-1574.
48. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014;69(1):3-16.
49. Danby SG, Brown K, Wigley AM, et al. The effect of water hardness on surfactant deposition after washing and subsequent skin irritation in atopic dermatitis patients and healthy control subjects. *J Invest Dermatol*. 2018;138(1):68-77.
50. Törmä H, Lindberg M, Berne B. Skin barrier disruption by sodium lauryl sulfate-exposure alters the expressions of involucrin, transglutaminase 1, profilaggrin, and kallikreins during the repair phase in human skin in vivo. *J Invest Dermatol*. 2008;128(5):1212-1219.
51. Walters RM, Anim-Danso E, Amato SM, et al. Hard water softening effect of a baby cleanser. *Clin Cosmet Investig Dermatol*. 2016;9:339-345.
52. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J Clin Cell Immunol*. 2014;5(2). https://doi.org/10.4172/2155-9899.1000202
53. Paller AS, Kong HH, Seed P, et al. The microbiome in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143(1):26-35.
54. Werfel T, Heratizadeh A, Niebuhr M, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol*. 2015;136(1):96-103.
55. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137(4):1071-1078. https://doi.org/10.1016/j.jaci.2015.10.049
56. Dharma C, Lefebvre DL, Tran MM, et al. Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: effects on allergic diseases. *Clin Exp Allergy*. 2018;48(1):48-59.
57. Flohr C, Mann J. New approaches to the prevention of childhood atopic dermatitis. *Allergy* 2014;69(1):56-61.
58. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823.
59. Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials*. 2017;18(1):343.
60. Ridd MJ, Redmond NM, Hollinghurst S, et al. Choice of Moisturiser for Eczema Treatment (COMET): study protocol for a randomized controlled trial. *Trials*. 2015;16(1):304.
61. Glatz M, Jo J, Kennedy E, et al. Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. *PLoS ONE*. 2018;13(2):e0192443. https://doi.org/10.1371/journal.pone.0192443
62. Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol*. 2017;139(6):1723-1734.
63. Prescott SL, Larcombe D-L, Logan AC, et al. The skin microbiome: impact of modern environments on skin ecology, barrier integrity, and systemic immune programming. *World Allergy Organ J*. 2017;10:29.
64. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci*. 2010;107(26):11971-11975.
65. Scharschmidt T, Vasquez K, Truong H-A, et al. A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. *Immunity* 2015;43(5):1011-1021.
66. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. *Science* 2014;346(6212):954-959.
67. Scharschmidt TC. Establishing tolerance to commensal skin bacteria: timing is everything. *Dermatol Clin*. 2017;35(1):1-9.
68. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. *Br J Dermatol*. 2013;169(5):983-991.
69. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22(5):850-859.
70. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008;358(14):1483-1494.
71. Geoghegan JA, Irvine AD, Foster TJ. *Staphylococcus aureus* and atopic dermatitis: a complex and evolving relationship. *Trends Microbiol*. 2018;26(6):484-497.
72. Fleury OM, McAleer MA, Feuillie C, et al. Clumping factor B promotes adherence of *Staphylococcus aureus* to corneocytes in atopic dermatitis. *Infect Immun*. 2017;85(6). https://doi.org/10.1128/IAI.00994-16
73. Feuillie C, Vitry P, McAleer MA, et al. Adhesion of *Staphylococcus aureus* to corneocytes from atopic dermatitis patients is controlled by natural moisturizing factor levels. *MBio* 2018;9(4).
74. Kennedy EA, Connolly J, Hourihane JO'B, et al. Skin microbiome before development of atopic dermatitis: early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *J Allergy Clin Immunol*. 2017;139(1):166-172.
75. Zipperer A, Konnerth MC, Laux C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. *Nature* 2016;535(7613):511-516.
76. Iwase T, Uehara Y, Shinji H, et al. Staphylococcus epidermidis Esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. *Nature* 2010;465(7296):346-349.
77. Seite S, Flores GE, Henley JB, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol*. 2014;13(11):1365-1372.
78. Gonzalez ME, Schaffer JV, Orlow SJ, et al. Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis. *J Am Acad Dermatol*. 2016;75(3):481-493.
79. Nisbet EK, Zelenski JM, Murphy SA. The nature relatedness scale: linking individuals' connection with nature to environmental

concern and behavior. *Environ Behav*. 2009;41(5):715-740. https://doi.org/10.1177/0013916508318748

80. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. *Arch Dermatol*. 2007;143(12):1570-1577. https://doi.org/10.1001/archderm.143.12.1570
81. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol*. 2011;128(3):646-652.
82. Marrs T, Flohr C. The role of skin and gut microbiota in the development of atopic eczema. *Br J Dermatol*. 2016;175:13-18.
83. Björkstén B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol*. 2001;108(4):516-520.
84. Watanabe S, Narisawa Y, Arase S, et al. Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. *J Allergy Clin Immunol*. 2003;111(3):587-591.
85. Song H, Yoo Y, Hwang J, Na YC, Kim HS. Faecalibacterium prausnitzii subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis. *J Allergy Clin Immunol*. 2016;137(3):852-860.
86. Nowrouzian FL, Lina G, Hodille E, et al. Superantigens and adhesins of infant gut commensal *Staphylococcus aureus* strains and association with subsequent development of atopic eczema. *Br J Dermatol*. 2017;176(2):439-445.
87. Nowrouzian FL, Ljung A, Nilsson S, Hesselmar B, Adlerberth I, Wold AE. Neonatal gut colonisation by *Staphylococcus aureus* strains with certain adhesins and superantigens is negatively associated with subsequent development of atopic eczema. *Br J Dermatol*. 2019;180(6):1481-1488. https://doi.org/10.1111/bjd.17451
88. Flohr C, Quinnell RJ, Britton J. Do helminth parasites protect against atopy and allergic disease? *Clin Exp Allergy*. 2009;39(1):20-32.
89. Silva M, Costa VA, Pereira T, et al. Severity of atopic dermatitis and Ascaris lumbricoides infection: an evaluation of CCR4+ and CXCR3+ helper T cell frequency. *Rev Soc Bras Med Trop*. 2012;45(6):761-763.
90. Ndibazza J, Mpairwe H, Webb EL, et al. Impact of anthelminthic treatment in pregnancy and childhood on immunisations, infections and eczema in childhood: a randomised controlled trial. *PLoS ONE*. 2012;7(12):e50325.
91. Flohr C, Tuyen LN, Quinnell RJ, et al. Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. *Clin Exp Allergy*. 2009;40(1):131-142.
92. Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. *Front Microbiol*. 2015;6:1543.
93. Pascal M, Perez-Gordo M, Caballero T, et al. Microbiome and allergic diseases. *Front Immunol*. 2018;9:1584.
94. Timm S, Schlünssen V, Olsen J, Ramlau-Hansen CH. Prenatal antibiotics and atopic dermatitis among 18-month-old children in the Danish National Birth Cohort. *Clin Exp Allergy*. 2017;47(7):929-936.
95. West CE, Jenmalm MC, Kozyrskyj AL, Prescott SL. Probiotics for treatment and primary prevention of allergic diseases and asthma: looking back and moving forward. *Expert Rev Clin Immunol*. 2016;12(6):625-639.
96. Foolad N, Armstrong AW. Prebiotics and probiotics: the prevention and reduction in severity of atopic dermatitis in children. *Benef Microbes*. 2014;5(2):151-160.
97. Makrgeorgou A, Leonardi-Bee JO, Bath-Hextall FJ, et al. Probiotics for treating eczema. *Cochrane Database Syst Rev*. 2018;11:CD006135.
98. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev*. 2013;3.https://doi.org/10.1002/14651858.CD006474.pub3
99. Boženský J, Hill M, Zelenka R, Skýba T. Prebiotics do not influence the severity of atopic dermatitis in infants: a randomised controlled trial. *PLoS ONE*. 2015;10(11):e0142897.
100. Chang Y-S, Trivedi MK, Jha A, Lin Y-F, Dimaano L, García-Romero MT. Synbiotics for prevention and treatment of atopic dermatitis. *JAMA Pediatr*. 2016;170(3):236.
101. Perkin M, Strachan D. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? *J Allergy Clin Immunol*. 2006;117(6):1374-1381.
102. Wickens K, Lane JM, Fitzharris P, et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 2002;57(12):1171-1179.
103. von Mutius E. Maternal farm exposure/ingestion of unpasteurized cow's milk and allergic disease. *Curr Opin Gastroenterol*. 2012;28(6):570-576.
104. Funkhouser LJ, Bordenstein SR. Mom knows best: the Universality of Maternal Microbial Transmission. *PLoS Biol*. 2013;11(8):e1001631.
105. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. In: Shiohara T, ed. *Pathogenesis and Management of Atopic Dermatitis*. Vol 41. Basel: KARGER; 2011:1-34.
106. Flohr C, Nagel G, Weinmayr G, Kleiner A, Strachan DP, Williams HC. Lack of evidence for a protective effect of prolonged breastfeeding on childhood eczema: lessons from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *Br J Dermatol*. 2011;165(6):1280-1289.
107. Kramer MS, Chalmers B, Hodnett ED, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA*. 2001;285(4):413-420.
108. Flohr C, Henderson AJ, Kramer MS, et al. Effect of an intervention to promote breastfeeding on asthma, lung function, and atopic eczema at age 16 years. *JAMA Pediatr*. 2018;172(1).
109. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol*. 2009;161(2):373-383.
110. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733-1743.
111. Peroni DG, Piacentini GL, Bodini A, Pigozzi R, Boner AL. Transforming growth factor-β_1 is elevated in unpasteurized cow's milk. *Pediatr Allergy Immunol*. 2009;20(1):42-44.
112. Pfefferle PI, Büchele G, Blümer N, et al. Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy: the PASTURE Study. *J Allergy Clin Immunol*. 2010;125(1):108-115.
113. Roduit C, Wohlgensinger J, Frei R, et al. Prenatal animal contact and gene expression of innate immunity receptors at birth are associated with atopic dermatitis. *J Allergy Clin Immunol*. 2011;127(1):179-185.
114. Foolad N, Brezinski EA, Chase EP, Armstrong AW. Effect of nutrient supplementation on atopic dermatitis in children. *JAMA Dermatol*. 2013;149(3):350.
115. Jin Y-Y, Cao R-M, Chen JI, et al. Partially hydrolyzed cow's milk formula has a therapeutic effect on the infants with mild to moderate atopic dermatitis: a randomized, double-blind study. *Pediatr Allergy Immunol*. 2011;22(7):688-694.
116. Osborn DA, Sinn JK, Jones LJ. Infant formulas containing hydrolysed protein for prevention of allergic disease. *Cochrane Database Syst Rev*. 2018;10:CD003664.
117. Osborn DA, Sinn JK. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev*. 2006;4:CD003741.
118. Vandenplas Y, Zakharova I, Dmitrieva Y. Oligosaccharides in infant formula: more evidence to validate the role of prebiotics. *Br J Nutr*. 2015;113(09):1339-1344.

119. Hascoët J-M, Hubert C, Rochat F, et al. Effect of formula composition on the development of infant gut microbiota. *J Pediatr Gastroenterol Nutr.* 2011;52(6):756-762.
120. Ellwood P, Asher MI, Björkstén B, et al. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. *Eur Respir J.* 2001;17(3):436-443.
121. Lee SY, Lee E, Park YM, Hong SJ. Microbiome in the gut-skin axis in atopic dermatitis. *Allergy Asthma Immunol Res.* 2018;10(4):354-362.
122. Schwarz A, Bruhs A, Schwarz T. The short-chain fatty acid sodium butyrate functions as a regulator of the skin immune system. *J Invest Dermatol.* 2017;137(4):855-864.
123. Shu M, Wang Y, Yu J, et al. Fermentation of Propionibacterium acnes, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant *Staphylococcus aureus*. *PLoS ONE* 2013;8(2):e55380.
124. Salem I, Ramser A, Isham N, Ghannoum MA. The gut microbiome as a major regulator of the gut-skin axis. *Front Microbiol.* 2018;9:1459.
125. Noval Rivas M, Burton OT, Oettgen HC, Chatila T. IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function. *J Allergy Clin Immunol.* 2016;138(3):801-811.
126. Rachid R, Chatila TA. The role of the gut microbiota in food allergy. *Curr Opin Pediatr.* 2016;28(6):748-753.
127. Roediger B, Kyle R, Le Gros G, Weninger W. Dermal group 2 innate lymphoid cells in atopic dermatitis and allergy. *Curr Opin Immunol.* 2014;31:108-114.
128. Haahtela T, Holgate S, Pawankar R, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. *World Allergy Organ J.* 2013;6(1):1-18.
129. Haahtela T, Laatikainen T, Alenius H, et al. Hunt for the origin of allergy - comparing the Finnish and Russian Karelia. *Clin Exp Allergy.* 2015;45(5):891-901.
130. Ruokolainen L, Paalanen L, Karkman A, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy.* 2017;47(5):665-674.
131. Prescott SL, Logan AC. Transforming life: a broad view of the developmental origins of health and disease concept from an ecological justice perspective. *Int J Environ Res Public Health* 2016;13(11):1075.
132. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med.* 2016;22(3):250-253.
133. Myles IA, Williams KW, Reckhow JD, et al. Transplantation of human skin microbiota in models of atopic dermatitis. *JCI Insight.* 2016;1(10). https://doi.org/10.1172/jci.insight.86955
134. Romano-Keeler J, Weitkamp JH. Maternal influences on fetal microbial colonization and immune development. *Pediatr Res.* 2015;77(1-2):189-195. https://doi.org/10.1038/pr.2014.163
135. Sausenthaler S, Koletzko S, Schaaf B, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr.* 2007;85(2):530-537.
136. Vuillermin PJ, Macia L, Nanan R, Tang ML, Collier F, Brix S. The maternal microbiome during pregnancy and allergic disease in the offspring. *Semin Immunopathol.* 2017;39(6):669-675.
137. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med.* 2009;1(6):6ra14.
138. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. *Sci Transl Med.* 2014;6(237):237ra65-237ra65.
139. Perez PF, Dore J, Leclerc M, et al. Bacterial imprinting of the neonatal immune system: lessons from maternal cells? *Pediatrics* 2007;119(3):000-000.
140. Rautava S, Collado MC, Salminen S, Isolauri E. Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial. *Neonatology.* 2012;102(3):178-184.
141. Warth B, Spangler S, Fang M, et al. Exposome-scale investigations guided by global metabolomics, pathway analysis, and cognitive computing. *Anal Chem.* 2017;89(21):11505-11513.
142. Loh M, Sarigiannis D, Gotti A, et al. Sensors might help define the external exposome. *Int J Environ Res Public Health.* 2017;14(4):434.
143. Jiang C, Wang X, Li X, et al. Dynamic human environmental exposome revealed by longitudinal personal monitoring. *Cell* 2018;175(1):277-291.
144. Steckling N, Gotti A, Bose-O'Reilly S, et al. Biomarkers of exposure in environment-wide association studies – opportunities to decode the exposome using human biomonitoring data. *Environ Res.* 2018;164:597-624.

How to cite this article: Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. *Allergy.* 2020;75:63–74. https://doi.org/10.1111/all.13946