

## INVESTIGATIVE REPORT

# Frequency of Atopic Dermatitis and Relevance of Food Allergy in Adults in Germany

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**Many factors may aggravate atopic dermatitis. The aim of this study was to determine the frequency of atopic dermatitis in an unselected population sample and to evaluate the role of food allergy. Patients with atopic dermatitis were recruited from the population in Berlin, Germany, using a postal questionnaire. Skin prick tests for allergens were performed, followed by food challenges. A total of 1739 questionnaires was returned. In all, 23.5% of patients stated that they had atopic dermatitis, and 146 persons (8.4%) fulfilled our atopic dermatitis criteria after a detailed telephone interview. Of these, 111 were examined, and 28 (1.6%) were identified as currently suffering from atopic dermatitis. Twenty-seven patients were further evaluated: 9/27 were found to be skin prick test negative, 19/27 were skin prick test positive either to pollen and/or food allergens. Nine of 27 were challenged with the suspected food allergen: 1/9 showed a worsening of the eczema, 3/9 had oral symptoms, and 5/9 were negative. In conclusion, only 20% of adults with a positive history of atopic dermatitis show active eczema lesions at a given time point. The data indicate that most individuals with atopic dermatitis were sensitized against pollen allergens and according to that, pollen-associated food allergens. A non-selected AD patient cohort does not frequently suffer from clinically relevant pollen-associated food allergy. *Key words: atopic dermatitis; food allergy; pollen allergy; IgE.***

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Atopic dermatitis (AD) is a frequent and chronic remittent skin disease characterized by intense pruritus. Over the last few decades the prevalence of AD has been increasing continuously. A standardized questionnaire based on the study from Werner et al. (1) suggested that approximately 10% of children and 2% of adults suffer from AD, which has a high impact on quality of life.

Two subtypes of AD are known: patients with *extrinsic* AD who exhibit many immunological deviations including increased total IgE levels, multiple type-I

sensitizations to several inhalant and/or food allergens and a CD4 dominated cellular infiltrate in the skin (2). By contrast, such immunological phenomena are not present in patients with *intrinsic* AD and the cellular infiltrates are CD4, but also CD8 positive (3).

Besides many exogenous factors, such as climate and microbial colonization of the skin or clothing, food allergy may be an important trigger factor in patients with AD (4). In childhood, classical food allergens, such as milk, egg and wheat, play a role as aggravating factors in up to 20–30% of severely AD-affected children (5). In adults, the role of food allergens as an aggravating factor is less frequent, although pollen-associated food allergens have been suggested to play a role in up to 15% of severely affected patients with AD (6).

Many patients with AD consume restrictive diets, although food allergens have not been proven as an eliciting factor by double-blind placebo-controlled food challenges (DBPCFC) (4). In young children this may lead to the potential risk of nutritional deficiencies, but also results in a decreased quality of life.

In the present study we analysed the frequency of AD and relevance of inhalant as well as food allergies in adult patients with AD, based on a representative population study in Germany.

## MATERIAL AND METHODS

### Population

We extracted 15,000 persons from the population in Berlin, Germany, as a random sample of all age groups (0–99 years) (Prevalence of Adverse Reactions to Nutrients – an Epidemiological study (PANE) cohort 1998–2000, Berlin) with German citizenship, as described previously (7). From this random sample, 13,300 individuals were selected by random sub-sampling and contacted by telephone and personal investigation. A standardized questionnaire containing elements and questions from the German-Health-Survey from 1998 (Robert Koch Institute, Berlin) was used. This approach was applied to improve comparability between the general German population regarding socio-demographic factors. All together 4093 questionnaires were returned, with 1739 in the age group 18–65 years.

### Questionnaire

The frequency, symptoms, clinical outcome and reproducibility of adverse reactions to food against one or several food items were assessed by the questionnaire. The description of "symptoms"

consisted of several possible hypersensitivity patterns of adverse food reactions, including worsening of eczema. Furthermore, the presence of atopic diseases such as AD, allergic rhinitis or allergic asthma was assessed. Based on the results of the questionnaire, all adults with a suspicion of the presence of AD ( $n=408$ ) were contacted again by telephone for a detailed interview. If this revealed a 12-month history of AD according to the criteria of Hanifin & Rajka (8), these individuals were asked to attend for a clinical investigation. The clinical status was determined in all patients by a severity score of atopic dermatitis (SCORAD). In addition, a complete history especially regarding food intake and its possible relevance as a trigger factor for the eczema was evaluated.

#### Skin prick test

The following allergen extracts were applied in skin prick testing: Dermatophagoides pteronyssinus (10 HEP (histamine equivalent in prick testing)), grass pollen (10 HEP), birch pollen (10 HEP), mugwort pollen (10 HEP), cat (10 HEP), dog (10 HEP), Alternaria (1:20 G/V), Cladosporium (10,000 DU/ml) and latex (100 RI). All extracts were kindly provided from ALK SCHERAX (Hamburg, Germany), except for Cladosporium, which was from Bencard (München, Germany).

The different food allergens (guar gum, carrageen, locust bean, pork meat, peanut, hen's egg, poppy seed, cow's milk, wheat flour, walnut, oatmeal, barley flour, rye flour, apple, celery, sesame, hazelnut, carrot and potato) were used exclusively as fresh native preparations in a prick to prick procedure, as described previously (9). These preparations were negative in a non-allergic control group. Only crab (1:20 G/V), mackerel (1:20 G/V), herring (1:20 G/V), mussel (1:20 G/V) and soy (1:20 G/V) allergen extracts were used as commercial allergen extracts because of their limited storing properties (ALK SCHERAX, Hamburg, Germany). Skin prick test were judged positive if a mean wheal diameter of 3 mm or greater was determined.

#### Detection of total and specific IgE

In all patients ( $n = 27$ ) total serum IgE levels, but also specific serum IgE levels including the most common inhalant allergens (SX1 which includes birch, grass, rye, mugwort, Cladosporium, Dermatophagoides pteronyssinus, cat and dog), food allergens (FX5 which includes hen's egg, cow's milk, fish, wheat, peanut and soy), profilin and latex were measured using the Pharmacia CAP-System (Freiburg, Germany, kindly provided by Pharmacia Diagnostics, Dr Burow). If DBPCFC were performed in the affected individuals with AD, specific IgE against the single allergens (birch, grass, hazelnut, apple, celery, peanut, carrot, mugwort, tomato, Dermatophagoides farinae and pteronyssinus, soy and crab) were determined additionally. Analysis of the correlation between total IgE level and the severity of the skin status showed no statistical significance ( $p>0.05$ ). However, there was a significant correlation between total IgE levels and positive specific IgE measured by SX1 ( $p<0.05$ ).

#### Double-blind placebo-controlled food challenge

If adverse reactions to food were expected in the individuals by either history, sensitization in the skin prick test and/or a positive detection of specific IgE to a particular food, DBPCFC was performed. The food items used in the provocation tests were blinded for taste, colour and consistency to the placebo exposure. The amount of food used in the provocation test was related to the individual history of the patient and to the level of regular consumption in the general population. The following amounts were used: vegetables (carrots and celery) and fruit (apple) 50 g, hazelnut and peanut 10 g, flour 20 g, cow's milk 200 ml, and one fresh hen's egg. The

DBPCFC was considered positive if the SCORAD increased by at least 15 points and if the placebo provocation test was negative.

#### Statistical analysis

For analysis  $\chi^2$  test was used,  $p < 0.05$  was considered as significant,  $p < 0.01$  as highly significant.

## RESULTS

### Prevalence of atopic dermatitis in the study population

Fig. 1 summarizes the data regarding the frequency of AD in the general population. Among 1739 adults the self-reported prevalence of AD in adults was 23.5% ( $n=408$ ). All 408 individuals were contacted by telephone and questioned again to confirm the suspicion of AD. According to the criteria of Hanifin & Rajka, AD could be confirmed in 146 individuals corresponding to a one-year prevalence of 8.4%. Of these 146 persons, 111 adults were clinically examined in our department. The diagnosis was confirmed, but active lesions of eczema exceeding the minimal symptoms, such as dry skin, was diagnosed in only 28 adults, giving a point prevalence of 1.6%. These 28 patients were investigated further. One dropped out for personal reasons. Analysis of the

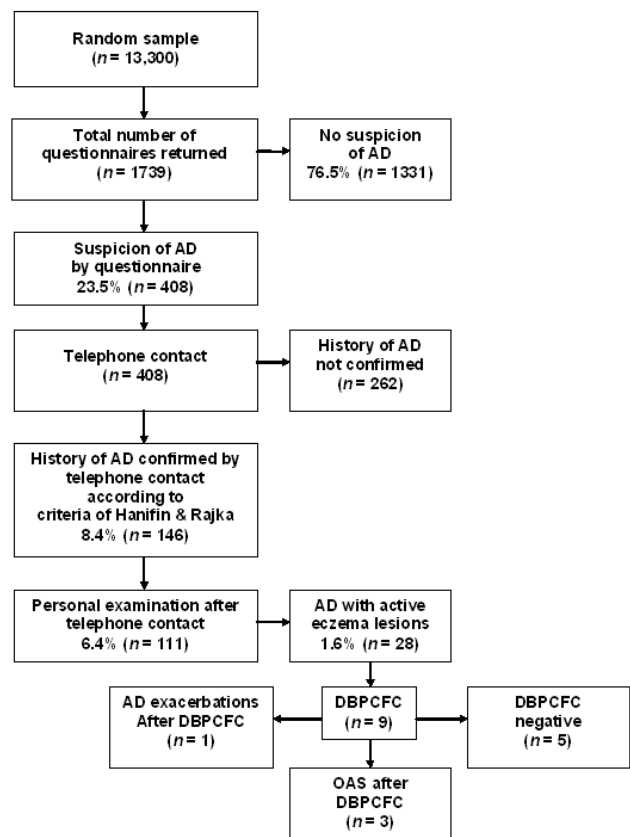


Fig. 1. Frequency of atopic dermatitis (AD) and food allergy in adult individuals based on a random sample from the population in Berlin/Germany. DBPCFC, double-blind, placebo-controlled food challenge; OAS, oral allergy syndrome.

severity scores in the remaining AD group revealed that most of the individuals suffered from mild AD ( $n=14$ ), 8 individuals exhibit a moderate status AD, and in only 5 individuals AD was severe at the time of examination. Most of the individuals were in the age range 18–25 years (12/28), 6 were in the range 26–35 years, 5 in the range 36–45 years, 3 in the range 46–55 years and 2 in the range 56–65 years.

#### Frequency of sensitization to inhalant and food allergens

Table I illustrates the results of the skin prick test using the most important inhalant allergens and cross-reactive food allergens. Many were sensitized to birch (15/27) and grass pollen (12/27), but sensitization was also frequent to animal dander, such as dog (11/27) and cat (9/27). Analysing food allergens a sensitization to carrots (8/27) and hazelnuts (8/27) as the most frequent, followed by sesame (7/27), apple, celery and ragweed (each 6/27) was observed. Sensitization to *Dermatophagoides pteronyssinus* was detectable in 6/27 patients by skin prick test. By contrast, sensitization to the classical food allergens, such as milk, wheat and egg, which play an important role in childhood, were rare in this study population (2/27). Other allergens, such as peanut, fish, mussel, meat, latex, *Alternaria*, carrageen and locust bean gum were exceptionally rare. Finally no sensitization was determined to guar gum, crab, mackerel and *Cladosporium* using the skin prick test.

#### IgE levels in the study group

The distribution of total serum IgE levels shows that increased total serum IgE levels were found in approximately two-thirds of the patients, whereas a normal total IgE was present in 10 individuals with AD. Specific IgE levels regarding the most frequent inhalant allergens

measured as SX1 containing birch, grass pollen, rye flour, mugwort, *Cladosporium*, house dust mite, cat and dog were positive in 22/27 patients of the study group. This indicates that most patients with AD were sensitized to the most common type-I allergens. However, the range of sIgE levels were wide and showed in one patient in CAP-class I (0.35–0.7 kU/l) and II (0.7–3.5 kU/l), in 10/27 in CAP-class III (3.5–17.5 kU/l), in 4/27 in CAP-class IV (17.5–50.0 kU/l), and in 3 patients in CAP-class V (50.0–100.0 kU/l) and VI (> 100.0 kU/l), respectively (Fig. 2). Due to rational allergen diagnostics single sIgE levels were only determined in the provocation group.

By contrast, in 20/27 investigated individuals with AD no specific IgE antibodies were detectable against the most frequent classical food allergens, indicating that these food allergens are no longer important in adults.

#### Pollen-associated food allergens are frequent in adult patients with atopic dermatitis

DBPCFC was performed if food allergens were suspected to cause any reactions or if sensitization was determined either by a positive specific IgE or a positive skin prick test. These criteria were fulfilled in 13/27 of the individuals. However, only 9 individuals gave informed consent for the oral provocation test. The birch pollen associated food allergens were most frequent ( $n=5$ ), followed by grass pollen associated food allergens ( $n=3$ ). One patient received a combination challenge including birch and grass pollen and milk and egg.

Three individuals developed an oral allergy syndrome, and in only one individual a worsening of the eczema with an increase of the SCORAD > 15 points was seen.

## DISCUSSION

In the present study we determined a self-reported frequency of AD in adults of 23.5% based on a standardized

Table I. Frequency of positive skin prick test reactions within the study group ( $n = 27$ ).

Food allergen	Positive skin prick test reaction ( $n$ )
Mackerel, <i>Cladosporium</i> , crab, guar gum	0
Carrageen, locust bean, <i>Alternaria</i> , latex, herring, pork, mussel, peanut	1
Hen's egg, poppy seed, cow's milk, wheat flour	2
Soy	3
Oatmeal, barley flour	4
Mugwort	5
<i>Dermatophagoides pteronyssinus</i> , rye flour, apple, celery	6
Sesame	7
Hazelnut, carrot	8
Cat	9
Potato	10
Dog	11
Grass pollen	12
Birch pollen	15

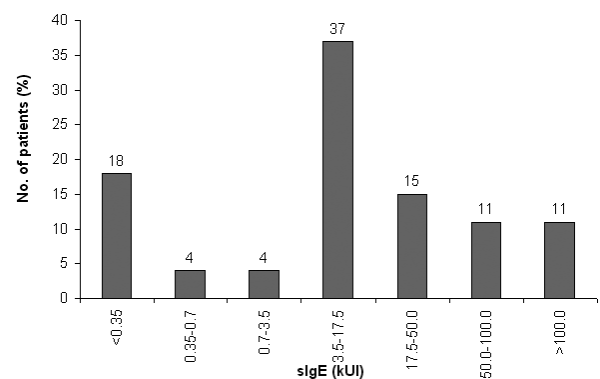


Fig. 2. Distribution of specific IgE (sIgE) levels determined by IgE-screening with inhalant (SX1 including birch, grass, rye, mugwort, *Cladosporium*, *Dermatophagoides pteronyssinus*, cat and dog) and food (FX5 including hen's egg, cow's milk, fish, wheat, peanut and soy) allergens within the study group ( $n = 27$ ).

questionnaire. Many studies, also based on questionnaires, reveal a wide range of prevalence rate, from 1% to 25%, and show that our results are within this previously reported range of AD frequency. The prevalence of AD differs not only by nation, but also by region. Within Germany, studies revealed prevalences in pre-school children of between 12.9% and 17.5% (1). These and other studies revealed that the overall frequency of AD has increased within the last 30 years. However, cross-sectional studies in adults are missing.

An important finding of the present study was the observation that the self-reported prevalence of AD was high. It decreased to 8.4% after diagnosis by a dermatologist. A possible reason for this decrease may be that many patients categorize other scaling disorders into the term atopic eczema. Such diagnoses include mycosis, psoriasis, seborrhoeic dermatitis or hand and foot eczema in general. However, it should be taken into consideration that we only determined the prevalence of AD by personal interview during the last 12 months.

The results of the skin prick test showed the most frequent sensitizations were to birch and grass pollen (55.6% and 44.4%), the cross-reactive food allergens (carrot, celery, hazelnut, sesame and apple) (22%), and flour (wheat, barley, and rye) (14.8%). These results emphasize the frequency of sensitization to pollen and pollen-associated food allergens in adult patients with AD.

By contrast, sensitization to the classical food allergens, such as milk or egg, were determined only rarely (7.4%). However, a clinical relevance of these pollen-associated food allergens is present only in a subgroup of patients. Only one patient exhibited a worsening of the eczema as measured by an increase in the SCORAD > 15 points. In 3 individuals the development of an oral allergy syndrome was observed, but 5 sensitized individuals with AD did not react at all. One could speculate that this frequency of positive reactions might be increased if repeated oral provocation tests are performed as described by Reekers et al. (6). However, previous studies were performed in selected groups and the frequency of a clinically relevant pollen-associated food allergy should not be overestimated in patients with AD. It is of use to perform double-blind placebo-controlled food challenges in order to determine the clinical relevance of such sensitizations. AD is a multifactorial skin disease and beside food allergens pseudo-allergens may also play a role as aggravating factors (10).

Total serum IgE was increased in 63% of the patients (17/27). This is in line with previous studies in which increased total serum IgE levels were observed in > 60% patients with AD (11). However, there was no association between the severity of AD and the total serum IgE levels (data not shown,  $p > 0.05$ ), which is also in line with previously published data (12).

Of the studied individuals with AD, 81.5% had specific

IgE antibodies against either inhalant or food allergens. This is in accordance with many other studies, suggesting that the extrinsic AD syndrome involves approximately 80% of patients with AD (13). However, whether and to what extent the inhalant allergens are also important trigger factors for the eczema reaction is not clear. The correlation between the presence of specific IgE levels and total serum IgE levels was clearly significant ( $p < 0.05$ , data not shown), indicating that total serum IgE levels may be used as an indicator for the presence of extrinsic AD syndrome.

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