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Childhood eczema and the importance of the physical environment

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Eczema (also known as atopic eczema or atopic dermatitis) is the commonest chronic inflammatory disease of early childhood in the developed world and is associated with significant morbidity in both childhood and adulthood.¹⁻³ The incidence and prevalence of eczema has increased significantly in the last 3 decades, with some suggestion that this rise in incidence has plateaued in recent years.⁴ While eczema has a strong genetic component that is slowly becoming more clearly understood, the rise in incidence in recent decades points to a very significant environmental component. The so-called hygiene hypothesis has been extensively examined 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 spend large periods of their working lives dealing with children and adults with atopic dermatitis will be aware that the physical environment features large in their experience of this disease. Familiar examples are the child who flares when returning back to school in September, an adult who struggles to deal with low humidity on long haul flights; patients with problematic eczema while living in northern Europe, who dramatically clear on holiday in southern Europe or South East Asia. While there may be additional factors such as psychological stress or changes in the microbiome or allergen exposures to explain these commonly noted phenomena; atmospheric humidity and UV exposure would seem obvious physical factors that deserve more exploration. The lack of definitive epidemiologic data implicating physical environmental factors in AD is largely due to the absence of suitably sized cohorts powered to examine these factors and the challenge of disentangling the roles of potential risk factors. Given that one highly important function of the epidermis is to form a primary epithelial physical barrier that is required to adapt to often very divergent environmental stresses; physical factors including temperature, UV radiation, humidity and days indoors deserve detailed examination. The

geographical variance in incidence within the US lends further credence to this line of enquiry. It is therefore very satisfying to see that in this edition of the *Journal* Eric Simpson, Jon Hanifin and Jonathan Silverberg present a very large scale ecological examination of the relationship between eczema prevalence and the physical environment. Their data both clarify and reemphasise the role of these environmental factors in the pathogenesis of eczema.

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 US. Silverberg *et al* conclude that outdoor climatic conditions influence the prevalence of eczema in the US. 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 the large size of the study, the fact that it is population-based involving 79,667 individuals across the US with 10,072 reporting the presence of eczema. In addition, the National Survey of children's Health utilised computer assisted telephone interviews with 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.⁵ Hence in this study, we can conclude that there appears to be an association between eczema prevalence at state level and climatic factors. However, we cannot definitively conclude 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 development 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; the questionnaire actually determined the prevalence of “eczema or other kinds of skin allergy”.⁶ They also present in supplementary tables 1 and 2 the results of analyses of seasonality; 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%) of the NSCH survey and restriction to those with landline telephones may have introduced some selection bias.

Weiland *et al* 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 (ISAAC) study. They reported positive correlations between eczema and latitude and negative associations with mean annual outdoor temperature with a tendency for a negative association of eczema symptoms with mean relative humidity indoors.⁷ These findings could be consistent with those observed by Silverberg *et al* as it is likely that mean indoor relative humidity relates to central heating use. Vocks *et al* studied an open cohort of individuals in Davos and demonstrated an inverse relationship between increasing outdoor temperature and levels of itch, while Kramer *et al* showed seasonal variations in a panel of children with eczema and proposed as

a *post hoc* hypothesis that winter and summer types of eczema existed.^{8,9} A small scale exploratory study undertaken by our group showed associations between eczema flares and heat and damp.¹⁰ However, our hypothesis testing study with individual measures of exposure (relative humidity, temperature and radiation) did not observe associations between eczema flares and climatic factors, with the exception of an association between shampoo exposure and eczema worsening in cold weather.¹¹ 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 play a role in eczema prevalence; one such study using standardised diagnostic criteria showed that the prevalence of eczema in Black Caribbean children in London was 14.9% compared to 5.6% in Kingston, Jamaica.¹² Similar studies in different populations and ethnicities demonstrate large differences in eczema prevalence for children migrating from warm countries to cooler climates with the migrant population developing rates of eczema which are the same or higher than the resident population. A major challenge is how to disentangle climatic factors from other environmental exposure in order to explain these differences.

How might environmental factors influence atopic dermatitis 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 outer stratum corneum (SC) and secondarily on the tight junctions within the stratum granulosum.

The discovery of loss-of-function mutations in *FLG* in eczema in 2006 renewed interest in the role of the epithelial barrier in eczema pathogenesis.¹³ A single loss-of-function mutation in *FLG* confers an approximate 3.3 times risk of eczema and even a small percentage difference in filaggrin expression due to intragenic copy number variation causes a significant increase in eczema risk.¹⁴ Thus environmental factors that interact with this key barrier protein could amplify eczema risk. The stratum corneum is required to adapt to severe physical environmental changes; in particular 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,¹⁵ and filaggrin appears to be an important player in this process. In their classic 1986 paper, Ian Scott and Clive Harding showed that a reduction in epidermal water content triggered filaggrin proteolysis.¹⁶ This was most dramatic at the birth transition between an aqueous and arid environment 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 moved between the extremes of a high humidity environment and a low humidity environment demonstrated profound changes in filaggrin physiology in relation to environmental humidity. Low humidity environments seem to reduce filaggrin expression by a mechanism unknown.¹⁷ The epidemiological data and these animal studies point in a consistent direction. There is now some clinical evidence to support a gene:environment interaction between *FLG* loss-of-function alleles and the physical environment. Recently, Hans Bisgaard and colleagues reported detailed phenotypic

information on the patterns of involvement in atopic dermatitis stratified by *FLG* loss-of-function mutations.¹⁸ Areas of the skin more exposed to weathering (dorsum of hands, face) were affected more often in the *FLG* mutation carriers, suggesting that these filaggrin deficient individuals had reduced ability to adapt to climactic 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 MHC II expression and induction of tolerogenic cytokines.¹⁹ 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 (t-UCA), is photo protective and is converted to its cis isomer, c-UCA by UV light. c-UCA is immunosuppressive, contributes to the acid mantle of the SC and may reduce staphylococcus adherence and proliferation.²⁰

Keeping a focus on the physical environment

Silverberg and colleagues 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 mechanism for the observed

association between eczema and climatic and environmental factors. This could lead to opportunities for early intervention and possibly climate-specific regimens if appropriate.

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Figure 1. Putative interactions between humidity, UV light and filaggrin.

There are many possible complex and interactive relationships between these physical factors and filaggrin. Based on murine data, low humidity leads to reduced filaggrin production and lower filaggrin reserves. This should lead to reduced filaggrin breakdown products in the stratum corneum including t-UCA. Exposure to UV light transforms t-UCA to its isomer c-UCA, which in turn is immunosuppressive. Low UV light means less c-UCA in the stratum corneum.

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