

# ECZEMA AND ALLERGIC SENSITISATION - WHAT IS THE LINK?

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## ABSTRACT

The association between eczema (atopic eczema, atopic dermatitis) and atopy (allergic sensitisation) has been debated for years. There is considerable variation between populations with stronger associations seen in industrialised vs low-income countries and hospital vs community settings. Up to two-thirds of children with eczema are not sensitised. The likelihood of allergic sensitisation increases with early-onset disease and disease severity. Sensitised children with eczema are more likely to develop asthma and hay fever. The current hypothesis is that allergic sensitisation to food and aero-allergens occurs across the impaired skin barrier seen in eczema, making this an important target for therapeutic intervention, either through primary eczema prevention, e.g. by using moisturisers in high-risk children from birth, or through proactive control of early-onset disease. Intervention studies are now required to test this hypothesis further.

## INTRODUCTION

Since the discovery of immunoglobulin E (IgE) in the late 1960s, there has been an ongoing debate about the role of allergic sensitisation or 'atopy' (raised specific IgE levels and skin-prick test positivity to environmental allergens) in childhood eczema (synonyms: 'atopic dermatitis' or 'atopic eczema'). Many individuals with eczema have very high serum total IgE levels. In addition, eczematous skin is rich in IgE-bearing antigen-presenting cells, and topical application of allergens, such as house-dust mite (HDM), can induce skin inflammation in sensitised individuals, as demonstrated in the atopy patch test. But does allergic sensitisation really play a key role in eczema aetiology? In other words, is sensitisation to environmental allergens a primary event in the development of childhood eczema or is atopy an epiphenomenon of the disease process?

Assuming a uniform causal role for allergic sensitisation, one would expect a strong association between atopy and childhood eczema with little variation between populations. There should also be a dose-response relationship between the degree of allergic sensitisation

(number of positive skin-prick tests or raised specific IgE levels) and eczema probability, and, most importantly, allergic sensitisation should occur before clinical eczema develops. This review article summarises our current understanding of the links between eczema and allergic sensitisation and highlights the clinical implications.

## THE STRENGTH OF THE ASSOCIATION BETWEEN ATOPY AND CHILDHOOD ECZEMA

A systematic review has shown that the prevalence of allergic sensitisation among eczema sufferers ranges widely, between 7% and 75%.<sup>1</sup> Whereas up to three-quarters of hospital patients are sensitised, in community settings sensitisation rates can be below 10%.

## THE IMPORTANCE OF DISEASE SEVERITY

One explanation for this discrepancy is disease severity, with more severe cases being seen in hospital departments.<sup>2</sup> It is likely that severely inflamed eczematous skin allows easier contact between IgE-bearing antigen-presenting cells and environmental allergens across an impaired skin barrier. Indeed, the majority of epidemiological studies that have examined the link between eczema severity and allergic sensitisation have confirmed a significant positive association. For instance, the Early Prevention of Asthma in Atopic Children (EPAAC) study conducted among over 2 000 children aged from 13 to 24 months with established moderate to severe childhood eczema from 10 European countries, Australia and South Africa demonstrated that the frequency of positive specific IgE responses to a standard panel of food and inhalant allergens increased with greater eczema severity.<sup>3</sup> Similar findings have been reported with regard to food sensitisation to cow's milk, egg, and peanut during the first year of life.<sup>4</sup>

## THE IMPACT OF GEOGRAPHY

Another factor that explains part of the varying degrees of association between eczema phenotype and sensitisation is geography. The EPAAC study<sup>3</sup> has shown great variation in sensitisation rates to foods and aeroallergens among children with eczema between countries, with particularly high prevalences of atopic eczema found in Australia (83%), the UK (79%), and Italy (76%), whereas infants with eczema from Belgium had significantly lower sensitisation rates (52%). Some of these differences may be due to varying degrees of environmental allergen exposure, but other lifestyle-related influences are likely to be involved, as a number of population-based cross-sectional studies from across the globe have suggested a significantly stronger association between allergic sensitisation and eczema in developed compared to developing nations.<sup>3</sup>

As part of phase II of the International Study of Asthma and Allergies in Childhood (ISAAC) around 30 000

8-12-year-old schoolchildren from 20 affluent and non-affluent countries were physically examined for flexural eczema, using the same standardised diagnostic criteria and physical examination.<sup>5</sup> Children were also skin-prick tested with a panel of six common environmental allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat, *Alternaria tenuis*, mixed tree and grass pollen). Investigators were encouraged to add allergens of local relevance. Large variations in the proportion of allergic sensitisation among children with flexural eczema were observed across study centres (Fig. 1). Not a single child with eczema was sensitised in Ghana or Palestine, while 74% of eczema sufferers in Hong Kong had at least one positive skin-prick test. The odds of allergic sensitisation in children with flexural eczema vs healthy controls varied correspondingly between 0.74 (95% confidence interval (CI) 0.31-1.81) in Pichincha (Ecuador) and 4.53 (95% CI 1.72-11.93) in Madrid (Spain).

It is interesting to note that ISAAC found a significant association between a country's socio-economic status (based on World Bank criteria) and the strength of the association between atopy and flexural eczema, with significantly stronger associations seen in affluent compared with non-affluent settings (combined age- and sex-adjusted odds ratio (OR)<sub>affluent</sub> = 2.69 [95% CI 2.31-3.13] vs OR<sub>non-affluent</sub> = 1.17 [95% CI 0.81-1.70]).

However, there was a linear relationship between the number of positive skin-prick test responses and the probability of having flexural eczema in the majority of affluent study centres. While the ISAAC study results overall point towards an association between allergic sensitisation and childhood eczema due to shared aetiologies linked to a 'western lifestyle' and affluence rather than direct causality, causality cannot be excluded where a dose-response relationship between the number of positive skin-prick tests and flexural eczema probability was observed.

## THE TEMPORAL RELATIONSHIP BETWEEN ATOPY AND CHILDHOOD ECZEMA

The main dilemma is that the majority of studies performed to date are cross-sectional in design. Only longitudinal and intervention studies can infer causality, however, and what is needed are well-designed birth cohorts that closely investigate the temporal relationship between allergic sensitisation and eczema phenotype. An Australian cohort study among 500 at-risk children followed up from birth until age 5 found that allergic sensitisation at 18 months was not associated with eczema at 5 years (adjusted OR = 0.78, 95% CI 0.23-2.64).<sup>6</sup> In the same cohort eczema phenotype at 18 months was a predictor of allergic sensitisation at 5 years (adjusted OR = 1.67, 95% CI 1.20-2.33), suggesting

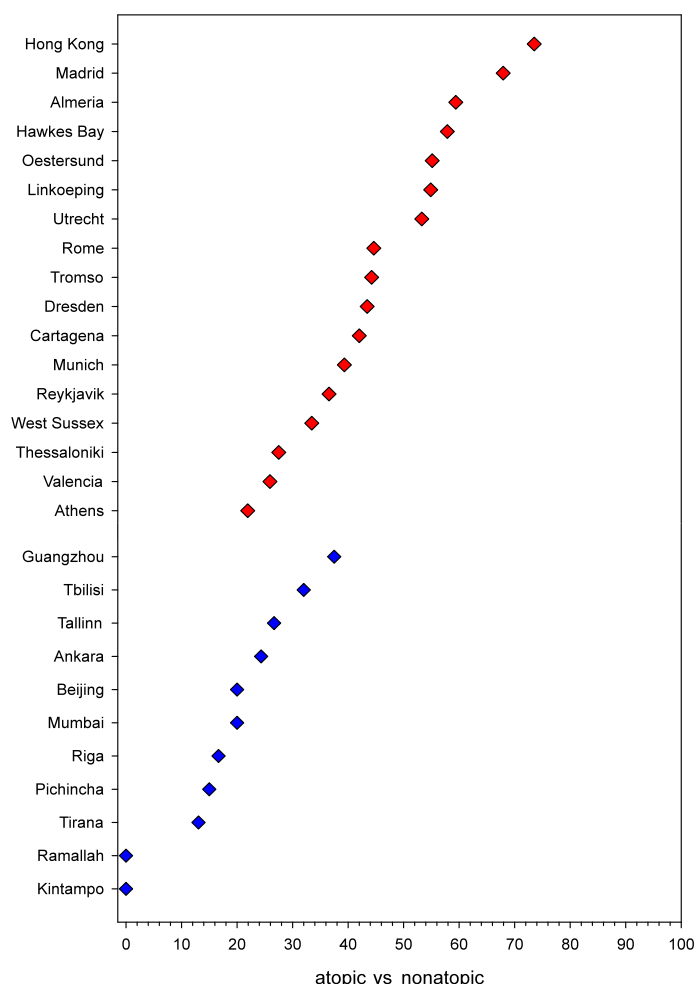


Fig. 1. Proportion of atopy among children with flexural eczema for all study centres. Study centres are arranged in order of proportion of atopy, separately for affluent (red) and non-affluent (blue) countries, based on gross national per capita income and World Bank criteria.

that sensitisation is a secondary rather than primary phenomenon in childhood eczema. This is in keeping with findings from a UK birth cohort among almost 600 children, where no clear relationship between levels of HDM exposure at 2 months of age, and eczema and HDM sensitisation risk at 8 years could be found.<sup>7</sup> In fact, higher levels of exposure to HDM at 2 years of age appeared to confer a degree of protection on later eczema and sensitisation risk, although results missed statistical significance, and require replication.

## THE 'ATOPIC MARCH'

A number of studies have suggested that early allergic sensitisation in childhood eczema predicts later food allergy and allergic respiratory disease, and some have gone so far to suggest that children with eczema almost invariably go through the so-called 'atopic march'.<sup>8</sup> This concept was originally based on cross-sectional study evidence and only a few prospective cohort studies have been conducted. A recent meta-analysis of 13 longitudinal studies suggested a pooled OR of 2.14 (95% CI, 1.67-2.75) for the risk of asthma after eczema, compared

with children without eczema, with only about a third of eczema sufferers developing asthma at a later stage.<sup>9</sup> Some studies have shown that only children with eczema plus sensitisation have a higher risk of allergic respiratory disease,<sup>10</sup> but, as mentioned above, similar observations have even been made in those with allergic sensitisation alone.<sup>1,8</sup> To complicate matters further, the Melbourne Atopy Cohort Study, a prospective birth cohort among 552 infants with a family history of allergic disease, has recently suggested that allergic sensitisation to foods at 6 months of age can predict eczema development up to age 7 (hazard ratio (HR) = 1.63, 95% CI 1.13-2.35) in those who develop eczema after the first 6 months of life, which would be in keeping with a causal relationship between atopy and later childhood eczema. In infants who get the disease before 6 months of age the risk of allergic sensitisation within the first 2 years of life was also significantly increased (HR = 3.47, 95% CI 1.65-7.32).<sup>10</sup>

### SKIN-BARRIER IMPAIRMENT - THE MISSING LINK?

The recent discovery of the common loss-of-function variants in the filaggrin (FLG) gene, encoding the epidermal barrier protein filaggrin, and the strong association with eczema, as well as other atopic diseases, have led to a heightened interest in the role of skin-barrier impairment in the development of eczema, allergic sensitisation and also food and respiratory allergies,<sup>11,12</sup> and this may provide the missing link between allergic sensitisation and childhood eczema.

The current hypothesis is that in individuals without a skin-barrier defect, there is full integrity of the epidermis, marked by minimal transepidermal water loss (TEWL) and adequate protection against microbes and environmental allergens. However, where people carry a skin-barrier gene mutation, such as a loss-of-function mutation in the FLG gene, TEWL is increased (Fig. 2). Environmental factors, such as frequent use of detergents<sup>13</sup> and water hardness,<sup>14</sup> are associated with an increase in eczema risk and are likely to contribute to skin barrier breakdown through reduction in natural moisturising factor, increase in skin pH and a subsequent upregulation in protease activity.<sup>15</sup> Animal work suggests that antigen-presenting cells in the superficial epidermis can make contact with environmental allergens, such as HDMs but also food protein, leading to sensitisation, which can trigger eczema flares and may also be an important precursor of food and respiratory allergies.<sup>16,17</sup> FLG loss-of-function mutations are consistently associated with eczema in the context of allergic sensitisation rather than the non-atopic phenotype of eczema with regard to both aeroallergens and foods.<sup>18-22</sup> A case-control study in humans also demonstrated a positive association between FLG mutation inheritance, eczema and challenge-proven peanut allergy in school children. The association between eczema and peanut allergy remained significant even after adjustment for FLG status.<sup>23</sup> Similar observations have recently been made in babies as young as 3 months of age, not only in relation to peanut but also other foods.<sup>24</sup> Furthermore, the same study found a strong correlation with eczema

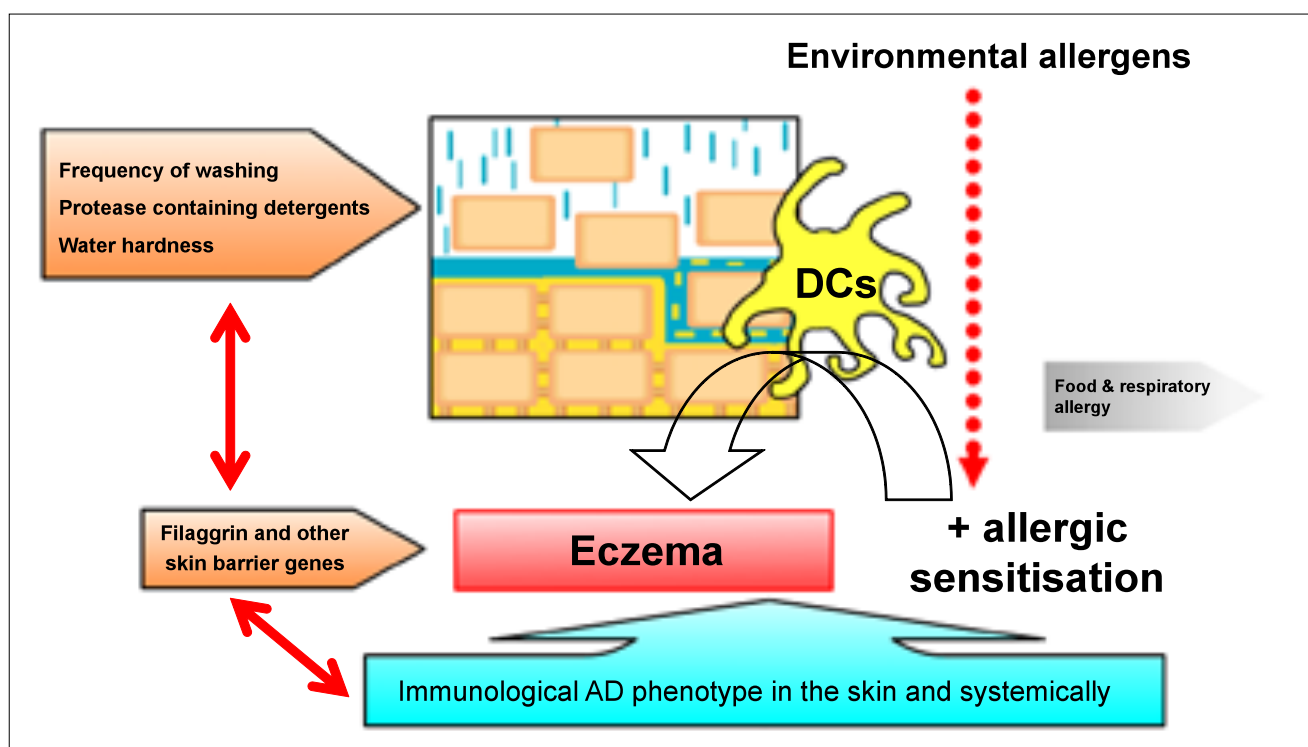


Fig. 2. The interplay between skin-barrier-related environmental, genetic and immunological factors in the development of eczema. DCs - dendritic cells.

severity in addition to skin barrier impairment (raised TEWL), further supporting the concept that the skin barrier can act as an important mediator of allergic sensitisation. In this paradigm, allergic sensitisation is mainly a secondary phenomenon in eczema rather than a primary cause.

## IMPLICATIONS FOR CLINICAL PRACTICE

In keeping with this paradigm is that even the most rigid methods to reduce HDM exposure have not shown a convincing effect on eczema activity, including in HDM-sensitised individuals.<sup>25</sup> Somewhat paradoxically, a longitudinal study showed that children with allergic mothers who were randomised to receive mite-allergen-impermeable mattress covers actually had a higher occurrence of eczema than those without.<sup>26</sup> While it is possible that other features of the mattress cover exacerbated eczema in this study, there is no evidence to support routine use of HDM-proof bed covers for eczema prevention.

Food antigen avoidance has been similarly disappointing. Although earlier studies suggested an increased risk for eczema in infants exposed to solid foods during the first few months of life,<sup>27</sup> research published since has either shown no association or even the opposite, i.e. that delayed introduction of solids was associated with a higher risk in eczema development.<sup>27</sup> Reverse causation has been proposed as an explanation, but no convincing evidence of parental allergy playing a role in feeding practices has been found.<sup>27</sup> Furthermore, observational data suggest that the gradual decrease in the proportion of young infants given solids at an early age over past decades has coincided with an around threefold increase in childhood eczema.<sup>28,29</sup> There is also mounting evidence from animal research that early introduction of potentially allergenic foods, such as cow's milk, might induce tolerance rather than allergy.<sup>30,31</sup> Similarly, food allergies are a rare phenomenon where allergenic foods, such as peanut, are introduced early into infants' diets compared with settings where allergenic foods are introduced later,<sup>27</sup> and a randomised controlled trial is currently under way in the UK to test whether the introduction of allergenic foods plus concomitant breastfeeding from 3 months of age is able to reduce the risk of developing food allergies and eczema compared to exclusive breastfeeding for 6 months (Enquiring About Tolerance (EAT) study, <http://www.eatstudy.co.uk>).

If allergen avoidance is not a promising strategy to prevent eczema and reduce disease severity, what else can we as clinicians advise patients? As outlined above, skin-barrier dysfunction appears to play a major role not only in eczema development but also allergic sensitisation to both foods and aeroallergens.<sup>32</sup>

Intensive emollient use in early life in addition to soap and detergent avoidance may therefore be a powerful method of primary prevention, especially in children who carry skin-barrier gene mutations and show early signs of skin-barrier impairment, such as skin dryness. This idea has already been trialled in a pilot study with encouraging results and a large-scale randomised controlled trial is now under way (Barrier Enhancement for Eczema Prevention (BEEP) trial, <http://www.beeperstudy.org/>).<sup>33</sup>

Others are working on new barrier-enhancing topical and systemic preparations to upregulate FLG expression in the epidermis and improve skin-barrier function as a potential means of disease prevention but also treatment.<sup>34-36</sup> In addition, proactive ('aggressive') topical anti-inflammatory therapy in early-onset eczema might not only be able to effectively reduce the frequency of disease flares, but might also reduce the risk of allergic sensitisation and even help to prevent some children from following the so-called 'atopic march'.<sup>37</sup> Intervention studies are clearly needed to prove this concept.

### Declaration of conflict of interest

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