

The impact of allergy on atopic eczema from data from epidemiological studies

Torsten Schäfer

Institute of Social Medicine, Lübeck University, Lübeck, Germany

Correspondence to Professor Torsten Schäfer, MPH, Scharbeutzer Straße 23, 23684 Scharbeutz, Germany
E-mail: torsten.schaefer4@gmx.de

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Purpose of review

We aimed to review the association between atopic eczema and allergic sensitization and food allergy and its determinants on the basis of current epidemiological literature.

Recent findings

About 50% of children with atopic eczema and about 35% of adults are sensitized to common allergens. Gender, geography (e.g. East and West Germany), and socioeconomic factors determine the proportion of atopic eczema with allergic sensitization. Allergic sensitization in addition to atopic eczema obviously increases the risk for respiratory allergies. Sensitization to house dust mites seems to be important and clinically relevant for atopic eczema. Population-based studies on the association between food allergy and atopic eczema are limited. Although, up to 40% of children in hospital settings react to certain food allergens by a flare-up of their atopic eczema, there is an indication that on a population basis, adults with atopic eczema do only react occasionally with a worsening of their skin disease due to food allergens.

Summary

Atopic eczema is not necessarily associated with allergic sensitization. Sensitization to house dust mites, however, seems to be clinically relevant. The impact of food allergy on atopic eczema is difficult to assess on the basis of epidemiological studies and more detailed studies are needed.

Keywords

allergic sensitization, atopic eczema, epidemiology, food allergy

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Introduction

Atopic eczema (or atopic dermatitis) constitutes together with allergic rhinitis and asthma the triad of atopic diseases. The disease manifestation depends on multiple genetic as well as environmental influences. Numerous names have been coined for this most frequent inflammatory skin disease in childhood reflecting different approaches and definitions of its association with atopy. The term ‘atopic eczema or atopic dermatitis syndrome’ [1] has not reached great acceptance and a more recent consensus was achieved by speaking of eczema in a general way allowing for an atopic and nonatopic variant depending on concomitant allergic sensitization [2]. We here suggest to use the term atopic eczema for all flexural forms of eczema, which fulfil typical diagnostic criteria as published by Williams *et al.* [3]. Atopy in this sense rather reflects the genetic predisposition of an association with allergic sensitization. Atopic eczema itself is not an (type I) allergy, but can well be associated with various forms of allergy. As atopic eczema is not defined by an allergic sensitization (often also referred to as allergy or atopy) there are types with and without concomitant allergic sensitization. Terms such as extrinsic and intrinsic type of

atopic eczema have been proposed. In this paper, we speak of atopic eczema with or without allergic sensitization. With allergic sensitization, we mean a positive skin or blood test, which detects allergen specific IgE antibodies. Besides the association of atopic eczema with allergic sensitization, the connection of atopic eczema and food allergy is considered in this review, which tries to mainly consider information from population-based epidemiological studies.

Atopic eczema and allergic sensitization in children

Not all patients with atopic eczema exhibit a positive allergy test with respect to the detection of allergen-specific IgE antibodies. A recent review [4] clearly showed that the proportion of allergic sensitization among patients with atopic eczema varies widely and is higher in a hospital setting (47–75%) as compared with population-based studies (7–78%). The International Study of Asthma and Allergies in Childhood (ISAAC) study [5**] has provided profound data on the association of atopic eczema and allergic sensitization. A total of 28,591 children (aged 8–12 years) from 20 countries

worldwide were clinically examined and flexural eczema was diagnosed according to the ISAAC protocol. In addition, skin prick tests (SPTs) were performed with at least six common aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, *Alternaria tenuis*, mixed tree and grass pollen). As a result, the point prevalence of atopic eczema was as low as 0.4% in Kintampo, Ghana and reached 14.2% in Östersund, Sweden. With respect to the association with allergic sensitization, it was found that none of the children with atopic eczema in Ramallah, Palestine or Kintampo exhibited a positive SPT, whereas 73.9% of the diseased children in Hong Kong did so. The age-adjusted and sex-adjusted odds ratios (ORs) of atopic eczema and allergic sensitization ranged between 0.74 (0.31–1.81) in Pichincha, Ecuador and 4.53 (1.72–11.93) in Madrid, Spain. This association was more pronounced in affluent (2.69, 2.31–3.13) than in nonaffluent countries (1.17, 0.81–1.70) confirming the finding that allergic sensitization is positively associated with the socioeconomic status. These findings were basically the same when using questionnaire data for eczema in the last 12 months or when including locally added allergens of the SPT. Interestingly, for selected counties, a linear association between the number of positive SPT responses and the chance of having atopic eczema could be established.

Differences of the proportions of atopic eczema with (extrinsic) and without (intrinsic) allergic sensitization were also observed between East and West Germany [6]. Prevalence data on atopic eczema based on a dermatological examination had not been available for East and West Germany at this time. It was also unclear what the proportions of extrinsic and intrinsic eczema type were and in how far these could explain differences in the prevalence. Repeated cross-sectional studies in 1991, 1994, and 1997 in 5–6-year-old preschool children of five different locations in West Germany ($n = 2075$) and six in East Germany ($n = 1929$) were carried out. Eczema cases were identified by an actual examination and a SPT with 4–6 common aeroallergens and milk and egg was performed. The overall prevalence of atopic eczema in these children was 10.4%; 26.6% of all children and 41.9% of those with atopic eczema exhibited at least one

reaction in the SPT [OR = 2.21, confidence interval (CI) 1.75–2.80; sensitization in eczema vs. no eczema]. Although 50.4% of the children with eczema in West Germany were sensitized, only 36.5% of the diseased children in East Germany reacted positively in the SPT (OR = 1.77, CI 1.12–2.79). Details are given in Table 1. In an extension of this study including children of the years 1994, 1997 and 2000, the role of allergic sensitization and atopic eczema was investigated with special attention to gender differences [7]. As shown in Table 2, early onset eczema (<2 years of life) in girls was strongly related to allergic sensitization at the age of 6 years (OR 3.7, 95% CI 2.7–5.1) whereas late onset eczema (≥ 2 years of age) was not (OR 1.0, CI 0.7–1.5). Boys were more often sensitized at the age of 6 years than girls (28.3% compared with 20.6%) and early and late onset eczema was related to allergic sensitization. The excess of current eczema in 6-year-old girls compared with boys was related to the intrinsic type. More girls than boys predominately played indoors which was associated with more eczema.

Data from the Early Prevention of Asthma in the Atopic Child (EPAAC) study revealed associations between disease severity and sensitization [8]. The study was designed to test the effect of levoceterizine in young children with atopic eczema aiming at the prevention of asthma. Of 2096 children (aged 13–24 months) with atopic eczema, 55.5% exhibited at least one positive test on specific IgEs to mixed grass and tree pollen, house dust mite (HDM), cat, egg, peanut, milk or *Alternaria*. When dividing the sample by disease severity [SCORing Atopic Dermatitis (SCORAD)] into four groups, it became clear that the proportion of sensitized children increased significantly with increasing disease severity for both inhalant (20.5–45.4%) and food (40.7–61.4%) allergens.

The 1-year period prevalence of atopic eczema based on the Hanifin and Rajka criteria in the Danish Allergy Research Centre cohort was 14.4% for 404 children at 6 years of age [9]. The proportion of children with concomitant allergic sensitization, as defined by positive SPT or s-IgE to at least one of 21 allergens, was 47%.

Table 1 Prevalence of extrinsic and intrinsic atopic eczema in preschool children from East and West Germany in different years of investigation (1991–1997)

Year	West Germany			East Germany			Intrinsic eczema (East vs. West Germany)
	Extrinsic	Intrinsic	Overall	Extrinsic	Intrinsic	Overall	OR (95% CI)
1991	6.9	5.6 (44.8)	12.5	7.8	10.3 (54.2)	19.0	1.61 (0.75–3.50)
1994	5.2	4.9 (48.5)	10.1	5.1	8.3 (61.9)	13.4	1.72 (0.70–4.21)
1997	1.8	3.3 (64.7)	5.1	3.3	8.1 (71.1)	11.4	1.27 (0.44–3.67)
1991–1997	4.8	4.7 (49.5)	9.5	4.9	8.5 (63.4)	13.4	1.77 (1.12–2.79)

CI, confidence interval; OR, odds ratio. Adapted from [6].

Table 2 Allergic sensitization and atopic eczema during different periods of life in boys (n = 2783) and girls (n = 2693) from Germany 1994–2000

	Percentage with eczema	Percentage eczema with atopy at age 6 years	Percentage eczema without atopy at age 6 years	Percentage with atopy at age 6 years	OR (95% CI) association eczema with atopy
Eczema at the day of investigation (point prevalence at the age of 6 years)					
Girls	8.7	2.8	5.9	20.6	2.0 (1.5–2.6)
Boys	6.1	3.1	3.1	28.3	2.7 (2.0–3.7)
All	7.4	2.9	4.4	24.6	2.2 (1.8–2.7)
Eczema in the last 12 months (period prevalence at the age of 6 years)					
Girls	6.5	2.2	4.3	20.6	2.0 (1.5–2.8)
Boys	4.6	2.2	2.4	28.3	2.4 (1.7–3.5)
All	5.5	2.2	3.4	24.6	2.1 (1.6–2.7)
Early onset eczema (first itchy rash before second birthday)					
Girls	5.8	2.7	3.0	20.6	3.7 (2.7–5.1)
Boys	5.2	2.7	2.5	28.3	2.8 (2.0–4.0)
All	5.5	2.7	2.8	24.6	3.2 (2.5–4.0)
Late onset eczema (first itchy rash after second birthday)					
Girls	6.0	1.3	4.7	20.6	1.0 (0.7–1.5)
Boys	4.3	1.8	2.5	28.3	1.9 (1.3–2.8)
All	5.1	1.6	3.6	24.6	1.4 (1.0–1.8)
Persistent eczema (early onset eczema and eczema in the last 12 months)					
Girls	2.4	1.2	1.2	20.6	3.8 (2.3–6.2)
Boys	2.3	1.3	1.0	28.3	3.5 (2.1–5.8)
All	2.3	1.2	1.1	24.6	3.6 (2.5–5.1)

CI, confidence interval; OR, odds ratio. Adapted from [7].

According to a clinical diagnosis, atopic eczema was present in 12.6% of 981 children at the age of 4 years of the Isle of Wight birth cohort study [10]. A total of 42.7% of the children with atopic eczema exhibited at least one positive reaction in the SPT with 12 common aeroallergens and food allergens.

Data from the Melbourne Atopy Cohort Study [11] furthermore indicated that children with atopic eczema and concomitant allergic sensitization are at greater risk of asthma (OR 3.52, 1.88–6.59) and allergic rhinitis (OR 2.91, 1.48–5.71) than those without allergic sensitization. In this study, 620 high-risk infants were followed up to 2 years of age and SPT to six common aeroallergens and food allergens were performed at 6, 12, and 24 months. The same study analysed the role of infantile eczema as a predictor of risk of childhood asthma [12[•]]. Eczema within the first 2 years of life was clearly associated with an increased risk of childhood asthma in boys (adjusted OR 2.45, 95% CI 1.31–4.46) but not in girls (OR 0.88, 95% CI 0.43–1.77, $P = .031$ for interaction) even with adjustment for the effects of early allergic sensitization and wheeze.

Atopic eczema and allergic sensitization in adults

The European Community Respiratory Health Survey (ECRHS) as another large population-based epidemiological study [13^{••}] has provided corresponding information on the association between atopic eczema and allergic sensitization for adults. A total of 8,206 adults (aged 27–56 years) from 25 European centres and Portland, USA were included. Atopic eczema was assessed by a questionnaire following the ISAAC protocol. In addition,

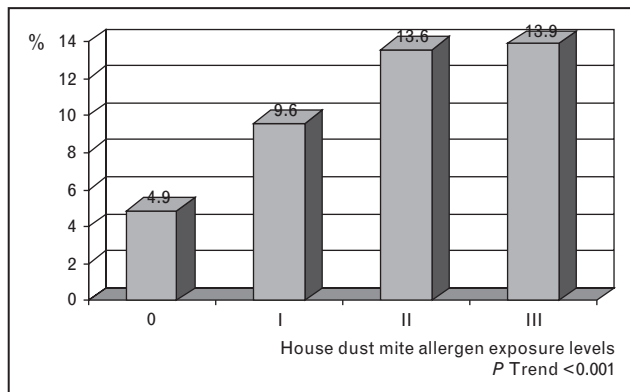
allergen-specific (HDM, cat, grass pollen, and *Cladosporium*) IgE was measured. The 12-month period prevalence of atopic eczema ranged from 2.2% in Switzerland to 17.6% in Estonia, with an overall prevalence of 7.1%. A significant association between any specific IgE and atopic eczema was found after adjustment for several confounders (adjusted OR 1.50, 1.19–1.90). It also became clear that only 35% of the adults with atopic eczema exhibited at least one positive finding in the IgE measurements. Considering the single allergens the strongest association by far was found with *Cladosporium* (adjusted OR 4.79, 2.46–9.31).

Atopic eczema and aeroallergens

An association between atopic eczema and exposure to aeroallergens was reported some 80 years ago when Walker [14] observed that some of his atopic eczema patients had exacerbations after contact with aeroallergens (horse, ragweed and timothy). Later, it was shown that the epicutaneous application of aeroallergens by the atopy patch test can provoke eczematous skin reactions in a subgroup of atopic eczema patients [15].

Our study of preschool children from Lübeck, Germany [16] revealed a significant relationship between the measured HDM allergen content in the dust of the children's homes and the prevalence of atopic eczema. A dermatological examination was performed, assessing atopic eczema on a clinical basis. Allergen exposure to HDMs was measured on the child's mattress using the semiquantitative rapid test Bio-Check Allergen Control (Dräger, Lübeck, Germany). Using allergen-specific antibodies (*D. pteronyssinus*, *D. farinae*), the exposure is

Figure 1 Relationship between prevalence of atopic eczema and measured house dust mite allergen exposure levels (0–III) in households of 606 school beginners



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classified into four categories (0–3), which reflect concentrations of 119, 812, 2,710 and 8,000 ng/g dust (geometric mean), respectively. Finally, 606 children participated and the four exposure categories (0–3) to HDM allergens revealed positive results in 19.7, 37.5, 18.2 and 24.7%, respectively. In 9.3% of the children, an actual atopic eczema was diagnosed and the prevalence increased significantly with increasing category of HDM exposure from 4.9 to 13.9% (Fig. 1).

In another epidemiological investigation in school children, we could demonstrate a significant linear relationship between disease severity as measured by SCORAD and the amount of HDM (*D. pteronyssinus*)-specific IgE [17]. For that purpose, a nested case–control study on atopic eczema was performed based on a cross-sectional study of 2201 East German school children aged 5–14 years. Atopic eczema and its severity were identified by dermatological examination. Total and allergen-specific IgE antibodies to grass and birch pollen, *Cladosporium herbarum*, *D. pteronyssinus*, and cat epithelium in serum were determined and additional information was obtained by a standardized questionnaire. The overall prevalence of actual atopic eczema was 2.5%. Children with atopic eczema were sensitized significantly more often than those without skin disease (75.0 vs. 36.3%, OR = 5.27, CI 2.54–11.15). This was observed for each single allergen. The prevalence of atopic eczema increased significantly with increasing Radio-Allergo-Sorbent-Test (RAST) class (Chi-square trend test for each allergen, $P < 0.0001$). Also, the prevalence of sensitization increased with the severity of the disease (Chi-square trend test for each allergen, $P < 0.0001$) (Table 3). This association was pronounced for HDM and cat allergen. Multiple linear regression analyses showed significant associations between the severity score of atopic eczema and concentrations of allergen-specific IgE to

Table 3 Prevalence of allergic sensitization, total IgE, and severity of atopic eczema in 2201 East German school children

Allergen	Eczema severity (score)				
	Absent	Mild	Moderate	Prominent	Severe
	0	1–3	4	5–7	>7
Grass pollen %	22.7	54.5	30.8	46.2	69.2*
n/N	449/1981	6/11	4/13	6/13	9/13
Birch pollen %	10.1	50.0	22.2	30.0	63.6*
n/N	173/1710	4/8	2/9	3/10	7/11
<i>Cladosporium</i> %	4.4	25.0	20.0	27.3	18.2*
n/N	75/1723	2/8	2/10	3/11	2/11
<i>Dermatophagoides pteronyssinus</i> %	14.0	27.3	38.5	46.2	57.1*
n/N	283/2019	3/11	5/13	6/13	8/14
Cat epithelium %	6.2	27.3	33.3	38.5	46.2*
n/N	122/1979	3/11	4/12	5/13	6/13
Total IgE (median, kU/l)	40.5	45.8	43.4	92.1	316.7**

* $P < 0.0001$ (chi-square trend test).

** $P = 0.002$ (Kruskal–Wallis test).

Adapted from [17].

dust mite ($P = 0.032$) and cat ($P = 0.014$) after adjustment for sex, age, location, and parental predisposition.

The birth cohort study from Kent, UK, however, failed to link the exposure to cat or HDM allergens, as measured shortly after birth, to atopic eczema, as defined by the UK criteria, up to the age of 8 years [18].

Atopic eczema and food allergy

It is well known that food allergens can provoke atopic eczema; however, data from epidemiological studies are scarce. In selected hospital-based groups of children, eczema flare-ups occur in 30–40% after double-blind placebo-controlled food challenge (DBPCFC) with food allergens [19]. A population-based study in adults from Germany [20] revealed that pollen-associated food allergy is infrequent in an unselected adult atopic eczema patient sample. On the basis of 1739 returned questionnaires from adults (18–65 years) from Berlin, Germany, 28 were identified as currently suffering from atopic eczema. Nine patients underwent DBPCFC with the suspected food allergen, but only one patient experienced a worsening of the atopic eczema.

Data from the above-mentioned Melbourne Atopy Cohort Study showed that allergic sensitization to food allergens (milk, eggs or peanuts) at the age of 6 months is a strong predictor for developing atopic eczema up to 7 years of age (hazard ratio 1.63, 1.13–2.35) [21].

Conclusion

Atopic eczema is not a type I allergy. We here understand the term atopy as an indicator of a genetic predisposition to develop allergic sensitization or classical atopic diseases. In this sense, allergic sensitization is an optional component rather than a prerequisite for the diagnosis of atopic

eczema. In fact, numerous population-based studies have shown that only a subgroup of patients with an exhibit allergic type I sensitization in parallel. It is reasonable to believe that on a population basis, about 50% of children with atopic eczema and about 35% of adults are sensitized to common allergens. It was shown that gender, geography (e.g. East and West Germany), and socioeconomic factors determine the proportion of atopic eczema with allergic sensitization. Additional allergic sensitization to atopic eczema obviously increases the risk for the development of respiratory allergies. Sensitization to HDM seems to be especially important and clinically relevant for atopic eczema. Only a few population-based data exist on the association of food allergy and atopic eczema. Although up to 40% of children in hospital settings react to certain food allergens by a flare-up of their atopic eczema, there is an indication that this proportion is lower in adults. Certainly, there is a need for large-scale, comprehensive epidemiological studies on that issue.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 492–493).

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