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Childhood Eczema and the Importance of the Physical Environment

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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.

Journal of Investigative Dermatology (2013) **133,** 1706–1709. doi:10.1038/jid.2013.128

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