

Correspondence

Xerosis is latitude dependent and affects the propensity to develop atopic disease

To the Editor:

We read with interest "Prevalence of eczema and food allergy is associated with latitude in Australia."¹ On the basis of cross-sectional questionnaire data, Osborne et al¹ show that the prevalence of atopic dermatitis (AD) and certain food allergies in 4- to 5-year-old and 8- to 9-year-old children varied significantly with their latitude of residence and that the prevalence was highest in the cooler, temperate climate. They interpreted their results as likely due to enhanced vitamin D status in children living nearest the equator, though serum 25-hydroxyvitamin D levels were not measured. While it is possible that the observed differences in atopic disorders could reflect differences in ambient ultraviolet exposure, a much more likely possibility is that the 4500-km long north-south border of Australia dictates latitude-dependent differences in environmental humidity that affect skin hydration and barrier function.

Loss-of-function mutations in the filaggrin gene commonly cause the dry and scaly skin of ichthyosis vulgaris and strongly predispose to both AD and food allergy. Reduced filaggrin expression impairs barrier function, while lowering the threshold of dermatitis. Yet, even AD without filaggrin gene mutations displays reduced filaggrin, in part due to T_H2 cytokine-induced downregulation of this protein.² Filaggrin is hydrolyzed in a humidity-sensitive fashion to its constituent amino acids and their deiminated carboxylic acid derivatives, collectively termed "natural moisturizing factor."³ This process normally begins as environmental humidities decline below 80% and accelerates as humidities continue to decline. Reduced quantities of filaggrin, whether primary or secondary, account for the prominent dry skin in AD, which steepens the gradient of water loss, accelerating the barrier abnormality in AD.⁴ Even in heterozygous filaggrin gene mutation carriers, little residual filaggrin can be detected, presumably due to further humidity-driven consumption of this protein.

Consumption of filaggrin likely accounts for wintertime flares of AD in temperate climates, driven by low environmental humidities (often <5%), due to forced air heating.⁴ In mice, 48 hours of exposure to a reduced humidity imposes stress sufficient to cause epidermal hyperplasia and mast cell degranulation.⁵ Accordingly, the observed latitude-dependent changes in AD in Australia likely reflect differences in environmental humidities in Melbourne versus subtropical in the north. Similar latitude-dependent variations in the incidence and severity of AD have been described in Finns living either in Helsinki or above the Arctic Circle.⁶

While it is true that sunlight often benefits AD, it does so primarily by attenuating epidermal hyperplasia and dermal inflammation. Sun exposure can also decrease psychological stress, another exogenous stressor, known to exacerbate AD.⁷ As for vitamin D, topical analogs of 1,25(OH)₂ vitamin D3 actually exacerbate AD, presumably by stimulating T_H2 cytokine production and/or the negative effects of vitamin D on barrier function.⁸ Finally, the Australian study¹ did not provide details on oral supplementary vitamin D intake, and therefore it is possible that vitamin D supplements recommended for children could also have reduced the possible likelihood that their results reflect effects of ultraviolet radiation on vitamin D status.

We thank Ms Joan Wakefield for proofreading the manuscript.

Jacob P. Thyssen, MD, PhD^{a,b,c}

Peter M. Elias, MD^{a,b}

From ^athe Dermatology Service, Veterans Affairs Medical Center, and ^bthe Department of Dermatology, University of California at San Francisco, San Francisco, Calif, and ^cthe Department of Dermato-Allergology, National Allergy Research Centre, Copenhagen University Hospital Gentofte, University of Copenhagen, Hellerup, Denmark. E-mail: jacpth01@geh.regionh.dk.

Disclosure of potential conflict of interest: J. P. Thyssen declares that he has no relevant conflicts of interest. P. M. Elias has received research support from the National Institutes of Health.

REFERENCES

1. Osborne NJ, Ukoumunne OC, Wake M, Allen KJ. Prevalence of eczema and food allergy is associated with latitude in Australia. *J Allergy Clin Immunol* 2012;129:865-7.
2. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, De Benedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007;120:150-5.
3. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol* 1986;115:84-92.
4. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;121:1337-43.
5. Denda M, Sato J, Tsuchiya T, Elias PM, Feingold KR. 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;111:873-8.
6. Remes ST, Korppi M, Kajosaari M, Koivikko A, Soininen L, Pekkanen J. Prevalence of allergic rhinitis and atopic dermatitis among children in four regions of Finland. *Allergy* 1998;53:682-9.
7. Garg A, Chren MM, Sands LP, Matsui MS, Marenus KD, Feingold KR, et al. Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders. *Arch Dermatol* 2001;137:53-9.
8. von BS, Jensen JM, Fartasch M, Proksch E. Topical vitamin D3 derivatives impair the epidermal permeability barrier in normal mouse skin. *Dermatology* 1997;194:151-6.

<http://dx.doi.org/10.1016/j.jaci.2012.06.041>