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Childhood Eczema and the Importance of the Physical Environment

Sinéad M. Langan[1,2] and Alan D. Irvine[3,4,5]

In this issue, Simpson and colleagues report a large-scale ecological study that reminds us of the importance of physical environmental factors in the development of atopic dermatitis. The mechanisms through which these factors influence AD development are incompletely understood, but further research in this area is likely to yield substantial insights into this very common childhood dermatological disease.

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Eczema (also known as atopic eczema or atopic dermatitis (AD)) is the commonest chronic inflammatory disease of early childhood in the developed world, and it is associated with significant morbidity in both childhood and adulthood (Ellis *et al.*, 2002; Johansson *et al.*, 2004; Odhiambo *et al.*, 2009). The incidence and prevalence of eczema has increased significantly in the past 3 decades, with some suggestion that this rise in incidence has plateaued in recent years (Williams *et al.*, 2008). Although eczema has a strong genetic component that is slowly becoming more clearly understood, the rise in incidence in recent decades points to a significant environmental component. The so-called hygiene hypothesis has been examined extensively as a possible explanation for the observed rise in incidence of these conditions, but the physical environment, first examined 60 years ago, is less well explored. All physicians who deal with children and adults with AD are aware that the physical environment features large in the lives of their patients. Familiar examples are children whose disease flares when they return to school in September, adults who struggle to deal with low humidity on long air flights, and patients with problematic eczema while living in northern Europe, but who clear markedly when on holiday in southern Europe or Southeast Asia. Although there may be additional factors such as psychological stress or changes in the microbiome or allergen exposures to explain these commonly observed phenomena, atmospheric humidity and UV exposure would seem to be obvious physical factors that deserve more exploration. The lack of definitive epidemiologic data implicating physical environmental factors in AD is largely because of the absence of suitably sized (powered) cohorts to examine such factors and to the challenge of disentangling the roles of potential risk factors. Given that one highly important function of the epidermis is to form an epithelial physical barrier to protect against a diverse array of environmental stresses, physical factors including temperature, UV radiation, humidity, and days indoors deserve detailed examination. The geographical variances in incidences within the United States lend further credence to this line of enquiry. It is therefore satisfying to see that in this issue of the *Journal* Silverberg *et al.* (2013) present a large-scale ecological examination of the relationship between eczema prevalence and the physical environment. Their data clarify and re-emphasize the roles of environmental factors in the pathogenesis of eczema.

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Eczema and the physical environment: what is the epidemiological evidence?

This large ecological study assessed the relationship between climatic factors assessed at the level of the state and the prevalence of eczema. Eczema prevalence was determined as part of the National Survey of Children's Health in the United States. Silverberg *et al.* (2013) conclude that outdoor climatic conditions influence the prevalence of eczema in the United States. Specifically, they demonstrate reduced eczema prevalence in areas with high relative humidity, high UV index, high mean temperature, reduced precipitation, and fewer days of central heating use. The strengths of this study are its large size, the fact that it is population based, involving 79,667 individuals across the United States, with 10,072 reporting the presence of eczema. In addition, the National Survey of Children's Health used computer-assisted telephone interviews that included interviewer training and quality control measures. The ecological design is suitable for hypothesis generation, which can lead to hypothesis testing, using appropriate study designs. A limitation of this study is the use of an ecological design, which does not permit inference about the impact of climatic factors on eczema at an individual level. This problem is known as the ecological fallacy or ecological bias, defined by Rothman as the failure of associations seen at one level of grouping to correspond to effect measures at the grouping level of interest (Rothman *et al.*, 2008). Hence in this study, we can conclude that there appears to be an association between eczema prevalence with state levels and climatic factors. However, we cannot

Clinical Implications

- Although atopic eczema has a strong genetic component, the rise in incidence in recent decades points to significant environmental components as well.
- The investigators present a large-scale ecological examination of the relationship between eczema prevalence and the physical environment (including humidity, temperature, and UVR).
- The data of Silverberg *et al.* (2013) clarify and re-emphasize the roles of these environmental factors in the pathogenesis of eczema.

conclude definitively that at an individual level exposure to climatic factors, e.g., humidity, UV, or central heating, impacts the likelihood of developing eczema, the possibility of developing chronic disease, or the onset of flares. Another important limitation highlighted by the authors is the lack of specificity of the eczema definition used and hence the possibility of misclassification. In fact, the questionnaire actually determined the prevalence of ''eczema or other kinds of skin allergy'' (Flohr *et al.*, 2009). The authors also present the results of analyses of seasonality in Supplementary Tables 1 and 2 of their article; these should be interpreted with caution, given that the outcome being reported is the period prevalence of eczema or other allergies. Finally, the relatively low response rates (46.7%) for the NSCH survey and its restriction to those with landline telephones may have introduced some selection bias.

Weiland *et al.* (2004) assessed associations between eczema prevalence and climate in an ecological study using validated diagnostic criteria as part of the International Study of Asthma and Allergies in Childhood. They reported positive correlations between eczema and latitude and negative associations with mean annual outdoor temperature, with a tendency toward a negative association between eczema symptoms and mean relative humidity indoors. These findings could be consistent with those observed by Silverberg *et al.* (2013) as it is likely that mean indoor relative humidity relates to central heating use. Vocks *et al.* (2001) studied an open cohort of individuals in Davos and demonstrated an inverse relationship between higher outdoor temperatures and levels of itch, whereas Krämer *et al.* (2005) showed seasonal variations in a panel of children with eczema, and they proposed, as a *post hoc* hypothesis, that winter and summer types of eczema existed (Vocks *et al.*, 2001; Krämer *et al.*, 2005) A small-scale exploratory study undertaken by our group showed associations between eczema flares and heat and dampness (Langan *et al.*, 2006). However, our hypothesis testing study with individual measures of exposure (relative humidity, temperature, and radiation) did not reveal associations between eczema flares and climatic factors, with the exception of an association between shampoo exposure and eczema worsening in cold weather (Langan *et al.*, 2009). One of the unique findings of this study was that we demonstrated that a combination of any three exposures acting in concert was associated with worsening of eczema.

Migrant studies provide strong evidence that environmental factors have a role in eczema prevalence. One such study, using standardized diagnostic criteria, showed that the prevalence of eczema in black Caribbean children in London was 14.9% compared with 5.6% in Kingston, Jamaica (Burrell-Morris and Williams, 2000). Similar studies in different populations and ethnicities demonstrate large differences in eczema prevalence for children migrating from warm countries to cooler climates, with migrant populations developing rates of eczema that are the same or higher than that of the resident population. A major challenge is how to disentangle climatic factors from other environmental exposures in order to explain these differences.

How may environmental factors influence AD pathogenesis and prevalence?

The epidermis functions as an important physical barrier to environmental danger. The physical epidermal barrier to water loss, toxins, microbial invasion, and allergen exposure is dependent primarily on an intact and functioning stratum corneum (SC) and secondarily on the tight junctions within the stratum granulosum.

The discovery of loss-of-function mutations in *FLG* in atopic eczema in 2006 renewed interest in the role of the epithelial barrier in eczema pathogenesis (Irvine *et al.*, 2011). A single loss-of-function mutation in *FLG* confers an approximate 3.3-fold risk of eczema, and even a small percentage difference in filaggrin expression because of intragenic copy number variation causes a significant increase in eczema risk (Brown *et al.*, 2012). Thus, environmental factors that interact with this key barrier protein could amplify eczema risk. The SC is required to adapt to severe physical environmental changes, especially to wide changes in temperature, humidity, and UV exposure. To this end, the SC has sophisticated homeostatic mechanisms, only some of which are understood, but dry environmental conditions certainly have an adverse effect on skin barrier function (Denda, 2000), and filaggrin appears to be an important factor in this process. In their classic 1986 paper, Scott and Harding (1986) showed that a reduction in epidermal water content would trigger filaggrin proteolysis. This was most obvious at transition from an aqueous to an arid environment at the time of birth, but the effect was replicated in adult rat skin. Under occlusion (100% epidermal humidity levels), filaggrin processing was inhibited. More recent work on *hairless* mice has shown that moving from a high-humidity environment to a low-humidity environment led to profound changes in filaggrin physiology. Low-humidity environments seem to reduce filaggrin expression by an unknown mechanism (Katagiri *et al.* 2003). The epidemiological data and these animal studies point in a consistent direction. There is new clinical evidence to

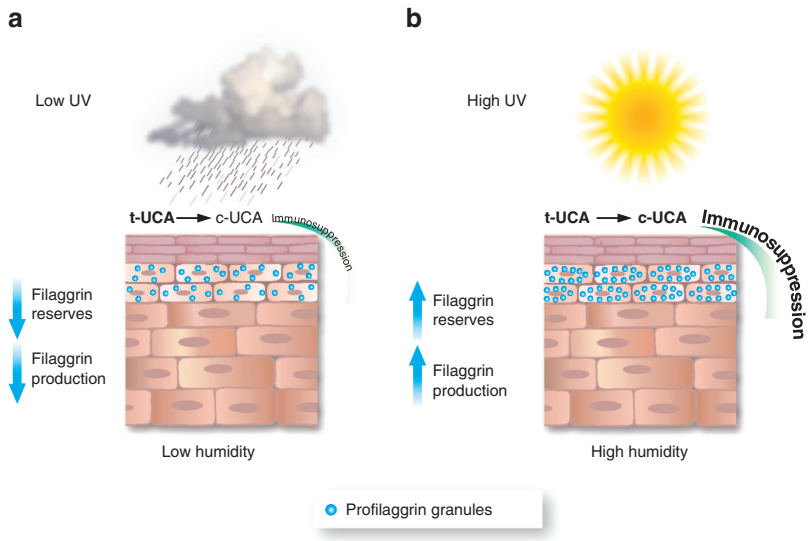

Figure 1. Possible interactions between humidity, UV light, and filaggrin. While the effect of the physical environment on filaggrin expression and processing has not been well studied in humans, mouse studies have generated data that allow hypothesis generation in this area. There are many possible complex and interactive relationships between low-humidity/low-UV environments and filaggrin. Low environmental humidity may both directly decrease filaggrin production and secondarily exhaust filaggrin reserves (**a**). UV light converts the filaggrinbreakdown product *trans*-urocanic acid (t-UCA) to the immunosuppressive *cis*-urocanic acid (c-UCA) isoform (**b**). Thus this environmental combination may act in concert to initially drive down stratum corneum natural moisturizing factor content, promoting dry skin and a cascade of events leading to atopic dermatitis. As a secondary effect, low levels of t-UCA in low-humidity environments would provide less substrate for production of c-UCA, a natural immunosuppressant in the skin. This reaction is known to be less efficient in low-UV environments, thus compounding the effect.

support a gene–environment interaction between *FLG* loss-of-function alleles and the physical environment. Bisgaard *et al.* have reported detailed phenotypic information on the patterns of involvement in AD after stratification according to *FLG* loss-of-function mutations (Carson *et al.*, 2012). Areas of the skin more exposed to weathering (dorsum of hands, face) were affected more often in *FLG* mutation carriers, suggesting that the filaggrin-deficient individuals have a reduced ability to adapt to climatic and physical stressors.

The epidermis also has a profound and complex relationship with UV light. Several UV–epidermal interactions may be important in the pathogenesis of eczema, including UV-induced immunosuppression through leukocyte apoptosis, inhibition of antigen-specific priming, suppression of major histocompatibility complex II expression, and induction of tolerogenic cytokines (Schwarz, 2005). UV-induced epidermal DNA methylation could also be mechanistically important. Relatively higher epidermal filaggrin in a higher-humidity environment could have an interactive (additive) effect with UV exposure (Figure 1). The SC filaggrin breakdown product *trans*-urocanic acid is photoprotective, and it is converted to its *cis*-isomer *cis*-urocanic acid by UV radiation. *cis*-Urocanic acid is immunosuppressive, it contributes to the acid mantle of the SC, and it may reduce staphylococcus adherence and proliferation (Miajlovic *et al.*, 2010).

Keeping a focus on the physical environment

Silverberg *et al.* (2013) have reminded us that the pathomechanistic contributions of the physical environment to this complex disease are important and need to be understood in the context of other pathogenic factors including the cutaneous microbiome, genetic, and epigenetic mechanisms, and both cutaneous and systemic innate and adaptive immune responses. Future research is required to try to understand the mechanisms of the association between eczema and climatic and environmental factors. This could lead to opportunities for early intervention and possibly to climate-specific treatment regimens.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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The Pharmacogenetics of Body Odor: As Easy as ABCC?

Sara Brown[1]

***ABCC11* genotype affects apocrine secretory cell function and determines individual body odor phenotype. Rodriguez *et al.* have applied genetic epidemiology using predetermined phenotype data to demonstrate an association between a single-nucleotide polymorphism (rs17822931) and the human behavior of deodorant application. Individuals with the *ABCC11* genotype predicting a nonodorous phenotype report a significantly lower frequency of deodorant use.**

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Personalized medicine

The combination of knowledge from the fields of cell biology, molecular genetics, and epidemiology creates a powerful tool with which to investigate interactions between human genotype and the requirement for, or response to, treatment. Such personalized medicine may be applied to optimize our use of pharmacological interventions. The report in this issue, Rodriguez *et al.* (2013), relates to the influence of one genetic variant on body odor. The research team has built on knowledge of genetic determinants of apocrine cell biology with the addition of genetic epidemiology, to describe a novel link between genetic variation and human behavior.

The ATP-binding cassette, subfamily C, member 11 (ABCC11)

ABCC11 (OMIM*607040), a gene on chromosome 16q21.1, encodes a protein from the ATP-binding cassette super-family with sequence homology to multidrug-resistant proteins (RefSeq Summary NM_145186); it includes two ATP-binding domains and two transmembrane regions (Tammur *et al.*, 2001). Multiple alternatively spliced variants are expressed in different human tissues, including the liver, gastrointestinal tract, kidney, breast, and skin (Human Protein Atlas, 2012). The ABCC11 protein is involved in the transport of small molecules across apical membranes, in a process that is most well characterized in apocrine secretory cells (Martin *et al.*, 2010), (Figure 1). A common nonsynonymous single-nucleotide polymorphism (SNP) in *ABCC11* and also a rarer 27-base-pair deletion are responsible for the determination of human ear wax type with a Mendelian pattern of inheritance (Yoshiura *et al.*, 2006). Individuals carrying the AA genotype of SNP rs17822931 have nonfunctional ABCC11 resulting in dry or ''rice-bran'' ear wax, whereas those carrying the dominant G allele (genotype GA or GG) produce functional ABCC11 protein, resulting in wet or ''honey type'' ear wax. The rs17822931 SNP genotype also largely determines the phenotype of human body odor and this follows a surprisingly simple pattern of Mendelian inheritance, as functional ABCC11 is essential for the biochemical formation of human axillary odor (Martin *et al.*, 2010).

Applied genetic epidemiology

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large population-based epidemiological study from the southwest of England. ALSPAC has made a significant contribution to the investigation of genetic and environmental factors in disease since its launch in 1991 (Pearson, 2012). Rodriguez *et al.* have made use of the resource available in ALSPAC to test the hypothesis that deodorant usage is determined by *ABCC11* genotype.

The group studied more than 6,000 mothers, over 7,000 children, and 5,000 male partners (presumed to be the children's fathers) for whom *ABCC11* genotype and body odor phenotype data were available. One limitation that is inherent to such large epidemiological studies is that data collected prospectively are necessarily limited by the use of predetermined questionnaires. The quantification of deodorant use was based on self-reported frequency of deodorant application by males during their partner's pregnancy and by mothers 8 months after birth, each in response to a question under the

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