
Changes in skin test reactivity among adults with atopic disease: a 3-year prospective study

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Background: Our knowledge about longitudinal predictors of atopy is limited.

Objectives: To describe changes in skin test reactivity during a 3-year period in a sample of adolescents and adults with atopic disease and to identify factors of importance for these changes.

Methods: From a sample of 1,186 candidates, ranging in age from 14 to 44 years, who in a screening questionnaire reported symptoms suggestive of respiratory allergic disease, 344 individuals with a positive skin prick test (SPT) result concomitantly with asthma and/or rhinitis were clinically studied on 2 occasions, 3 years apart.

Results: In total, 134 (39% of the study population) had a different SPT result at follow-up compared with baseline, based on a diagnostic criterion of 3 mm for a positive test result; 77 (22%) developed de novo sensitizations to 1 or more allergens, 45 (13%) had remission of 1 or more sensitizations, and 12 (4%) both gained and lost sensitizations. Female sex (odds ratio = 1.90 [1.02–3.57], $P = .04$) significantly predicted incidence of 1 or more sensitizations.

Conclusions: Four of 10 adults with atopic disease will have changes in SPT status during a 3-year period, and most will gain new sensitizations. Women with atopic disease are at increased risk of developing new sensitizations compared with men.

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INTRODUCTION

Many studies have reported a rise in the prevalence of atopic diseases, including allergic rhinitis, asthma, and atopic dermatitis, in children and adults in the past decades.^{1–3} Most studies report atopy frequencies of 30% to 40% in children and young adults.^{2–7} Several reports have revealed factors associated with the development of atopic disease^{2,3,6} or factors that appear to protect against it.⁸ However, to our knowledge, there are only a few previous follow-up studies that concern the natural course of atopic disease.^{2,9,10} Most of these longitudinal studies were performed on children, and most were restricted to nonselected community samples.^{3–5,7,11}

Atopy is an objectively measurable trait related to the presence of rhinitis and asthma; however, our knowledge about its longitudinal predictors in adults is limited. The skin prick test (SPT) is a common instrument for the evaluation of specific sensitizations, and changes in SPT status have been shown to be clinically relevant.⁹ Sensitization measured by SPT can be interpreted as a correlate of disease. Furthermore, it can also be a precursor of symptoms¹² or can persist without clinical relevance in the future.

The aim of this study was to describe changes in skin test reactivity during a 3-year period in a sample of adults diagnosed as having atopic disease and to identify factors of importance for these changes.

METHODS

Study Population

A short questionnaire adopted from the American College of Allergy, Asthma and Immunology on respiratory health and use of medication was mailed to a random sample of 10,877 candidates, 14 to 44 years of age, who lived in urban Copenhagen, Denmark.^{13,14} Fifty-four percent of the questionnaires were returned ($n = 5,849$). Among these, only candidates who reported symptoms suggestive of asthma or allergy or who were taking any medication for these conditions were invited to take part in a clinical examination.

A total of 1,186 participants (58% men), with a mean age of 29 years, participated in the clinical examination in which a respiratory physician performed a questionnaire-based interview, tested skin test reactivity and lung function, and measured airway responsiveness. Of the 1,186 participants, an SPT was performed in 1,097 (93%). Of these, 830 were diagnosed as having either asthma and/or rhinitis; that is, 318 had both asthma and rhinitis, 341 had rhinitis only, and 171 had asthma only, whereas 267 had neither asthma nor rhinitis.

The 830 patients with asthma and/or rhinitis, in whom an SPT was performed, were invited to participate in a second examination 3 years later (median follow-up time, 2.4 years). In all, 442 patients (53% of the 830 examined at baseline) underwent both SPTs and thus were available for the follow-up analysis.

All participants were told about the study verbally and in writing, and all patients and parents or guardians gave their informed consent. The Scientific Ethics Committee of Denmark approved the study.

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Clinical Interview

Patients were asked about the presence of symptoms of rhinitis and asthma. Rhinitis was identified by the presence of considerable episodes of rhinorrhea, nasal congestion, and/or sneezing apart from periods with colds. Asthma was identified as considerable recurrent episodes of wheezing, shortness of breath, chest tightness, and/or cough at rest, after exertion, or subsequent to allergenic or unspecific stimuli apart from periods with respiratory tract infections. The severity of rhinitis and asthma was classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Initiative for Asthma (GINA) guidelines, respectively.^{15,16} The dose of any current medical treatment for asthma and allergy was registered for antihistamines, inhaled corticosteroids (ICS), nasal steroids, short-acting β_2 -agonists, long-acting β_2 -agonists, and/or specific immunotherapy. The patients were interviewed about their smoking habits, and the number of pack-years was calculated (current tobacco consumption [grams per day] $\times$ duration of smoking [years]).

Airway Responsiveness Test

A spirometry was performed, and airway responsiveness to inhaled methacholine was measured in accordance with the method of Yan et al.¹⁷ The dose-response slope (DRS) was calculated as the decline in forced expiratory volume in 1 second (FEV₁) divided by the highest dose of methacholine given. Logarithmically transformed DRS values were used for the analysis.

Skin Prick Test

The participants were requested to discontinue use of medications that contained antihistamines at least 3 days before skin testing. Skin prick tests were performed using standard dilutions of 10 aeroallergens common in tempered areas of the Northern Hemisphere. The allergens used were birch, grass (*Timothy*), mugwort, horse, dog, cat, house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and mold (*Alternaria iridis* and *Cladosporium herbarium*), with positive and negative references being histamine, 10 mg/mL in 50% glycerol, and glycerol, 50%, respectively. The concentrations of allergens were 10 histamine equivalent prick (HEP) (Soluprick SQ System; ALK, Albelló, Denmark). The test was performed on the volar side of the forearm in a standardized order. Prick sites were at least 2 cm apart; disposable lancets (ALK, Albelló, Denmark) with a 1-mm tip were used. Reactions were read after 15 minutes. Wheal reactions were outlined with a fine marker and transferred to paper with transparent tape. The reaction to each of the allergens was regarded as positive if the mean wheal diameter ($[d_1 + d_2]/2$) was 3 mm or greater. The patient was considered atopic if 1 or more positive reactions were found.

For the follow-up analysis, an incident case was defined as a person having at least 1 new positive reaction (wheal diameter ≥ 3 mm) on the second SPT when the test outcome of the first SPT was truly negative (wheal diameter = 0 mm) for the same specific test allergen. A remitting case was

defined as a person having at least 1 new truly negative test reaction (wheal diameter = 0 mm) on the second SPT when the reaction to the same specific test allergen on the first SPT was truly positive (wheal diameter ≥ 3 mm).

Statistical Analysis

The data were analyzed with the statistical package SPSS, version 14.0 (SPSS Inc, Chicago, Illinois). For categorical variables, a χ^2 test was used to compare dropouts with those who remained in the study, whereas a *t* test was used whenever data were continuous. Multinomial logistic regression analysis with backward elimination was used to examine the impact of variables on the susceptibility to develop new allergic reactions and to lose reactions, respectively, between the 2 points in time. In this analysis, SPT status (unchanged vs incidence and remission at follow-up) was the dependent variable; sex, age, season of examination, time to follow-up, use of specific immunotherapy, antihistamines, ICS, nasal steroids, smoking (pack-years), severity of asthma and rhinitis, FEV₁, FEV₁/forced vital capacity, logDRS, number of positive reactions to the SPT, and the mean diameter of the histamine control at baseline were independent variables. Results are expressed as odds ratios. *P* < .05 was considered statistically significant.

RESULTS

Of the 442 patients with asthma and/or rhinitis who had an SPT performed twice, 98 had a negative SPT result at baseline. Among these, 8 patients had a doubtful test result on 1 or more specific allergens (wheal size >0 but <3 mm), leaving 90 patients with a truly negative test result but with respiratory symptoms consistent with asthma and/or rhinitis. Complete longitudinal data on patients with atopic disease were thus available for 344 patients (63% of the included patients diagnosed as having atopic disease at baseline). This left 202 dropouts between the first and second SPTs. The 202 dropouts were compared with the 344 patients who completed the study with respect to sex, age, use of nasal steroids, short-acting β_2 -agonists, long-acting β_2 -agonists, ICS, airway responsiveness, rhinitis, asthma, lung function, and smoking. The differences between the analytic sample and the dropouts were small and insignificant, except for a somewhat higher age (*P* = .03) among the dropouts.

Of the 344 patients with atopic disease who completed the study, 49% were women and 51% men. The median age was 30 years. In total, 134 (39.0% of the study population) had a different SPT result at follow-up compared with baseline, based on a diagnostic criterion of 3 mm for a positive test result. We identified 77 incident cases (22.4%; 95% confidence interval [CI], 4.4% [SD]), 45 remitting cases (13.1%; 95% CI, 3.6% [SD]), 12 cases in whom both incidence and remission were observed (3.5%; 95% CI, 1.9% [SD]), and 210 cases with an unchanged SPT (61.0%; 95% CI, 5.2% [SD]) between the first and the second examinations (Fig 1). Incidence exceeded remission for most allergens tested, most prominently for dog (Table 1 and Table 2). Restricting the

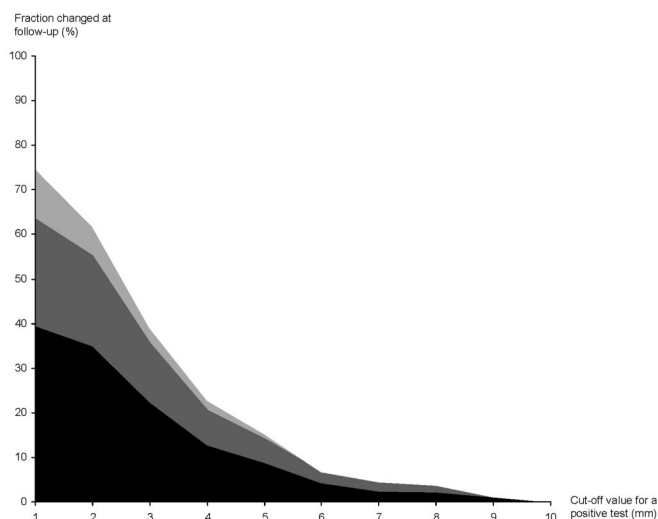


Figure 1. Fraction (%) of subjects with a different skin prick test at follow-up compared with baseline as a function of different cutoff values (wheal diameter in millimeters) for a positive test result. Black area denotes patients with 1 or more new sensitizations at follow-up (incident cases); dark gray area denotes patients who have lost 1 or more sensitizations at follow-up (remitting cases); light gray area denotes patients who have both gained and lost 1 or more sensitizations at follow-up. Example: If one would choose 3 mm as the diagnostic criterion for a positive reaction on the skin prick test, 22% of all patients will have 1 or more new sensitizations at follow-up, 13% will lose 1 or more sensitizations at follow-up, and 4% will both gain and lose 1 or more sensitizations at follow-up, leaving 61% of all patients unchanged at follow-up.

analysis to only include 71 patients who were monosensitized at baseline revealed a similar pattern of change; that is, 16 (22.5%) were incident cases, 5 (7.0%) were remitting cases, and 1 (1.4%) was both incident and remitting, whereas 49 (69.0%) were unchanged.

Logistic regression analysis applied to the 3-mm criterion showed that female sex (odds ratio, 1.90; 95% CI, 1.02–3.57; $P = .04$) significantly predicted incidence of 1 or more sensitizations.

Among the 90 patients with a negative SPT result at baseline but with asthma and/or rhinitis, 5 incident cases (5.6%) were observed at follow-up. Among these, 1 patient had development of 2 new sensitizations, whereas 4 patients had 1 new sensitization. Among the 344 patients with a positive SPT result at baseline, 6 patients (1.7%) reverted to nonatopic status at follow-up. Among these, 1 patient was sensitized to 2 allergens at baseline, whereas the remaining 5 patients were monosensitized.

DISCUSSION

Immediate skin test reactivity to common environmental allergens provides a valuable aid to physicians in diagnosing and treating allergic conditions. Factors other than allergic symptoms, such as sex and age, have been shown to influence skin test reactivity prevalence.^{2,18,19} In our study population of

atopic adults, SPT sensitization status changed in 39% during a period of approximately 2½ years. Most of these acquired new sensitizations; for example, the incidence was greater than the remission. In this aspect, the results of the present longitudinal study agree with results from previously published reports.^{2,3,5} Nevertheless, according to the previous publications of Boulet et al,¹⁰ prevalence and degree of allergic sensitization reaches a peak in adolescence (16 to 25 years) and thereafter diminishes with age. Their study was performed on a large sample of individuals of any age who had been referred to specialized allergy clinics. Most of their study population had atopic disease (80%) and consisted predominantly of adults (70.5% ≥16 years) and was to a certain degree comparable to our study sample. However, some of the differences in the results may be explained by a differing SPT allergen selection. Only 6 of the allergens they tested for were included in our selection of 10 allergens.¹⁰

Our results indicate that women with atopic disease were twice as likely as men to become sensitized to additional allergens. This is consistent with the findings of Barbee et al,² who found a higher incidence of sensitization in women than in men 25 to 44 years of age, although their study was based on a community population and not on atopic adults exclusively. Others reported no differences in incidence between sexes³ or they found a higher incidence in men,¹⁰ but these differences may be caused by discrepancies between study populations.

We used the standard cutoff of the SPT wheal diameter of 3 mm to illustrate our results; however, other studies have described wheal cutoffs varying from 2 to 5 mm.^{7,13} We observed a linear decline in the tendency to change SPT status as a function of increasing stringency of the cutoff value for a positive test result. At the extreme ends of the spectrum, a high chance of false-positive and false-negative results can be expected. Choosing cutoff values in the middle section, that is, between 2 and 5 mm, probably reflects true change.⁹

A shortage of the study is the limited information on exposure to some allergens—for example, there was no information on exposure to furry pets. A total of 10% (35 study patients) initially free of dog allergy became sensitized to dog during the study. By assuming that the study patients who became sensitized to dog allergens must have been exposed to dogs, our results could indicate that having a dog may be a risk factor for additional sensitization. However, according to the data of Liccardi et al,²⁰ direct dog exposure in adults with respiratory allergy is not associated with greater cutaneous response to dog allergens compared with nonexposed patients. Additionally, there are a few possible sources of bias that could influence the occurrence of dog sensitization. Dog allergen extracts have been reported to be contaminated with house dust mite, therefore causing false-positive reactions among patients sensitized to house dust mite.²¹ Furthermore, several studies report IgE cross-reactivity among cat, horse, and dog dander because of similarities in albumin from these allergens.^{22–24}

Table 1. Distribution of Skin Test Reactivity to Different Test Allergens Among 344 Adult Atopic Patients

Allergen	Positive first SPT, No. (%)	Incident cases, No. (%)	Remitting cases, No. (%)	Unchanged
Birch	149 (43.3)	12 (3.5)	12 (3.5)	320
Grass	212 (61.6)	11 (3.2)	7 (2.0)	326
Mugwort	75 (21.8)	10 (2.9)	9 (2.6)	325
Horse	50 (14.5)	6 (1.7)	3 (0.9)	335
Dog	135 (39.2)	35 (10.2)	10 (2.9)	299
Cat	151 (43.9)	10 (2.9)	9 (2.6)	325
<i>Dermatophagoides pteronyssinus</i>	135 (39.2)	9 (2.6)	6 (1.7)	329
<i>Dermatophagoides farinae</i>	104 (30.2)	14 (4.1)	4 (1.2)	326
<i>Alternaria iridis</i>	24 (7.0)	5 (1.5)	6 (1.7)	333
<i>Cladosporium herbarium</i>	9 (2.6)	2 (0.6)	5 (1.5)	337

Abbreviation: SPT, skin prick test.

Table 2. Frequency of Positive (≥ 3 mm) Skin Prick Test Reactions Among 344 Adult Atopic Patients

No. of sensitizations	No. (%) of patients with first SPT	No. (%) of patients with second SPT
1	71 (20.6)	55 (16.0)
2	96 (27.9)	75 (21.8)
3	62 (18.0)	55 (16.0)
4	38 (11.0)	63 (18.3)
5	40 (11.6)	32 (9.3)
6	26 (7.6)	24 (7.0)
7	5 (1.5)	14 (4.1)
8	3 (0.4)	6 (1.7)
9	2 (0.6)	0 (0)
10	1 (0.3)	1 (0.3)
0	0 (0)	19 (5.5)
Mean	3.03	3.15

Abbreviation: SPT, skin prick test.

One could have wished for a third additional SPT examination to better show the pattern of longitudinal change. Perhaps measuring specific and total IgE also could have strengthened the findings on changes in skin reactivity; on the other hand, the SPT appears to be a good measure for the serum IgE levels. In particular, measuring specific IgE appears only to add prognostic information in the case of a mismatch between symptom history and SPT result. We studied symptomatic individuals only, and the long-term repeatability of a positive SPT reaction appears to be highest in the presence of a supportive history.⁹ On the contrary, we found evidence of new-onset sensitization among 6% of the nonsensitized symptomatic individuals, indicating that the rate of de novo sensitization is probably higher in such individuals compared with asymptomatic nonsensitized individuals.^{9,25}

To our knowledge, this is one of few longitudinal studies that have investigated changes in skin test reactivity in a large cohort of atopic adults. We conclude that a substantial proportion of adults with atopic disease have a change in SPT

status during a relatively short period. Most of these change for the worse, whereas a considerable proportion also tends to show remittance of 1 or more sensitizations. These results can be used for guidance in the evaluation of adult patients with atopic disease and may be useful for the prognostic evaluation of sensitized individuals. However, further longitudinal studies are required to determine the relationship among the timing of allergic sensitization, the natural progression of the sensitization, and the clinical course of atopic disease.

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