Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: https://www.tandfonline.com/loi/ierm20

Environmental risk factors and their role in the management of atopic dermatitis

Robert Kantor & Jonathan I. Silverberg

To cite this article: Robert Kantor & Jonathan I. Silverberg (2017) Environmental risk factors and their role in the management of atopic dermatitis, Expert Review of Clinical Immunology, 13:1, 15-26, DOI: 10.1080/1744666X.2016.1212660

To link to this article: https://doi.org/10.1080/1744666X.2016.1212660

Published online: 28 Jul 2016.

EXPERT REVIEW OF CLINICAL IMMUNOLOGY, 2017
VOL. 13, NO. 1, 15–26
http://dx.doi.org/10.1080/1744666X.2016.1212660

Taylor & Francis
Taylor & Francis Group

REVIEW

Environmental risk factors and their role in the management of atopic dermatitis

Robert Kantor[a] and Jonathan I. Silverberg[b]

[a]Department of Dermatology, Northwestern University, Chicago, IL, USA; [b]Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University, Chicago, IL, USA

ABSTRACT

Introduction: The etiology of atopic dermatitis (AD) is multifactorial with interaction between genetics, immune and environmental factors.

Areas covered: We review the role of prenatal exposures, irritants and pruritogens, pathogens, climate factors, including temperature, humidity, ultraviolet radiation, outdoor and indoor air pollutants, tobacco smoke exposure, water hardness, urban vs. rural living, diet, breastfeeding, probiotics and prebiotics on AD.

Expert commentary: The increased global prevalence of AD cannot be attributed to genetics alone, suggesting that evolving environmental exposures may trigger and/or flare disease in predisposed individuals. There is a complex interplay between different environmental factors, including individual use of personal care products and exposure to climate, pollution, food and other exogenous factors. Understanding these complex risk factors is crucial to developing targeted interventions to prevent the disease in millions. Moreover, patients require counseling on optimal regimens for minimization of exposure to irritants and pruritogens and other harmful exposures.

ARTICLE HISTORY
Received 26 May 2016
Accepted 11 July 2016
Published online 28 July 2016

KEYWORDS
Eczema; atopic dermatitis; environment; prenatal; pregnancy; irritant; allergen; climate; humidity; temperature; ultraviolet; precipitation; latitude; pollution; hygiene hypothesis; pathogen; bacteria; virus; herpes; skin-barrier; inflammation; gene-environment

1. Introduction

Atopic dermatitis (AD) is one of the most common chronic diseases of childhood associated with significant morbidity and health-care costs. The etiology of AD is believed to be multifactorial with interaction between genetics, immune, and environmental factors. Rising prevalence of AD over the past six decades has been established [1], with prevalence estimates of 10–12% in children throughout the United States and as high as 20% in some US states [2,3] and 7–10% in US adults [3,4]. Importantly, such a rapid rise in prevalence suggests a major role for environmental factors [5].

2. Pathogenesis of AD

A fundamental debate exists as to whether AD is driven primarily by barrier dysfunction (outside–inside hypothesis) or primarily by an inflammatory response to irritants and environmental allergens (inside–outside hypothesis) [5]. Previous studies demonstrated loss-of-function variants in the filaggrin gene (FLG) with an autosomal semidominant pattern of inheritance [6]. These FLG variants result in decreased expression of the protein filaggrin, which is a constituent of natural moisturizing factor and required for normal skin barrier function. Impaired barrier function increases vulnerability to environmental insults and increased transepidermal water loss (TEWL) [7]; levels of TEWL correlate with AD severity [8]. Another pathophysiologic component to barrier deficiency might involve suboptimal tight junctions immediately below the stratum corneum secondary to reduced claudins [9,10]. Skin barrier dysfunction can also be acquired secondary to irritants and mechanical disruption [11]. Skin barrier dysfunction can trigger inflammation through release of thymic stromal lymphopoietin (TSLP) and other cytokines by damaged keratinocytes [12,13].

On the other hand, AD has been found to be associated with variants of a number of genes primarily involved in immune pathways, including IL-4R, IL-18, IL-31, etc. [14–16] The complex immune dysregulation in AD is increasingly being recognized. T-helper (Th)-2 inflammation, including interleukins (IL)-4 and -13, plays a dominant role in both acute and chronic AD lesions, whereas Th-1 inflammation, including interferon-gamma, appears to play a role largely in chronic AD lesions [17]. IL-4 signaling occurs through the JAK1,3-STAT6 pathway, and mice constitutively expressing STAT6 develop AD-like skin disease [18–20]. Epidermal Th-2 cellular expansion occurs in AD, and Th-2 cytokines are known to suppress epidermal differentiation and antimicrobial peptide (AMP) production, thus contributing to the typical skin phenotype of this condition [10]. Additional immune aberrancies implicated in subsets of AD include increased IL-22 in acute AD [12,21], impaired IL-17 immune responses [22], and increased IL-31 [23]. IL-22 has been linked to epidermal hyperplasia and disturbed terminal differentiation in AD [21]. IL-17 regulates AMP in keratinocytes, and its downregulation may contribute toward increased skin infections in AD patients [21]. IL-31 is associated with skin-homing T cells [24] and pruritus [25] in AD. Finally, phosphodiesterases (PDEs) and cyclic adenosine monophosphate were found to play an important role in AD in the 1980s [26]. Recently, PDE4 has emerged as a promising therapeutic target in AD [27]. It is

CONTACT Jonathan I. Silverberg jonathanisilverberg@gmail.com

likely that both the outside–inside and inside–outside hypotheses are relevant in different patient subsets. Regardless of 'the chicken or the egg', all patients have a combination of immune dysregulation and skin barrier dysfunction.

Malassezia is a species of commensal yeast that is part of the normal skin flora but has been implicated in the pathogenesis of AD. Patients with AD have higher rates of sensitization to Malassezia compared to healthy controls [28], and levels of Malassezia-specific immunoglobulin E correlate well with AD severity [29]. Malassezia-specific T cells from the skin and blood of AD patients secreted Th-1, Th-2, Th-17, and Th-22 cytokines [30]. However, it is unclear whether Malassezia are truly pathogenic or increased as an epiphenomenon in AD. Moreover, it is unknown how strong of an effect Malassezia have in AD aside from other established mechanisms.

Environmental exposures may play a role in AD through epigenetic alterations, including microRNA and DNA methylation. Two studies found upregulation of miR-155, miR146a, miR-17-5p, and other miRNA in AD lesions, but downregulation of miR-122a, miR-326, miR-133b, and other miRNA [31,32]. miR-155 in Th cells from AD lesions was associated with enhanced cutaneous T-cell proliferative responses [31]. A study of keratinocytes from skin lesions of 10 humans with AD and 10 without AD found that promoter hypomethylation of the TSLP gene was associated with TSLP overexpression in AD lesions [33]. A case–control study of 28 humans with AD and 29 healthy controls found multiple differentially methylated CpG sites in the epidermis of AD lesions compared to healthy controls [34]. The differential methylation may modulate transcript levels of genes involved in epidermal differentiation and innate immunity [34]. These epigenetic signals raise intriguing questions about the role of gene–environment interactions in AD.

This review explores the effects of environmental risk factors on inflammation and skin barrier dysfunction in pediatric AD and relevant strategies for patient management.

3. Environmental risk factors

Much research has been done to better understand environmental risk factors in AD. The motivation for such research is to identify potentially modifiable risk factors of AD. Interventions aimed at reducing exposure to or harmful sequelae from environmental triggers of AD could prevent or mitigate disease. The prevalence of AD appears to be higher in wealthier, developed regions compared with developing regions [2,35–44]. Moreover, the prevalence of AD dramatically increased over the past 50 years worldwide and continues to increase in a number of countries [1,45]. While the reasons for such increases are unknown, environmental factors have been considered as potential contributors toward these trends [5]. However, there are myriad environmental exposures that might play either harmful or protective roles in AD. There is likely a complex interplay between genetic factors predisposing to AD and environmental triggers and/or exacerbants. This review will explore several major environmental exposures, including maternal exposures during pregnancy, skin irritants, climate, pollutants, tobacco smoke, water hardness, urban and rural living, and diet (Table 1).

Table 1. Environmental exposures implicated in atopic dermatitis.

In utero
Maternal stress [46–51]
Cigarette smoke [52]
Antibiotic exposure [53,54]
Alcohol consumption [55–57]
Omega-3 long-chain polyunsaturated fatty acids [58]
Probiotics [59,60]
Skin exposures
Irritants [61–64]
Pruritogens [65,66]
Early life exposure to dirt and pathogens ('hygiene hypothesis')
Farm and rural living [67,68]
Manure and microbial exposure in the home [68,69]
Bacterial endotoxins, helminthes, herpesviridae, farm animals, dogs, unpasteurized milk, early day care [70–74]
Chickenpox infection [73]
Respiratory syncytial virus [73,75–78]
Skin flora
Staphylococcus aureus and microbial diversity [79–82]
Malassezia [28–30]
Climate [3,83–89]
Temperature [84–88,90]
Humidity [84,85,87,88,90–93]
Ultraviolet radiation [85,88,90,94–96]
Precipitation [85,86,90]
Air pollutants [97,98]
Outdoor pollutants [97–104]
Indoor pollutants [97,105–109]
Cigarette smoking [52]
Water hardness [110–113]
Urban living [114]
Diet and adiposity [115–122]
Breast-feeding [123–128]
Probiotics [59,60]
Prebiotics [129,130]

3.1. Maternal exposures during pregnancy

Some maternal exposures during pregnancy may predispose toward increased risk of AD in childhood, including stress, smoking, antibiotics, and alcohol consumption. A recent systematic review identified six observational human studies that examined the relationship between maternal stress during pregnancy and development of childhood AD [131]. Five of six studies found significant associations of stress and strain related to employment and adverse life events with AD at ages 6 and 14 years [46–50]; one of these studies found that only maternal stress during the second and third trimesters was associated with increased risk of AD [47]. The sixth study found an association between maternal stress and AD in the first 2 years of life [51]. While the mechanisms of such association remain unknown, maternal stress has been proposed to modulate the hypothalamic–pituitary axis and program the developing immune system in the fetus [131]. However, there may be confounding exposures during maternal stress that might play a role in AD, such as smoking, socioeconomic status, changes in diet, etc.

A recent systematic review of 23 observational studies found no association between maternal exposure to cigarette smoke and risk of childhood AD [52]. Prenatal exposure to antibiotics might play a harmful role in AD by altering fetal skin and gut microbiome, in line with the 'hygiene hypothesis' (reviewed in Section 3.3). Indeed, prenatal antibiotic exposure was found to be associated with small but significantly increased risk of AD in early childhood in two prospective

birth cohort studies [53,54]. Finally, two observational studies found that maternal consumption of alcoholic beverages was associated with increased risk of AD in infancy [55] and at age 7 years [56]. However, one study found no association between prenatal exposure to alcohol and childhood AD [57]. More studies are needed to determine whether these and other prenatal exposures increase risk of childhood AD.

In contrast, some maternal exposures may actually lower the risk of AD in childhood, including dietary exposures and probiotics. A systematic review of studies found that intake of omega-3 (n-3) long-chain polyunsaturated fatty acids during pregnancy may reduce the risk of AD and other allergic disorders in the first 12 months of life [58]. The effects of probiotics during pregnancy are reviewed in Section 3.11.

3.2. Irritants and pruritogens

Intrinsic barrier dysfunction can be worsened when environmental factors such as soap and detergent cause further epidermal barrier breakdown, and irritants and allergens can interact with the immune system and promote inflammation [132]. A study of patients with AD, inactive AD, and allergic respiratory disease without dermatitis found that all three groups showed significantly lower thresholds to irritancy by sodium lauryl sulfate [61]. The mechanisms for increased irritancy in AD are likely multifactorial. A German case–control study of patients with occupational irritant contact dermatitis (ICD) and healthy controls found that patients with either history of AD or common FLG null variants had significantly higher risk of ICD; however, those with both AD and FLG variants were at highest risk of ICD [62]. These results suggest that FLG variants may play an important role but are not the only mechanism. Indeed, another study found that repeated single and tandem exposures to sodium lauryl sulfate and sodium hydroxide resulted in significantly lower levels of NMF in patients with AD, regardless of whether they had FLG variants [63]. The lack of difference between AD patients with or without FLG variants may be related to the fact that inflammation can downregulate filaggrin levels in the skin. A study of children and adults with AD found that skin barrier was similarly worse in severe AD patients with or without FLG variants compared to mild AD and/or healthy controls, particularly increased TEWL, decreased filaggrin immunostaining, and increased serum levels of TSLP [64].

Aside from barrier disruption, some common environmental exposures may be pruritogens in AD, i.e. directly or indirectly worsen itch. For example, AD patients often report worsened itch secondary to personal care products containing fragrances, even without any positive reactions to fragrances observed during patch testing (personal observation). Indeed, a recent study of 24 healthy subjects found that cutaneous application of cinnamaldehyde (a member of the fragrance family) rapidly induced itch, hyperknesis (prolonged and stronger itch to punctate mechanical stimulus), and alloknesis (itch evoked by light touch that is not typically pruritic), as well as a vasomotor response and increased skin temperature [65]. Pruritus secondary to cinnamaldehyde and other fragrances and irritants may be directly mediated by thermoreceptive transient receptor potential ankyrin 1 channel [66]. It is possible that AD patients have greater susceptibility to such pruritogens.

Finally, cutaneous exposure to some common contact allergens may specifically affect expression of critical genes involved in different inflammatory pathways [133]. In particular, nickel, rubber, and fragrances were associated with decreased expression of genes involved in Th-1 and Th-2 inflammation and increased Th-17 and IL-23 skewing [133]. While more research is needed on this topic, these results suggest that common skin contactants in the environment may specifically upregulate inflammatory responses.

3.3. Hygiene hypothesis

The 'hygiene hypothesis' posits that early life exposure to different pathogens can steer the immature immune system away from allergic inflammation [134]. That is, exposure to dirt and pathogens in developing countries may actually protect against developing AD and allergic disease. Such hygienic exposures might account for the increased prevalence of AD over the past 50 years, as well as regional differences of disease prevalence.

There are several intriguing observations that indirectly support the 'hygiene hypothesis'. A previous study found that children born outside the United States had dramatically lower odds of AD and allergic disease than those born in the United States [135]. One potential explanation is that less hygienic environmental exposures protect against developing AD and allergic disease. However, the odds of AD increased after residing in the United States for 10 or more years [135]. This suggests that the protective effects of early life exposures may eventually wear off. Numerous studies demonstrated lower odds of AD and allergic disease in farm and rural children, though the inverse associations were more consistent for respiratory atopy [67,68]. The protective effects may be related to exposure to manure and microbial exposure in the home [68,69]. Several different pathogens have been suggested to have a protective role against AD and atopy in general, including bacterial endotoxins, helminthes, herpesviridae, farm animals, dogs, unpasteurized milk, and the abundant infectious exposures of early day care [70–74]. Silverberg et al. found that a single episode of wild-type varicella-zoster virus (chickenpox) infection in the first 8–10 years of life was inversely associated with subsequently developing AD [73], as well as long-term decreased serum IgE levels, peripheral blood lymphocyte, monocyte, and basophil counts [75].

On the other hand, not all microbial exposures protect against AD. While herpesvirus infections early in life may help prevent AD, infections with herpes simplex and Coxsackie virus in patients with established AD can lead to eczema herpeticum and Coxsakium, respectively [136,137]. Moreover, some studies found that infections with respiratory syncytial virus may actually increase the risk of disease [73,75–78]. Finally, it is well established that patients with AD have increased colonization of both lesional and nonlesional skin with *Staphylococcal aureus* and decreased microbial diversity [79–82]. Further work needs to be done to determine which

types of infections are harmful or protective against AD [70,71].

3.4. Climate

Climate factors have anecdotally been regarded by many clinicians as playing an important role in AD. Yet, until recently, there was little evidence to support this notion. One study found that relocating children with AD from the home subarctic/temperate climate of Norway to a subtropical climate in Gran Canary for 4 weeks improved skin symptoms and quality of life [3,83–88]. The climate in a given geographic location is determined by a combination of multiple factors, including temperature, humidity, and precipitation, as well as related factors, such as ultraviolet (UV) exposure. Association of AD with climate factors is important to understand, as long-term climate change may have epidemiological repercussions [89].

3.4.1. Temperature

Data regarding an association between temperature and AD prevalence are conflicting. A 2004 epidemiological study demonstrated reduced childhood AD with higher mean annual outdoor temperature in Europe [84]. Moreover, a study of the ISAAC Phase III survey in Spain found a negative association between outdoor temperature and AD prevalence [85]. Likewise, Silverberg et al. found a lower prevalence of AD in US states with higher quartile temperature [90]. One study that looked at multiple meteorological variables and symptom severity in eczema found that rising air temperature was actually associated with decreased pruritus, but it must be noted that the temperature change was from very cold (−17° C) to moderate (+18°C) [86]. The mechanisms for how higher temperatures might be protective in AD are unclear. It is possible that ambient temperature directly affects keratinocytes [138]. People living in warmer climates use less indoor heating, which may trigger or aggravate AD [90]. Moreover, people living in warmer climates may spend more time outdoors and consequently have more UV exposure, which may protect against AD [90].

However, studies from cohorts in Brazil and the United States found that higher temperatures are associated with poorly controlled AD [87,88]. Heat may play a harmful role in some AD patients by provoking perspiration, which is one of the most commonly reported aggravants in children with AD [139–143]. Perspiration may have an irritant effect on the skin mediated by the acidic pH of sweat, possibly promoting Th-2 inflammation [88], increased cutaneous blood flow due to vasodilation in hot environments [142], and possibly a neuroanatomic mechanism mediated by C nerve fibers [144]. The worsening of AD symptoms by increased temperature likely explains patient preference toward lighter clothing, thereby allowing for better skin ventilation and facilitating heat dissipation [86]. The disparate results between the protective effects of temperature in the population and harmful effects in AD patients require consideration. It may be that higher temperature directly or indirectly protects unaffected individuals from developing AD, whereas higher temperatures are not tolerated well by patients with established AD.

3.4.2. Humidity

Humidity may have multiple effects on atopic skin. Higher humidity may offset increased TEWL in AD skin. However, higher humidity may also provoke perspiration, which can be irritating and aggravate pruritus. A study in murine models showed that low humidity induces epidermal DNA synthesis, causes mast cell degranulation, and leads to epidermal hyperplasia in response to barrier disruption [91]. Another study demonstrated that transferring mice from a humid to dry environment resulted in increased acute TEWL, which may be explained by altered distribution of epidermal lamellar bodies encountered on electron microscopy [92]. Low humidity may also reduce production of filaggrin and deplete its reserves [93].

Associations with both indoor and outdoor humidity have been explored. Indoor relative humidity is inversely associated with eczema prevalence, i.e. higher indoor humidity is associated with lower rates of AD [84,90]. However, conflicting results have been found about whether outdoor humidity is positively or inversely associated with AD prevalence [85,87,88,90]. Further epidemiological research on humidity and AD is warranted, particularly because humidifiers are commonly used as an adjunctive treatment by AD patients.

3.4.3. UV radiation

Narrowband UVB and UVA1 are established modalities of phototherapy for children and adults with AD refractory to topical treatments [94–96]. Thus, it is logical that exposure to UV radiation would protect against AD. Indeed, Silverberg et al. found lower prevalence of childhood AD among US states with highest quartile issued UV index [90]. Conversely, AD prevalence was higher in states with increased stratospheric ozone [90], which filters UVB and UVC. A Spanish study of children aged 6 to 7 years found an inverse association between childhood AD and mean annual number of sunny hours [85]. However, a prospective cohort study found greater long-term sun exposure to be associated with poorly controlled disease [88].

UV radiation has several potentially beneficial mechanisms in AD. First, it facilitates conversion of trans-urocanic acid, a breakdown product of filaggrin, into the cis-urocanic acid isoform that has immunosuppressive effects [45]. Moreover, UVA and UVB may suppress superantigen production by *S. aureus* [83]. UVB also stimulates cutaneous synthesis of previtamin D from 7-dehydrocholesterol. Some studies found that AD is associated with low vitamin D levels [145] and that oral vitamin D supplementation improves AD severity [146,147]. Thus, the beneficial effects of UVB may be related to increased vitamin D levels.

3.4.4. Latitude

The equator is a line of zero latitude; thus, as one moves away from the equator, the absolute latitude value rises. An analysis of data from the ISAAC study found that the prevalence of childhood AD symptoms was positively associated with latitude and inversely associated with mean annual outdoor temperature [84]. Moreover, an Australian study found that the prevalence of AD at ages 4 to 5 and 8 to 9 years was higher in

central and southern regions, i.e. further from the equator [148]. However, a Brazilian study found no association between latitude and AD prevalence in children aged 6 to 7 years, but an inverse association between latitude and prevalence of AD and severe AD in adolescents [87]. As with other climate variables, the associations with latitude may be related to a combination of effects from temperature, UV radiation and vitamin D levels, and behavioral differences [84,148].

3.4.5. Precipitation

Higher mean annual precipitation is associated with increased eczema as demonstrated by studies in Spain [85] and the United States [90]. One study examined the influence of meteorological events on the severity of itch, finding that snowfall was associated with increased pruritus, whereas thunderstorms were associated with decreased pruritus [86]. Silverberg et al. posited that the association between AD and higher precipitation may be indirectly related to concomitantly lower UV levels and temperatures, more time spent indoors, and greater exposure to indoor heating.

3.5. Air pollutants

Air pollutants are particulate or gaseous airborne substances that are harmful to human health. Air pollutants are known risk factors for asthma, but their role in AD is not well established [97]. A potentially harmful role for air pollutants has been considered due to the susceptibility of skin to their direct exposure. Moreover, many air pollutants have seasonal trends that follow climate factors and might play a harmful role in seasonal flares of AD. For example, NO_2, NO_3, SO_2, and CO have a seasonal course in the United States and peak in the cold weather months [98]. Thus, environmental studies of AD must account for both the climate factors and pollutant levels simultaneously to address potential confounding.

Air pollutants may originate from indoor and/or outdoor environments and can interact with the skin by binding to stratum corneum, becoming metabolized or even penetrating the epidermis and entering systemic circulation through dermal capillaries [97].

3.5.1. Outdoor pollutants

Outdoor air pollutants originate from both natural (wildfires, volcanoes, and dust storms) and man-made sources (motor vehicles, power plants, and biomass burning) and include combustion products such as sulfur dioxide (SO_2), carbon monoxide (CO), and nitrogen dioxide (NO_2), as well as particulate matter (PM) [97]. It can be difficult to assess health effects of individual ambient pollutants, because these substances are rarely produced in isolation. Synergistic effects of multiple pollutants can be missed when studying the effects of a single pollutant [99]. For example, a study of 317,926 Taiwanese children found a significant positive association between traffic-related pollution and AD in both sexes [100]. However, analysis of individual traffic-related pollutants only revealed associations of AD with NO_x and CO in females [100].

A study of 4907 French children found associations of both lifetime and 1-year history of AD with NO_x, CO, NO_2, PM_{10}, and benzene pollutants [101]; these are major urban pollutants believed to be primarily influenced by vehicular traffic. A US population-based study found the prevalence of childhood AD to be associated with mean annual NO_2, sulfur dioxide (SO_2), and sulfur trioxide (SO_3), but inversely associated negatively with mean annual nitrate (NO_3), organic carbon (OC), $PM_{2.5}$, and PM_{10} [98]. The observed inverse associations may have been related to the co-occurrence of those pollutants with protective climatic factors.

A German birth cohort study found that the rates of AD in the first 6 years of life increased with proximity of residential address to the nearest main roads [102]; distance to the nearest main road was used as a proxy measure for traffic-related air pollutants. The highest odds of AD occurred in children <50 m from a main road [102]. The authors posited that residents living closer to heavy traffic are exposed to both higher amounts of and more toxic pollutants that are freshly emitted.

Two longitudinal studies assessed the relationship between outdoor pollution and childhood AD symptom severity. A South Korean study of 41 children aged 8–12 years collected symptom diaries for 67 days and found significant associations between pruritus severity and daily ambient PM concentrations [103]. A longer term study of 22 Korean children using symptom diaries for 18 months also found associations of AD symptoms with levels of outdoor air pollutants [104].

3.5.2. Indoor pollutants

Indoor air pollution can arise from stoves, construction materials, biological sources, and combustion products also found in outdoor air pollution [97]. A case–control study of Sweden children found that AD was associated with lower ventilation in the home, particularly in the child's bedroom, with a dose-dependent relationship observed [105]. A German birth cohort study found an association between indoor renovation activities (painting, floor covering, and new furniture) before birth and in the first years of life and lifetime prevalence of AD, possibly related to high levels of volatile organic compounds (VOCs) [106]. A questionnaire-based Korean study found that severity of childhood AD was specifically associated with painting, floor covering, and wallpaper changing in the home [107]. A South Korean study demonstrated that moving into a newly built house during the first year of life was associated with development of AD in both primary and middle school children, likely related to VOC exposure [108]. This study also explored gene–environment interactions and found that children with a genetic susceptibility to AD were more likely to have the disease when exposed to environmental risk factors [108]. Carson et al. found a predilection for AD lesions on exposed body areas in children with filaggrin variants, suggesting that barrier defects may predispose to insult from environmental factors, e.g. pollution and climate [97,109]. Taken together, it appears that multiple outdoor and indoor pollutants may trigger and/or exacerbate childhood AD.

3.5.3. Mechanisms of pollutants

There are likely multiple mechanisms for the harmful effects of different pollutants. A study of skin biopsies from 75 AD patients found an association between AD severity and reactive oxygen species (ROS) associated damage, supporting the

hypothesis that ROS generated by environmental exposures cause oxidative damage to proteins in the stratum corneum [149]. Even short-term exposure to NO_2 or VOC caused significantly increased TEWL in both healthy individuals and those with AD [150,151]. VOC may also contribute to Th-2 polarization, suggesting potentially direct effects of pollutants on the immune system [152].

3.6. Tobacco smoke exposure

Tobacco exposure, including cigarette and cigar smoking, continues to be a major global health concern. Smoke exposure affects both humoral and cellular immunity [153], causes oxidative damage and diminished skin barrier function [154], and has an irritant effect on skin. A strong association between pediatric asthma and environmental tobacco smoke is well established [155], and smoke-free legislation has contributed to lower rates of asthma-related hospital visits [156]. However, conflicting results have been found among the numerous epidemiological studies investigating whether tobacco exposure is associated with AD.

Given the conflicting evidence, a systematic review and meta-analysis of 86 studies with 680,176 patients (598,296 children) from 39 countries was performed to determine whether AD is associated with active smoking, passive exposure to tobacco smoke, and maternal smoking during pregnancy [52]. The authors found significant associations of childhood AD with active smoking and exposure to passive smoke, but not maternal smoking during pregnancy. Of note, many of these studies were cross-sectional and unable to determine the temporality of the association, i.e. whether smoking preceded AD onset or vice versa. Regardless, it appears that AD patients are more likely to be exposed to tobacco, which highlight their increased risk for tobacco-related comorbidities, e.g. malignancy and cardiovascular disease [157–159].

3.7. Water hardness

Hard water contains high mineral content, typically calcium and magnesium ions. Topical exposure to hard water has been hypothesized to aggravate AD by several mechanisms: (1) calcium and magnesium in high concentrations are skin irritants; (2) greater quantities of soap are needed to achieve lather when cleansing with hard water [110–112,160] The health effects of hard water have been examined in cardiovascular disease, growth retardation, and reproductive failure [161]. However, their effects in AD remain controversial.

An observational study in the UK found that water hardness was associated with both lifetime and 1-year prevalence of AD in children aged 4–11, but not 11–16 years [111]. Similarly, a Japanese ecological study demonstrated higher prevalences of AD in urban areas with the highest water hardness [112]. Moreover, a cross-sectional study of 358 Belgian children in kindergarten found that AD prevalence was associated with increased water hardness overall, particularly very hard water [110]. In contrast, an observer-blinded, randomized control trial found no therapeutic benefit of ion-exchange water softeners on AD severity in geographic regions in the UK with hard water [113] Together, there is inconclusive evidence for association between AD and water hardness, and additional prospective studies are needed.

3.8. Urban versus rural living

AD prevalence appears to be higher in urban compared with rural or suburban areas. Schram et al. performed a systematic review in 2010 and found some evidence for an urban–rural discrepancy in AD prevalence [114]. Eleven of the 26 included studies showed significantly higher risk for AD, one showed a significantly lower risk, and 14 showed no significant association of AD in urban areas [114]. Urban living may be associated with increased stress, greater proximity to automobile traffic and related pollutants, higher exposure to other pollutants, fewer protective exposures such as manure and farm animals, and other lifestyle and cultural factors that might impact skin care. Future studies are needed to pinpoint the precise factors for why urban living might predispose to AD.

3.9. Diet

The impact of diet on AD needs to be parsed by different stages of life, i.e. prenatal/*in utero*, early childhood and adulthood exposures. Some individual observational studies have suggested that dietary modifications may impact pediatric AD. A questionnaire-based follow-up study of a prospective birth cohort found no association of pediatric AD and maternal consumption of most foods, except for an inverse association with maternal fish consumption [115]. Another prospective birth cohort also found a significant inverse association between high maternal fish intake and AD in the first 2 years of life [116]. The protective effect of maternal fish intake was also found at 1 year of age in a third study [117]. Early introduction of fish during infancy may even prevent childhood AD [118,119]. The beneficial effect of fish is thought to be due to anti-inflammatory properties of omega-3 polyunsatured fatty acids [116,117]. A recent Cochrane review examined evidence from five randomized or quasi-randomized trials that included 952 participants and concluded that maternal antigen avoidance diets in pregnancy do not protect against AD in the first 18 months of life [120]; however, there is a dearth of longer term studies. Thus, it appears that maternal dietary restriction during pregnancy does not protect against AD, though maternal consumption of fish during pregnancy might be protective.

Analysis of data from the multinational, multiphase, cross-sectional ISAAC study found that pediatric AD was associated with specific dietary habits in childhood and adolescence [121]. In particular, fast food, butter, margarine, and pasta were positively associated with AD, while milk was inversely associated with AD at ages 13 to 14 years. Moreover, fast food was positively associated with severe AD in children aged 6 to 7 years, whereas eggs, fruit, meat, and milk were inversely associated with AD. These results suggest that western diet may play a harmful role in AD and that a healthy balanced diet may help to prevent or mitigate AD. Of note, potential confounding of adiposity, e.g. body mass index, was not

addressed in multivariate models. However, excess adiposity may play a harmful role in pediatric and adult AD, as demonstrated by a recent meta-analysis [122]. Future studies are needed to determine optimal dietary recommendations for persons with AD.

3.10. Breast-feeding

A prospective cohort of 256 infants found that prolonged breast-feeding was associated with significantly lower prevalence of AD at ages 1 and 3 years; intermediate and prolonged breast-feeding was associated with nonsignificantly lower prevalences of AD at ages 5, 10, and 17 years [123]. However, numerous studies were subsequently performed with conflicting results. A meta-analysis of 18 prospective studies was performed in 2001 and found that breast-feeding throughout the first 3 months of life was protective in children with a family history of atopy, but this effect was diminished in those without family history of atopy [124]. Another meta-analysis of prospective cohort studies was performed in 2008 and found insufficient evidence that exclusive breast-feeding for at least 3 months is protective against AD, even in children with a positive family history of atopy [125]. The conflicting results observed are likely due to confounding effects from differences of region, health literacy, socioeconomic status, and other health behaviors in mothers who exclusively breast-feed versus those who do not. Moreover, even less is known about the optimal timing for introducing solid foods and its impact on AD. However, the few available studies do not support an association between delayed introduction of solid foods beyond 6 months of age and AD prevalence [126–128]. Further research is necessary to determine whether breast-feeding is truly protective in childhood AD and the complex relationship between breast-feeding and introducing solid foods.

3.11. Probiotics and prebiotics

Probiotic supplementation involves introduction of live bacteria to the gut and has been studied as both a protective and therapeutic measure in AD. Two meta-analyses of placebo-controlled trials found that maternal use of probiotics during pregnancy and/or infancy was associated with lower rates of AD developing in their children [59,60]. However, there was insufficient evidence to support probiotics as a treatment modality for existing AD [59,162]. The mechanisms for prevention of AD by probiotics harkens back to the hygiene hypothesis, whereby the early exposure to gut microbes steers the immune system away from a Th-2 skew [60] or upregulates Th-1 cytokine production [163].

Prebiotic supplementation is the provision of directed nourishment to facilitate proliferation of biologically desirable microbes in the gut. Two studies have shown evidence that prebiotic oligosaccharide supplementation during infancy has prophylactic benefits against developing AD [129,130]. The protective effects of prebiotic oligosaccharides may be through promotion of bacterial growth or immunomodulatory effects.

Despite extensive research regarding diet and nutrition in AD, there is only limited evidence to support clinical and public health interventions for AD. Maternal intake of fish, probiotics, and possibly prebiotic oligosaccharides may protect against pediatric AD. However, there is limited evidence to support dietary avoidance as a prevention or treatment strategy for AD.

4. Expert commentary

The prevalence of AD has increased over the past several decades in virtually every country worldwide, with continued increased still being observed in some countries [164]. The rapidly increasing global prevalence cannot be attributed to genetics alone, suggesting that environmental exposures may be triggering and/or flaring disease in predisposed individuals. There is a complex interplay between different environmental factors, including individual use of personal care products and exposure to climate, pollution, food, and other exogenous factors. It is even more challenging to sort out the individual versus combined synergistic effects of different environmental factors, as well as the direct effects of environmental factors on AD skin versus indirect effects by influencing health behaviors. Gene–environment interaction is central to the complex pathophysiology of AD. It is doubtful that the above-mentioned factors that are harmful in AD are sufficient to cause the disease without an underlying predisposition. Rather, environmental risk factors likely contribute toward AD by being pruritogens and irritants, upregulating inflammatory processes and/or worsening skin barrier function.

Understanding these complex risk factors is crucial to developing targeted interventions to prevent the disease in millions. Currently, the most promising prevention strategies for AD appear to be maternal use of probiotics during pregnancy and initiating regular moisturizing early in infancy. Moreover, understanding the mechanisms by which environmental factors trigger AD may uncover novel disease mechanisms and future therapeutic targets. For example, recognition of the role of microbiome in AD has resulted in the development of several promising new treatment approaches [165]. Finally, understanding the role of environmental factors in patients with AD is essential to achieve optimal outcomes. For example, patients with predictably increased disease activity in the winter months warrant proactive treatment strategies to prevent upcoming flares [166]. Moreover, patients require counseling on optimal regimen for bathing, minimization of exposure to irritants and pruritogens, etc.

Of the factors discussed in this review, many lack sufficient evidence to support universal recommendations for disease prevention or treatment. Protective factors against AD include living in regions with higher UV irradiation, maternal intake of fish, probiotics, and/or prebiotic oligosaccharides during pregnancy. Vitamin D supplementation is a safe and well-tolerated adjunctive treatment approach that may provide modest benefit in AD, particularly winter disease flares [166]. In contrast, low indoor humidity, excess heat and sweat, some indoor and outdoor air pollutants, active and passive exposure to tobacco smoke, and hard water may play a harmful role in AD. While these factors may not be detrimental to all AD patients, their

inclusion in clinical assessment and decision-making may help improve disease control. For example, use of an indoor humidifier may offset low indoor humidity levels during the winter. Unfortunately, no studies have rigorously assessed this treatment approach, despite its widespread use anecdotally. Avoidance of tobacco smoke and hard water might be helpful, but these can be very challenging for patients, and the clinical benefit of their avoidance in AD remains unclear.

5. Five-year view

The pathophysiology of AD appears to be far more complex than previously recognized. Inherited variants of the FLG gene and resultant barrier defects are only detected in a minority of AD patients. The increasingly recognized role of different inflammatory pathways will change the direction of AD research. Much of the prior research on environmental risk factors of AD focused on their harmful effects on skin barrier. However, we anticipate that future research will shift focus toward the impact of environmental factors on systemic and cutaneous inflammation in AD. Over the next 5 years, research in AD will continue to explore gene–environment interactions and how it pertains to pathophysiology, disease severity, and treatment outcomes. More sophisticated methods for assessing the genotypes and clinical phenotypes of AD will improve clinical and epidemiological research. In particular, it will allow for proper identification of patient subsets where different environmental factors play a crucial role in the clinical disease course.

Key issues

- The rapidly increasing prevalence of and epigenetic alterations observed in AD indicate a strong role of dynamic environmental factors.
- Prenatal intake of omega-3 long-chain polyunsaturated fatty acids and probiotics may decrease risk of childhood AD. Whereas, prenatal exposure to stress, antibiotics and alcohol consumption may increase risk of childhood AD.
- Early life exposures to dirt and pathogens, including bacterial endotoxins, helminthes, herpesviridae, farm animals, dogs, unpasteurized milk and early day care may decrease risk of AD.
- Environmental insults to the skin occurring throughout life may trigger or exacerbate AD, including irritants, pruritogens, harsh climate factors, airborne pollutants and tobacco smoke exposure.
- Western diet and excess adiposity may worsen AD. Whereas, intake of probiotics and prebiotics may protect against AD.

Funding

This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), grant number [K12HS023011], and the Dermatology Foundation. No honorarium, grant or other form of payment was given to anyone to produce the manuscript.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Deckers IA, McLean S, Linssen S, et al. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. PLoS One. 2012;7:e39803.
• **This systematic review demonstrates that the prevalence of atopic dermatitis has increased worldwide.**
2. Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011;131:67–73.
3. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol. 2013;24:476–486.
4. Silverberg JI, Garg NK, Paller AS, et al. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. J Invest Dermatol. 2015;135:56–66.
5. Cork MJ, Robinson DA, Vasilopoulos Y, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J Allergy Clin Immunol. 2006;118:3–21; quiz 22–23.
6. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38:441–446.
7. Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. J Dermatol Sci. 2013;70:3–11.
8. Gupta J, Grube E, Ericksen MB, et al. Intrinsically defective skin barrier function in children with atopic dermatitis correlates with disease severity. J Allergy Clin Immunol. 2008;121:725–730 e722.
9. De Benedetto A, Rafaels NM, McGirt LY, et al. Tight junction defects in patients with atopic dermatitis. J Allergy Clin Immunol. 2011;127:773–786 e771–777
10. Malajian D, Guttman-Yassky E. New pathogenic and therapeutic paradigms in atopic dermatitis. Cytokine. 2015;73:311–318.
11. Fluhr JW, Akengin A, Bornkessel A, et al. Additive impairment of the barrier function by mechanical irritation, occlusion and sodium lauryl sulphate in vivo. Br J Dermatol. 2005;153:125–131.
12. Leung DY. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. Allergol Int. 2013;62:151–161.
13. Oyoshi MK, Larson RP, Ziegler SF, et al. Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. J Allergy Clin Immunol. 2010;126:976–984, 984 e971–975.
14. Novak N, Kruse S, Potreck J, et al. Single nucleotide polymorphisms of the IL18 gene are associated with atopic eczema. J Allergy Clin Immunol. 2005;115:828–833.
15. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. Br J Dermatol. 2000;142:1003–1006.
16. Schulz F, Marenholz I, Folster-Holst R, et al. A common haplotype of the IL-31 gene influencing gene expression is associated with nonatopic eczema. J Allergy Clin Immunol. 2007;120:1097–1102.
17. Gittler JK, Shemer A, Suarez-Farinas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012;130:1344–1354.

18. Bao L, Zhang H, Chan LS. The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. Jakstat. 2013;2:e24137.
19. Sehra S, Yao Y, Howell MD, et al. IL-4 regulates skin homeostasis and the predisposition toward allergic skin inflammation. J Immunol. 2010;184:3186–3190.
20. Sehra S, Bruns HA, Ahyi AN, et al. IL-4 is a critical determinant in the generation of allergic inflammation initiated by a constitutively active Stat6. J Immunol. 2008;180:3551–3559.
21. Nograles KE, Zaba LC, Shemer A, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. J Allergy Clin Immunol. 2009;123:1244–1252 e1242.
22. Eyerich K, Pennino D, Scarponi C, et al. IL-17 in atopic eczema: linking allergen-specific adaptive and microbial-triggered innate immune response. J Allergy Clin Immunol. 2009;123:59–66 e54.
23. Raap U, Wichmann K, Bruder M, et al. Correlation of IL-31 serum levels with severity of atopic dermatitis. J Allergy Clin Immunol. 2008;122:421–423.
24. Bilsborough J, Leung DY, Maurer M, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. J Allergy Clin Immunol. 2006;117:418–425.
25. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006;117:411–417.
26. Grewe SR, Chan SC, Hanifin JM. Elevated leukocyte cyclic AMP-phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP-agonist hyporesponsiveness. J Allergy Clin Immunol. 1982;70:452–457.
27. Zane LT, Chanda S, Jarnagin K, et al. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Immunotherapy. 2016;8(8):853–866.
28. Johansson C, Sandstrom MH, Bartosik J, et al. Atopy patch test reactions to Malassezia allergens differentiate subgroups of atopic dermatitis patients. Br J Dermatol. 2003;148:479–488.
29. Glatz M, Buchner M, Von Bartenwerffer W, et al. Malassezia spp.-specific immunoglobulin E level is a marker for severity of atopic dermatitis in adults. Acta Derm Venereol. 2015;95:191–196.
30. Balaji H, Heratizadeh A, Wichmann K, et al. Malassezia sympodialis thioredoxin-specific T cells are highly cross-reactive to human thioredoxin in atopic dermatitis. J Allergy Clin Immunol. 2011;128:92–99 e94.
31. Sonkoly E, Janson P, Majuri ML, et al. MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative responses by targeting cytotoxic T lymphocyte-associated antigen 4. J Allergy Clin Immunol. 2010;126:581–589 e581–520.
32. Sonkoly E, Wei T, Janson PC, et al. MicroRNAs: novel regulators involved in the pathogenesis of psoriasis? PLoS One. 2007;2:e610.
33. Luo Y, Zhou B, Zhao M, et al. Promoter demethylation contributes to TSLP overexpression in skin lesions of patients with atopic dermatitis. Clin Exp Dermatol. 2014;39:48–53.
34. Rodriguez E, Baurecht H, Wahn AF, et al. An integrated epigenetic and transcriptomic analysis reveals distinct tissue-specific patterns of DNA methylation associated with atopic dermatitis. J Invest Dermatol. 2014;134:1873–1883.
35. Odhiambo JA, Williams HC, Clayton TO, et al. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124:1251–1258 e1223.
36. Purvis DJ, Thompson JM, Clark PM, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. Br J Dermatol. 2005;152:742–749.
37. Tay YK, Kong KH, Khoo L, et al. The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. Br J Dermatol. 2002;146:101–106.
38. Martin PE, Koplin JJ, Eckert JK, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. Clin Exp Allergy. 2013;43:642–651.
39. Xu F, Yan S, Li F, et al. Prevalence of childhood atopic dermatitis: an urban and rural community-based study in Shanghai, China. PLoS One. 2012;7:e36174.
40. Belyhun Y, Amberbir A, Medhin G, et al. Prevalence and risk factors of wheeze and eczema in 1-year-old children: the Butajira birth cohort, Ethiopia. Clin Exp Allergy. 2010;40:619–626.
41. Kay J, Gawkrodger DJ, Mortimer MJ, et al. The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol. 1994;30:35–39.
42. Schultz Larsen F, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. J Am Acad Dermatol. 1996;34:760–764.
43. Sugiura H, Umemoto N, Deguchi H, et al. Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago. Acta Derm Venereol. 1998;78:293–294.
44. Kanwar AJ, De D. Epidemiology and clinical features of atopic dermatitis in India. Indian J Dermatol. 2011;56:471–475.
45. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. Allergy. 2014;69:3–16.
46. Larsen AD, Schlunssen V, Christensen BH, et al. Exposure to psychosocial job strain during pregnancy and odds of asthma and atopic dermatitis among 7-year old children – a prospective cohort study. Scand J Work Environ Health. 2014;40:639–648.
47. Hartwig IR, Sly PD, Schmidt LA, et al. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. J Allergy Clin Immunol. 2014;134:160–169.
48. Wang IJ, Wen HJ, Chiang TL, et al. Maternal employment and atopic dermatitis in children: a prospective cohort study. Br J Dermatol. 2013;168:794–801.
49. De Marco R, Pesce G, Girardi P, et al. Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood. Pediatr Allergy Immunol. 2012;23:724–729.
50. Wen HJ, Wang YJ, Lin YC, et al. Prediction of atopic dermatitis in 2-yr-old children by cord blood IgE, genetic polymorphisms in cytokine genes, and maternal mentality during pregnancy. Pediatr Allergy Immunol. 2011;22:695–703.
51. Sausenthaler S, Rzehak P, Chen CM, et al. Stress-related maternal factors during pregnancy in relation to childhood eczema: results from the LISA Study. J Investig Allergol Clin Immunol. 2009;19:481–487.
52. Kantor R, Kim A, Thyssen J, et al. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. J Am Acad Dermatol. Forthcoming 2016.
    - **This systematic review supports an association of AD with active smoking and passive exposure to tobacco smoke, but not maternal exposure to tobacco during pregnancy.**
53. Dom S, Droste JH, Sariachvili MA, et al. Pre- and post-natal exposure to antibiotics and the development of eczema, recurrent wheezing and atopic sensitization in children up to the age of 4 years. Clin Exp Allergy. 2010;40:1378–1387.
54. McKeever TM, Lewis SA, Smith C, et al. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. Am J Respir Crit Care Med. 2002;166:827–832.
55. Linneberg A, Petersen J, Gronbaek M, et al. Alcohol during pregnancy and atopic dermatitis in the offspring. Clin Exp Allergy. 2004;34:1678–1683.
56. Carson CG, Halkjaer LB, Jensen SM, et al. Alcohol intake in pregnancy increases the child's risk of atopic dermatitis. the COPSAC prospective birth cohort study of a high risk population. PLoS One. 2012;7:e42710.
57. Shaheen SO, Rutterford C, Zuccolo L, et al. Prenatal alcohol exposure and childhood atopic disease: a Mendelian randomization approach. J Allergy Clin Immunol. 2014;133:225–232 e221–225.
58. Best KP, Gold M, Kennedy D, et al. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. Am J Clin Nutr. 2016;103:128–143.

- **This systematic review supports the prenatal intake of omega-3 long-chain fatty acids to decrease the risk of childhood AD.**

59. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. J Allergy Clin Immunol. 2008;121:116–121 e111.
60. Pelucchi C, Chatenoud L, Turati F, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology. 2012;23:402–414.
61. Nassif A, Chan SC, Storrs FJ, et al. Abnormal skin irritancy in atopic dermatitis and in atopy without dermatitis. Arch Dermatol. 1994;130:1402–1407.
62. Visser MJ, Landeck L, Campbell LE, et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. Br J Dermatol. 2013;168:326–332.
63. Angelova-Fischer I, Dapic I, Hoek AK, et al. Skin barrier integrity and natural moisturising factor levels after cumulative dermal exposure to alkaline agents in atopic dermatitis. Acta Derm Venereol. 2014;94:640–644.
64. Mocsai G, Gaspar K, Nagy G, et al. Severe skin inflammation and filaggrin mutation similarly alter the skin barrier in patients with atopic dermatitis. Br J Dermatol. 2014;170:617–624.
65. Hojland CR, Andersen HH, Poulsen JN, et al. A human surrogate model of itch utilizing the TRPA1 agonist trans-cinnamaldehyde. Acta Derm Venereol. 2015;95:798–803.
66. Dhaka A, Viswanath V, Patapoutian A. Trp ion channels and temperature sensation. Annu Rev Neurosci. 2006;29:135–161.
67. Alfven T, Braun-Fahrlander C, Brunekreef B, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle – the PARSIFAL study. Allergy. 2006;61:414–421.
68. Kilpelainen M, Terho EO, Helenius H, et al. Farm environment in childhood prevents the development of allergies. Clin Exp Allergy. 2000;30:201–208.
69. Braun-Fahrlander C, Gassner M, Grize L, et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. Clin Exp Allergy. 1999;29:28–34.
70. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Curr Probl Dermatol. 2011;41:1–34.
71. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? Br J Dermatol. 2005;152:202–216.
72. Pelucchi C, Galeone C, Bach JF, et al. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. J Allergy Clin Immunol. 2013;132:616–622 e617.
73. Silverberg JI, Norowitz KB, Kleiman E, et al. Association between varicella zoster virus infection and atopic dermatitis in early and late childhood: a case-control study. J Allergy Clin Immunol. 2010;126:300–305.
74. Calvani M, Alessandri C, Paolone G, et al. Correlation between Epstein Barr virus antibodies, serum IgE and atopic disease. Pediatr Allergy Immunol. 1997;8:91–96.
75. Silverberg JI, Kleiman E, Silverberg NB, et al. Chickenpox in childhood is associated with decreased atopic disorders, IgE, allergic sensitization, and leukocyte subsets. Pediatr Allergy Immunol. 2012;23:50–58.
76. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ. 2001;322:390–395.
77. Welliver RC, Wong DT, Sun M, et al. The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. N Engl J Med. 1981;305:841–846.
78. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol. 2006;118:209–213.
79. Higaki S, Morohashi M, Yamagishi T, et al. Comparative study of staphylococci from the skin of atopic dermatitis patients and from healthy subjects. Int J Dermatol. 1999;38:265–269.
80. Matsui K, Nishikawa A, Suto H, et al. Comparative study of *Staphylococcus aureus* isolated from lesional and non-lesional skin of atopic dermatitis patients. Microbiol Immunol. 2000;44:945–947.
81. Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. Br J Dermatol. 1974;90:525–530.
82. Wang M, Karlsson C, Olsson C, et al. Reduced diversity in the early fecal microbiota of infants with atopic eczema. J Allergy Clin Immunol. 2008;121:129–134.
83. Byremo G, Rod G, Carlsen KH. Effect of climatic change in children with atopic eczema. Allergy. 2006;61:1403–1410.
84. Weiland SK, Husing A, Strachan DP, et al. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. Occup Environ Med. 2004;61:609–615.
85. Suarez-Varela MM, Garcia-Marcos Alvarez L, Kogan MD, et al. Climate and prevalence of atopic eczema in 6- to 7-year-old school children in Spain ISAAC Phase III. Int J Biometeorol. 2008;52:833–840.
86. Vocks E, Busch R, Frohlich C, et al. Influence of weather and climate on subjective symptom intensity in atopic eczema. Int J Biometeorol. 2001;45:27–33.
87. Sole D, Camelo-Nunes IC, Wandalsen GF, et al. Prevalence of atopic eczema and related symptoms in Brazilian schoolchildren: results from the International Study of Asthma and Allergies in Childhood (ISAAC) phase 3. J Investig Allergol Clin Immunol. 2006;16:367–376.
88. Sargen MR, Hoffstad O, Margolis DJ. Warm, humid, and high sun exposure climates are associated with poorly controlled eczema: PEER (Pediatric Eczema Elective Registry) cohort, 2004–2012. J Invest Dermatol. 2014;134:51–57.
89. Reid CE, Gamble JL. Aeroallergens, allergic disease, and climate change: impacts and adaptation. Ecohealth. 2009;6:458–470.
90. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. J Invest Dermatol. 2013;133:1752–1759.
91. Denda M, Sato J, Tsuchiya T, et al. Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: implication for seasonal exacerbations of inflammatory dermatoses. J Invest Dermatol. 1998;111:873–878.
92. Sato J, Denda M, Chang S, et al. Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. J Invest Dermatol. 2002;119:900–904.
93. Langan SM, Irvine AD. Childhood eczema and the importance of the physical environment. J Invest Dermatol. 2013;133:1706–1709.
94. Clayton TH, Clark SM, Turner D, et al. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. Clin Exp Dermatol. 2007;32:28–33.
95. Garritsen FM, Brouwer MW, Limpens J, et al. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. Br J Dermatol. 2014;170:501–513.
96. Jury CS, McHenry P, Burden AD, et al. Narrowband ultraviolet B (UVB) phototherapy in children. Clin Exp Dermatol. 2006;31:196–199.
97. Ahn K, The role of air pollutants in atopic dermatitis. J Allergy Clin Immunol. 2014;134:993–999; discussion 1000.
98. Kathuria P, Silverberg JI. Association between small particle air pollution, climate and childhood eczema prevalence and severity: a US population-based study. Pediatr Allergy Immunol. 2016;27(5):478–485.
99. Chen T-M, Gokhale J, Shofer S, et al. Outdoor air pollution: nitrogen dioxide, sulfur dioxide, and carbon monoxide health effects. Am J Med Sci. 2007;333:249–256.
100. Lee Y-L, Su H-J, Sheu H-M, et al. Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children. J Invest Dermatol. 2008;128:2412–2420.
101. Pénard-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;36:33–40.
102. 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;177:1331–1337.

103. Song S, Lee K, Lee Y-M, et al. Acute health effects of urban fine and ultrafine particles on children with atopic dermatitis. Environ Res. 2011;111:394–399.
104. Kim J, Kim E-H, Oh I, et al. Symptoms of atopic dermatitis are influenced by outdoor air pollution. J Allergy Clin Immunol. 2013;132:495–498 e491.
105. Bornehag CG, Sundell J, Hägerhed-Engman L, et al. Association between ventilation rates in 390 Swedish homes and allergic symptoms in children. Indoor Air. 2005;15:275–280.
106. Herbarth O, Fritz GJ, Rehwagen M, et al. Association between indoor renovation activities and eczema in early childhood. Int J Hyg Environ Health. 2006;209:241–247.
107. Lee JH, Suh J, Kim EH, et al. Surveillance of home environment in children with atopic dermatitis: a questionnaire survey. Asia Pac Allergy. 2012;2:59–66.
108. Lee J-Y, Seo J-H, Kwon J-W, et al. Exposure to gene-environment interactions before 1 year of age may favor the development of atopic dermatitis. Int Arch Allergy Immunol. 2012;157:363–371.
109. Carson CG, Rasmussen MA, Thyssen JP, et al. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. PLoS One. 2012;7:e48678.
110. Chaumont A, Voisin C, Sardella A, et al. Interactions between domestic water hardness, infant swimming and atopy in the development of childhood eczema. Environ Res. 2012;116:52–57.
111. McNally NJ, Williams HC, Phillips DR, et al. Atopic eczema and domestic water hardness. Lancet. 1998;352:527–531.
112. Miyake Y, Yokoyama T, Yura A, et al. Ecological association of water hardness with prevalence of childhood atopic dermatitis in a Japanese urban area. Environ Res. 2004;94:33–37.
113. Thomas KS, Dean T, O'Leary C, et al. A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children. PLoS Med. 2011;8:e1000395.
114. Schram ME, Tedja AM, Spijker R, et al. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. Br J Dermatol. 2010;162:964–973.
115. Willers SM, Devereux G, Craig LC, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. Thorax. 2007;62:773–779.
116. 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;85:530–537.
117. Romieu I, Torrent M, Garcia-Esteban R, et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. Clin Exp Allergy. 2007;37:518–525.
118. Alm B, Aberg N, Erdes L, et al. Early introduction of fish decreases the risk of eczema in infants. Arch Dis Child. 2009;94:11–15.
119. Oien T, Storro O, Johnsen R. Do early intake of fish and fish oil protect against eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. J Epidemiol Community Health. 2010;64:124–129.
120. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Evid Based Child Health. 2014;9:447–483.
121. Ellwood P, Asher MI, Garcia-Marcos L, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. Thorax. 2013;68:351–360.
122. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. J Am Acad Dermatol. 2015;72:606–616 e604.
•• **This meta-analysis supports an association between AD and obesity in children and adults.**
123. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet. 1995;346:1065–1069.
124. Gdalevich M, Mimouni D, David M, et al. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. J Am Acad Dermatol. 2001;45:520–527.
125. 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;161:373–383.
126. Filipiak B, Zutavern A, Koletzko S, et al. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. J Pediatr. 2007;151:352–358.
127. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. Pediatrics. 2006;117:401–411.
128. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. Pediatrics. 2008;121:e44–e52.
129. Gruber C, Van Stuijvenberg M, Mosca F, et al. Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. J Allergy Clin Immunol. 2010;126:791–797.
130. Moro G, Arslanoglu S, Stahl B, et al. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child. 2006;91:814–819.
131. Andersson NW, Hansen MV, Larsen AD, et al. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. Allergy. 2016;71:15–26.
• **This systematic review supports an association between maternal stress during pregnancy and AD in their children.**
132. Cork MJ, Danby SG, Vasilopoulos Y, et al. Epidermal barrier dysfunction in atopic dermatitis. J Invest Dermatol. 2009;129:1892–1908.
133. Correa da Rosa J, Malajian D, Shemer A, et al. Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin. J Allergy Clin Immunol. 2015;135:712–720.
134. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax. 2000;55 Suppl 1:S2–S10.
135. Silverberg JI, Simpson EL, Durkin HG, et al. Prevalence of allergic disease in foreign-born American children. JAMA Pediatr. 2013;167:554–560.
136. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am. 2015;35:161–183.
137. Peng WM, Jenneck C, Bussmann C, et al. Risk factors of atopic dermatitis patients for eczema herpeticum. J Invest Dermatol. 2007;127:1261–1263.
138. Denda M, Sokabe T, Fukumi-Tominaga T, et al. Effects of skin surface temperature on epidermal permeability barrier homeostasis. J Invest Dermatol. 2007;127:654–659.
139. Dawn A, Papoiu AD, Chan YH, et al. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol. 2009;160:642–644.
140. Williams JR, Burr ML, Williams HC. Factors influencing atopic dermatitis-a questionnaire survey of schoolchildren's perceptions. Br J Dermatol. 2004;150:1154–1161.
141. Langan SM, Bourke JF, Silcocks P, et al. An exploratory prospective observational study of environmental factors exacerbating atopic eczema in children. Br J Dermatol. 2006;154:979–980.
142. Ständer S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. Exp Dermatol. 2002;11:12–24.
143. Yosipovitch G, Goon AT, Wee J, et al. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. Int J Dermatol. 2002;41:212–216.
144. Yosipovitch G, Goon A, Wee J, et al. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. Br J Dermatol. 2000;143:969–973.
145. Peroni DG, Piacentini GL, Cametti E, et al. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. Br J Dermatol. 2011;164:1078–1082.
146. Amestejani M, Salehi BS, Vasigh M, et al. Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. J Drugs Dermatol. 2012;11:327–330.

147. Camargo CA Jr., Ganmaa D, Sidbury R, et al. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J Allergy Clin Immunol. 2014;134:831–835 e831.
148. Osborne NJ, Ukoumunne OC, Wake M, et al. Prevalence of eczema and food allergy is associated with latitude in Australia. J Allergy Clin Immunol. 2012;129:865–867.
149. Niwa Y, Sumi H, Kawahira K, et al. 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;149:248–254.
150. Eberlein-König B, Przybilla B, Kühnl P, et al. Influence of airborne nitrogen dioxide or formaldehyde on parameters of skin function and cellular activation in patients with atopic eczema and control subjects. J Allergy Clin Immunol. 1998;101:141–143.
151. Huss-Marp J, Eberlein-König B, Breuer K, et al. Influence of short-term exposure to airborne der p 1 and volatile organic compounds on skin barrier function and dermal blood flow in patients with atopic eczema and healthy individuals. Clin Exp Allergy. 2006;36:338–345.
152. Lehmann I, Rehwagen M, Diez U, et al. Enhanced in vivo IgE production and T cell polarization toward the type 2 phenotype in association with indoor exposure to VOC: results of the LARS study. Int J Hyg Environ Health. 2001;204:211–221.
153. Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol. 2002;2:372–377.
154. Egawa M, Kohno Y, Kumano Y. Oxidative effects of cigarette smoke on the human skin. Int J Cosmet Sci. 1999;21:83–98.
155. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129:735–744.
156. Been JV, Nurmatov UB, Cox B, et al. Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. Lancet. 2014;383:1549–1560.
157. Andersen YM, Egeberg A, Gislason GH, et al. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. J Allergy Clin Immunol. 2016;138(1):310–312.
158. Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. Allergy. 2015;70:1300–1308.
159. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol. 2015;135:721–728 e726.
160. Ananthapadmanabhan KP, Moore DJ, Subramanyan K, et al. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. Dermatol Ther. 2004;17 Suppl 1:16–25.
161. Sengupta P. Potential health impacts of hard water. Int J Prev Med. 2013;4:866–875.
162. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, et al. Probiotics for the treatment of eczema: a systematic review. Clin Exp Allergy. 2009;39:1117–1127.
•• **This meta-analysis supports the maternal intake of probiotics during pregnancy to decrease the risk of AD in their children.**
163. van der Aa LB, Heymans HS, van Aalderen WM, et al. Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. Pediatr Allergy Immunol. 2010;21:e355–e367.
164. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab. 2015;66 Suppl 1:8–16.
165. Nakatsuji T, Gallo RL. Dermatological therapy by topical application of non-pathogenic bacteria. J Invest Dermatol. 2014;134:11–14.
166. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. J Am Acad Dermatol. 2014;71:1218–1233.