INTRODUCTION

Atopic dermatitis (AD) (syn. atopic eczema) is a chronic inflammatory skin condition, affecting up to 20% of children and 5%-10% of adults. 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 (Th2 and Th22). IL-4 and IL-13 in particular drive eosinophil and mast cell recruitment and IL-31 secretion, a key cytokine involved in itch sensation. 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 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 (e.g., 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 expose 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
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.” 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. A recent review by Cecchi et al 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.

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, 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. 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. 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. 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.

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. 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
course via neuroendocrine pathways and induction of a Th2 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 Th2 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 Th2 cytokines then drive the characteristic inflammation and pruritus
associated with AD and downregulate filaggrin expression, further compromising the structural integrity of the epidermal barrier. 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. 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.

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. 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. 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. The mechanism underpinning this may involve the reduction of profilaggrin expression induced by SLS. 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. 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. 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. 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. 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 (e.g. to house dust mite, tree or grass pollen) is often a key factor, leading to disease exacerbations during the pollen season.

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. Emerging data from the Canadian Healthy Infant Longitudinal Development study analysed the patterns of allergen sensitization in 2629 infants at ages 1 and 3. 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. Emollient therapy from birth may be a feasible and cost-effective method of preventing AD development, with several ongoing trials in the area. 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 Streptococcus salivarius populations reported to exert a protective effect. 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).

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. 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. The healthy skin microbiome is topographically diverse and is dominated by four phyla—Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes. The functions of the cutaneous microbiome are diverse and are centred around bi-directional interactions with the epidermal barrier and systemic immunity. Based on evidence from mouse models, the postnatal development of a diverse skin microbiome includes rapid colonization with commensal microbiota, such as Staphylococcus aureus.
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.\textsuperscript{55,64} 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.\textsuperscript{67} These findings may provide a mechanistic explanation for the relationship between early life antibiotic exposure and the demonstrated risk of subsequent AD development.\textsuperscript{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 Propionibacterium diversity and enhanced Staphylococcus colonization.\textsuperscript{69} Staphylococcus aureus is a pathogen of particular significance, as it abundantly colonizes over 90\% of patients with AD.\textsuperscript{70} Staphylococcus aureus produces several surface and secreted virulence factors and superantigens, driving the production of specific IgE and a consequent influx of T_{h}2 cells and release of associated cytokines that perpetuate pruritus and further disrupt the epidermal barrier.\textsuperscript{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.\textsuperscript{72,73} The aim of manipulating the AD microbiome is restoration of microbial diversity, as demonstrated during recovery following AD flares.\textsuperscript{69} Coagulase-negative staphylococci, whose carriage is reduced in AD even at presymptomatic stages, produce peptides bactericidal to S aureus and inhibit biofilm formation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 benefiting from reduced psychological stress and the immunomodulatory effects thereof.\textsuperscript{79} Indeed, dog ownership has consistently demonstrated to confer a protective effect against development of AD.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 SEI M superantigen were less likely to develop AD, although the mechanisms contributing to this remain to be elucidated.\textsuperscript{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_{h}2 cytokine–dominated milieu, which may result in an allergic phenotype once the infection is removed.\textsuperscript{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.\textsuperscript{89,90} In contrast, a randomized placebo-controlled trial of helmith 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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. 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. No effect on AD prevalence was observed between the two groups. 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. 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. Two studies of amino acid–based formula reported conflicting results, and no statistically significant effect was observed for soy-based formula. Whey-based formula, particularly with added prebiotic oligosaccharides, alters the infant gut microbiome to resemble that of a breastfed infant, with abundant Bifidobacteria. 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. Further research is required into the precise biological effect 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. 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 Treg 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 Treg cells—two mechanisms that are known to be dysregulated in AD. 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 Treg2 phenotype.

The Treg2-Treg 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 Treg cells into Treg2 cells via reduced TGF-β signalling and enhanced IL-4 production by ILC2 cells in response to IL-33. 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.

### 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. 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. This was highly correlated with lower prevalence of allergic diseases, including AD. 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. 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
Subjective 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.

With regard to timing, the perinatal period is likely to be crucial. Maternal exposures, including diet and smoking, have demonstrated effect on the foetal immune system, and the mechanism underpinning this may indeed involve the microbiome. 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. 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. 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).

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. 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 microbiobial exposomes at the molecular and organism levels for individuals, as well as for distinct locations. 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. 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.

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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