

Age-dependency of sensitization to aero-allergens in asthmatics

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Skin reactivity (intracutaneous test) to histamine and allergens was studied cross-sectionally in a Dutch asthmatic patient population from childhood to old age (4–75 years). It was found that the histamine skin reactivity rose significantly ($p < 0.05$) during childhood, was significantly higher in the 10–15-year age group, and was constant between 20 and 75 years of age. The mean wheal index (histamine ratio) of all allergens was constant during childhood, and decreased after the age of 25 for grass pollen and house-dust mite and after the age of 15 for the other allergens. The prevalence of a positive skin test decreased with age, except for grass pollen. During childhood the indoor allergens, cat dander and house-dust mite, were the most important, while after the age of 15 sensitivity to an outdoor allergen, grass pollen, increased markedly. At all ages house-dust mite was the most important allergen. After the age of 25 the prevalence of every allergen declines. The prevalence of a positive skin test to *Cladosporium* was unexpectedly high in childhood (10–40%). It can be concluded that the prevalence of a positive skin test declines with age, except for grass pollen. The degree of sensitization in asthmatics peaked in the age groups between 20 and 40 and sensitivity to indoor allergens developed earlier than sensitivity to outdoor allergens.

Clinical aspects

Skin tests producing immediate wheal and flare reactions are widely used for the detection of allergy in patients referred for asthmatic problems. For good evaluation of a skin test it is important to know the influence of age on skin reactivity. In this study we evaluated the wheal index (histamine ratio) of the skin test and the prevalence of a positive skin test using a set of 6 standardized common aero-allergens and one non-standardized, cross-sectionally, in a Dutch asthmatic patient population (4–75 years). Since standardized allergens were used, the prevalences between the different allergens could be compared. It was found that the histamine skin reactivity peaked at the age of 15 and was lower in all other age groups. Therefore, when comparing skin test results in different age groups, it may be important to use wheal indices instead of absolute values. Except for grass pollen the prevalence of a positive skin test decreased with age. During childhood indoor allergens are the most important, while after the age of 15 sensitivity towards outdoor allergens increases. House-dust mite is the most important allergen at all ages. Surprisingly, a fungal allergen (*Cladosporium herbarum*) was found to be of significance in young children (prevalence 10–40%). The prevalence of at least one positive skin test in asthmatics declined with age, while the degree of sensitization (expressed as the mean wheal index) peaked in young adults (20–40 years of age).

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Skin reactivity to different allergens may vary with age. Young children have lower skin reactivity towards house-dust, house-dust mite, animal dander, grass pollen and moulds than adults (3, 9, 10, 12, 21), while in the elderly skin reactivity towards short

ragweed, rye grass, oak, Bermuda grass, cat and dog dander, house-dust and alternaria is decreased (2, 6, 7, 9). Others did not find decreased skin reactivity (11) in the older age group.

Some authors have reported lower histamine skin reactivity in newborn infants compared with adults (13, 21). Others have also found a lower histamine skin reactivity during childhood compared with adults (17), and also in elderly people skin reactivity was found lower (7, 17); however, conflicting results have been published (4, 16).

Since in most studies non-standardized extracts were used, prevalence rates and the variation in sensitivity with age could not be compared between allergens. To overcome this problem we conducted a study using a set of 6 standardized allergens and one non-standardized. Since no fully standardized extract of *Cladosporium* was available, we used a partially purified allergen. The prevalence rates and wheal sizes were studied cross-sectionally in asthmatic patients from childhood to old age in order to detect differences in the prevalences of positive skin tests to allergens, and in the degree of sensitization, as measured by wheal size, between children and adults and between adults and the elderly.

In addition, the skin reactivity towards histamine was studied from childhood to old age and the result was used to correct the response to the allergen in the skin test.

Material and methods

Patients and study design

Asthmatic patients (499), who were newly referred to specialists at 6 asthma centres in The Netherlands, were randomly skin tested using intracutaneous test (ICT). The age of the patients varied from 4–75 years with a mean of 32.4 years, and 48% were male. These patients were divided into 12 age groups with a minimum of 27 patients per group.

Patients were not allowed to use antihistamines or oral corticosteroids during the 48 h prior to testing, in accordance with the report on skin test standardization (18).

Allergen preparations

Standardized extracts (ALK, Hørsholm, Denmark, obtained through Laboratorium Diephuis BV, Groningen, The Netherlands) of grasses-5 (*Alopecurus pratensis*, *Dactylus glomerata*, *Lolium perenne*, *Phleum pratense* and *Festuca pratensis*), trees-3 (*Alnus glutinosa*, *Betula verucosa* and *Corylus avellana*), weeds-2 (*Plantago lanceolata* and *Artemisia vulgaris*), house-dust mite (*Dermatophagoides pteronyssinus*), cat and dog dander were used in the study in concentrations of 30 BU/ml. *Cladosporium herbarum*

was used in a concentration of 0.05 mg/ml. All allergen extracts were dissolved in PBS pH 7.4 and contained 0.5% phenol and 0.03% HSA. The solutions were kept between 4 and 8°C for a maximum of 3 months and used at ambient temperature. For *Phleum pratensis*, *Betula verucosa*, house-dust mite and cat dander we found no loss of potency during 3 months of storage at 4–8°C, using the skin test method of Turkeltaub (20).

Intracutaneous test

Intracutaneous testing was performed in accordance with Dreborg's guidelines (5). Briefly, 0.03 ml allergen extract was injected into the skin of both forearms at ventral sites at least 4 cm apart, using a 0.5 ml syringe (Monoject® No. 8881-500501, Sherwood Medical, St. Louis, USA). The results were recorded after 15 min, by circumscribing the wheal in ink and transferring the imprint to adhesive tape. The mean wheal diameter was calculated by adding the longest diameter to the orthogonal diameter measured at one half of the longest diameter, and dividing by two. Patients with a wheal size of the positive control <5 mm or negative control >5 mm were excluded. The results of all patients were used to calculate mean wheal sizes.

Wheal indices were calculated by dividing the wheal size by the histamine wheal of each patient and a wheal index ≥ 0.7 was regarded as a positive skin reaction. The wheal index was used in the calculations to correct for possible differences in injection technique between the 6 participating centres and for age-dependent skin sensitivity.

The positive control was histamine phosphate (base) 0.01 ml/ml; the diluent was used as a negative control. In a pilot study the reproducibility of this ICT procedure was estimated in 41 patients. The coefficient of variation within patients was 5.66% and between patients 11.6%. On the basis of the results of the reproducibility determination, it was decided to perform a single skin test for each allergen.

Statistical analysis

Mann-Whitney's test (non-parametric) was used to calculate differences of wheal indices between age groups. Mean wheal indices and their standard deviations were calculated and Mann-Whitney's test was performed using the SPSS/PC + software package (14).

Results

In this study the mean histamine wheal was 10.6 mm (range 5.00–16.5 mm, CV 16.9%) in adults (15–75

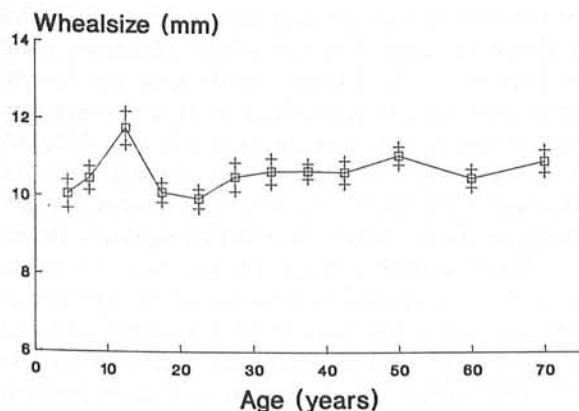


Fig. 1. Wheal size of histamine (mm) from childhood to old age.

years) and 10.8 mm (range 6.00–17.0 mm, CV 20.1%) in children (4–15 years).

Fifty-nine of 499 (11.9%) patients reacted to the negative control. In these patients the mean wheal was 4.33 mm (range 1.00–11.5 mm, CV 50.1%). Because of a wheal size ≥ 5 mm on the negative control, the results of 21 patients were excluded. No patients had a wheal size of the positive control < 5 mm.

Fig. 1 shows the wheal size of the histamine solution between 4 and 75 years. The histamine wheal is significantly ($p < 0.05$) larger in the 10–15-year age group compared with the other age groups. There is no significant change in histamine skin reactivity from 15 to 75 years of age.

The wheal index of the allergen preparations is depicted in Fig. 2a and 2b. There is no significant ($p < 0.05$) change in the mean wheal size from childhood to the age of 25 for grass pollen and house-dust mite, or to the age of 15 for the other allergens. After the age of 15 or 25 the wheal index steadily decreases.

The indoor allergens, cat dander and house-dust mite, show the highest wheal index during childhood, whereas during adulthood the wheal index of the same indoor allergens equal that of an outdoor allergen, grass pollen.

The mean wheal indices of all allergens of all patients and of all patients with a positive skin test are shown in Fig. 2c. After the age of 15, the mean wheal index decreased significantly with age, and the mean wheal index of all patients with a positive skin test reaction peaked in the age groups between 20 and 40.

Fig. 3 shows the prevalences of sensitivity towards allergens from childhood to old age. Except for grass pollen, there is an overall decrease in the prevalence of positive skin tests. *Cladosporium* reactivity declines strongly during childhood (40–10%). During childhood house-dust mite and cat dander are the most important allergens, with a prevalence between

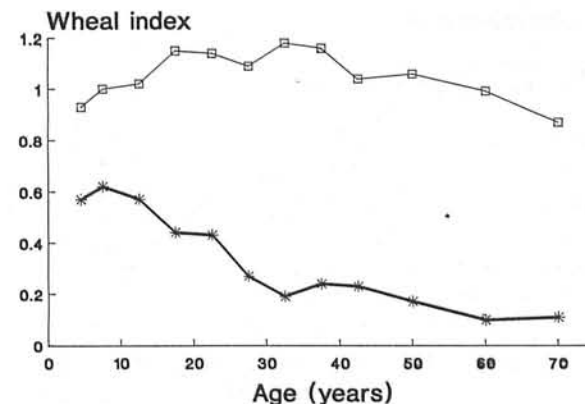
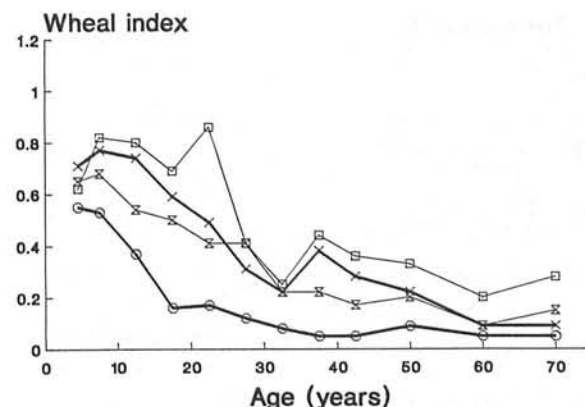
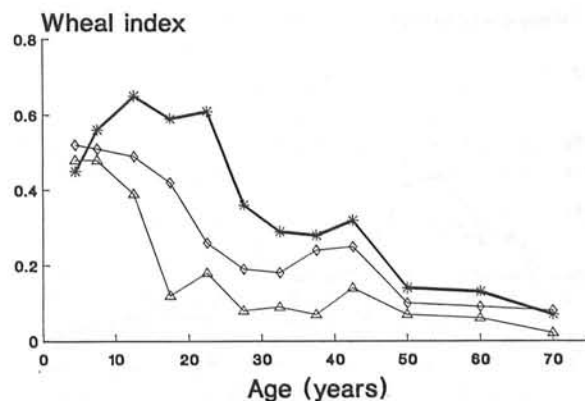


Fig. 2. Wheal index of grasses-5 (*), trees-3 (◇) and weeds-2 (Δ) (A); of house-dust mite (□), cat dander (×), dog dander (⊗) and *Cladosporium herbarum* (○) (B), and the mean wheal index of all allergens (C) in all patients (*) and in patients with a positive skin test (□) from childhood to old age.

40 and 68%, while after the age of 15 grass pollen predominates. At practically all ages weeds have little significance, with a prevalence between 0 and 20%. House-dust mite is always the most important allergen, followed by grass pollen and cat and dog dander in adults and cat and dog dander in children.

The prevalence of atopy, defined as at least one positive skin test, is shown in Fig. 3c and declines slowly with age.

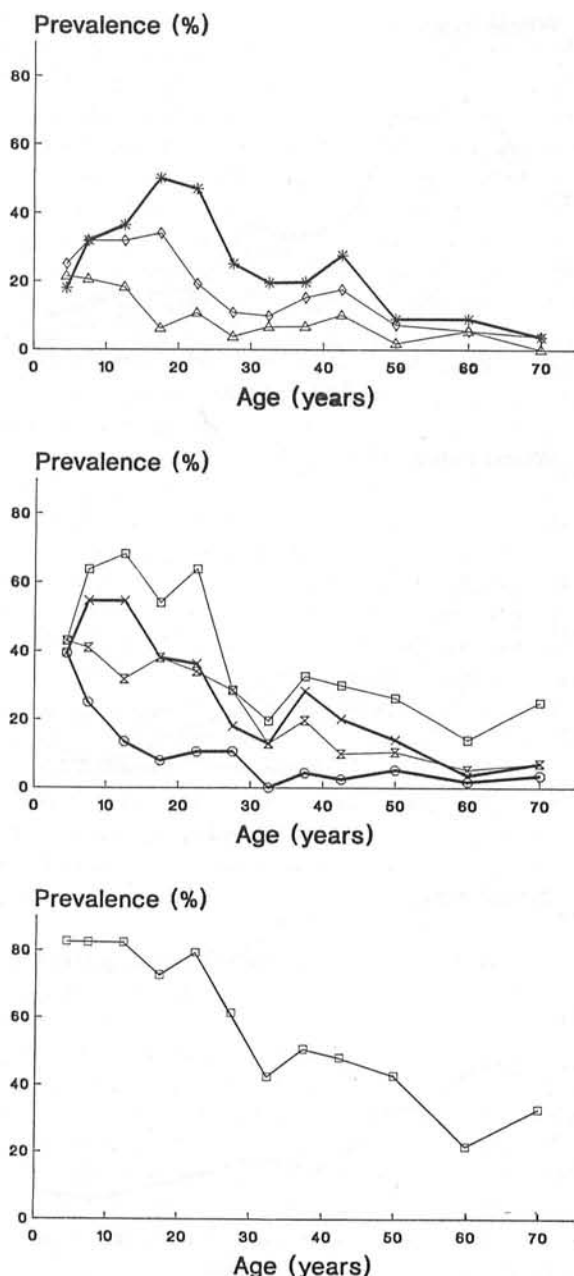


Fig. 3. Prevalence of a positive skin test to grasses-5 (*), trees-3 (◇) and weeds-2 (△) (A); to house-dust mite (□), cat dander (×), dog dander (⊗) and *Cladosporium herbarum* (○) (B) and the mean prevalence of a positive skin reaction to all allergens (C) from childhood to old age.

Discussion

Since standardized allergens with comparable potency (concentration 30 BU/ml) were used in this study, conclusions can be drawn about the prevalence rates of sensitivity to the different allergens. Thus differences in prevalences can mainly be ascribed to a difference in sensitization to the allergens and not to differences in the potency of the allergen extracts.

Sensitivity to outdoor allergens, such as grass pollen, develops later than to indoor allergens, probably because of the higher exposure of young children to indoor allergens. In this study house-dust mite was always the predominant allergen. After the age of 25, the prevalence of each allergen declines. *Cladosporium* may be an important indoor allergen during childhood, with a prevalence between 10 and 40%. However, this allergen preparation is not fully standardized and equilibrated. Aas et al. (1) reported a positive skin prick test prevalence of 60% in children (age 8–15 years) using a purified and biologically quantitated *Cladosporium herbarum* extract. However, these children were selected on the basis of a history suggestive of allergy to moulds. Others reported a positive skin prick test prevalence of 3% (8) and 0.7% (15) in a patient population, which is lower than the mean prevalence of 9.4% found in this study. This difference may be because those studies included patients suffering from rhinitis, whereas in our study only asthmatics were included. The prevalence of a positive skin test in asthmatics is highest during childhood; however, the strength of the skin reaction peaks in young adulthood between the ages of 20 and 40.

Since this was a cross-sectional study, conclusions drawn about the influence of ageing on the prevalence of a positive skin test and the strength of the skin reaction, should not be considered conclusive. Only a longitudinal study can show that our results are not caused by factors (environmental influence) other than age.

As far as we know, this is the first study relating prevalence with age from childhood to old age using standardized allergenic extracts. Our results are in accordance with those of Freidhoff et al. (7), who also found a decline in prevalence between 20 and 55 years of age for short ragweed, rye grass, cat and dog dander, house-dust and *Alternaria*. They also agree with the results of Gergen et al. (9), who found an overall decrease in the prevalence rates to 8 common aero-allergens during 20 and 74 years of age.

Using specific IgE, de Groot et al. (3) found that among the inhalant allergens, house-dust mite was the most frequent sensitizer, followed by grass pollen and cat dander. This finding corresponds well with our results. They also reported that indoor allergens (mites, animal danders) had more significance in the age group 0–4 years than outdoor allergens (pollen). However, they did not investigate fungal allergens.

Histamine skin reactivity peaks at 10–15 years and is lower in all other age groups. This is in accordance with the conclusions of Brociek et al. (17). Since both allergy and end-organ sensitivity determine the severity of symptoms, these data do not

necessarily imply that the disease is most severe when the skin reactivity peaks. Skin test reactivity remains constant from the age of 20 to 75. This confirms the work of Schwarzenbach et al. (16) and Delespesse et al. (4). Thus, while histamine skin sensitivity remains constant, the wheal indices slowly decrease after the age of 15 or 25. This decline in sensitivity is therefore not caused by a decline in skin sensitivity, but probably by a decreased amount of specific IgE attached to mast cells.

The results presented in this paper only apply to this particular population: a population of patients who were newly referred to specialists at asthma centres.

Only when standardized and equilibrated allergens are used for skin testing will it be possible to compare the prevalence of a positive skin test towards different allergens. It can be concluded that in this patient population, sensitivity to grass pollen developed later than sensitivity to indoor allergens. *Cladosporium* was an important allergen in childhood, and house-dust mite was the most important in all age groups.

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