



Contents lists available at ScienceDirect



Natural history of skin prick test reactivity

A 20-year prospective study of a random population sample of children and adolescents

Jesper Schou Nielsen, MD^{*}; Howraman Meteran, MD^{*}; Charlotte Suppli Ulrik, MD, DMSci^{†,‡}; Celeste Porsbjerg, MD, PhD^{*,‡}; Vibeke Backer, MD, DMSci^{*,‡}

^{*} Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark

[†] Department of Pulmonary Medicine, Hvidovre Hospital, Hvidovre, Denmark

[‡] Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Article history:

Received for publication January 25, 2017.

Received in revised form April 10, 2017.

Accepted for publication May 1, 2017.

ABSTRACT

Background: Allergic reactions to airborne allergens may have important consequences for affected individuals and are believed to be unstable through life, although evidence from longitudinal studies is limited.

Objective: To assess changes in skin prick reactivity during 20 years in a random population sample of children and adolescents in relation to symptoms of rhinitis.

Methods: A total of 983 individuals, aged 7 to 17 years, were randomly selected in 1986 and invited to 4 examinations during a 20-year period. During each examination, a skin prick test was performed using common local aeroallergens (ie, birch, grass, mugwort, horse, dog, cat, house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*] and 2 molds [*Alternaria iridis* and *Cladosporium herbarum*]).

Results: The prevalence of allergy to any tested allergen peaked at the ages of 13 to 23 years. Rates of sensitization were variable. In the group of individuals tested more than once (n = 592), 16% developed sensitization during the study period and 9% became desensitized. In the group of individuals tested at all 4 examinations (n = 148), 34% developed sensitization and 22% became desensitized. In the group who developed sensitization, 55% had rhinitis, 17% had asthma, and 70% had eczema. In the group who became desensitized, 30% had rhinitis, 10% had asthma, and 50% had eczema.

Conclusion: This 20-year prospective study found that sensitization is common, but its prevalence in individuals is also variable over time. Furthermore, through puberty and early adulthood a large number of individuals develop sensitization and a smaller number become desensitized. In addition, we found that symptoms of rhinitis rarely preceded sensitization.

© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Allergy to airborne allergens is an increasing health problem^{1–3} and is associated with poor quality of life,⁴ primarily caused by an increase in symptoms in the upper and lower airways. Left untreated, allergies can result in an worsening of asthma symptoms,⁵ worsening of allergic rhinitis, and development of rhinosinusitis with polyposis⁶ and can lead to an exacerbation of atopic dermatitis.^{7,8} It has been estimated that improved treatment of allergic diseases in the skin and respiratory system can reduce the financial costs related to allergic diseases.⁹

An important tool in diagnosing an allergy is the skin prick test (SPT).^{10,11} However, our knowledge of changes over time in reactivity and the clinical implications of sensitization to the different groups of aeroallergens (ie, pollen, fur, house dust mites, and mold) remains limited. The few longitudinal studies completed have mostly observed the study population for a period of 2 to 8 years and found that sensitization is developed through childhood and puberty^{12,13} and lost in late adulthood.¹⁴ The aim of the present study was, therefore, to examine the change in SPT reactivity in a random population sample of children and adolescents during a 20-year period.

Methods

Material and Methods

The study participants were randomly selected from the Danish civil registration list based on each potential participant's

Reprints: Howraman Meteran, MD, Bispebjerg University Hospital, Respiratory Research Unit, Bispebjerg Bakke 23, Copenhagen NV, Copenhagen 2400, Denmark; E-mail: hmeteran@gmail.com.

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2017.05.001>

1081-1206/© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

year of birth between 1969 and 1979 and the date of birth falling during the first week of each month of the relevant year. Therefore, 983 children and adolescents aged 7 to 17 years from Copenhagen, Denmark, were identified and invited by letter to participate in a study that focused on asthma, allergy, and airway hyperresponsiveness. Participants 18 years or older gave written consent for participation; for participants younger than 18 years, written consent were obtained from the parents. The participants were examined 4 times during a 20-year period (1986, 1992, 1998, and 2006). Mean age when included in 1986 was 12 years.

Of the 983 individuals, 527 (54%) participated in the first examination, and 519 completed an SPT; 662 (67%) participated in the second examination, and all participants completed an SPT; 532 participated in the third examination, and 525 participants completed an SPT; and 297 (30%) participated in the fourth examination, and all participants completed an SPT (Table 1). A total of 835 individuals (85%) completed 1 or more SPT; 200 individuals (20%) completed 1 SPT; 250 individuals (25%) completed 2 SPTs; 237 individuals (24%) completed 3 SPTs; and 148 individuals (15%) completed SPTs in all 4 examinations. Study participants providing data from only 1 SPT were only included in the cross-sectional analyses.

Exclusion Criteria

Participants who were taking medication for asthma or allergies were asked not to use antihistamine for at least 24 hours before the SPT.

Skin Prick Test

SPTs were performed on the volar surface of the forearm with standard dilutions of allergens in 50% glycerol (ALK, Hørsholm, Denmark). The allergens used were birch, grass (timoté), mugwort, horse, dog, cat, house dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), *Cladosporium herbarium*, and *Alternaria iridis* (mold) (ALK-Abello, Hørsholm, Denmark).

Histamine hydrochloride (10 mg/mL) in 50% glycerol was used as a positive reference, and a negative reference (50% glycerol) was also included. The reactions were read after approximately 15 to 20 minutes. Double testing was used, so each allergen was tested 2 times at each examination, and reactions were measured as the largest diameter of the wheal for each reaction (D1 and D2). A reaction to each of the allergens was regarded as positive if the mean wheal diameter [(D1 + D2)/2] was at least 3 mm.¹⁵ In case of reaction to the negative reference, a positive result was recorded when the difference between the mean wheal diameter of the reaction to the allergen and that to the negative reference exceeded 3 mm. A positive SPT result was defined as a positive reaction to at least one of the allergens.¹⁵ Sensitization was defined as a positive SPT result.

Longitudinal Analyses

Individuals tested more than once were eligible for partial longitudinal analysis. Changes in sensitization to allergens were noted. Only individuals tested 4 times were eligible for full longitudinal analysis.

Statistical Analysis

The χ^2 test was used to compare the prevalence over time. Descriptive statistics were calculated using SPSS statistical software, version 22.0 (SPSS Inc, Chicago, Illinois). All individuals gave informed consent at each examination, and the local ethics committee in Copenhagen approved the study.

Results

Overall Prevalence of Sensitization

During the 20-year study period, the overall prevalence of sensitization increased from 24% at the first examination to 35% at the fourth examination ($P < .001$) (Fig 1). In the same examinations (ie, the first and fourth), sensitization to pollen increased from 13% to 30% ($P < .001$), with grass being the most common allergen, increasing from 7% to 23% ($P < .001$), birch increasing from 7% to 15% ($P < .001$), and mugwort increasing from 5% to 9% ($P = .03$) (Table 2). Sensitization to animal dander increased from 10% to 17% ($P = .006$), sensitization to house dust mites remained the same (14% vs 13%) ($P = .92$), and sensitization to molds increased from 3% to 6% ($P = .05$) (Fig 1).

Longitudinal Findings

In the group of individuals who had SPTs performed more than once, 16% developed sensitization and 9% became desensitized (Table 3). With respect to the group of individuals who underwent the SPT at all 4 examinations ($n = 148$ [14% of total cohort]), 34% developed sensitization, with the highest rate of sensitization between the first and second examinations. In terms of desensitization, 22% became desensitized during the study, peaking between the second and third examinations, with 15% becoming desensitized (Fig 2).

Symptoms

Of the 148 individuals participating in all examinations, 47 individuals developed sensitization during the study. Of these, 26 individuals (55%) had symptoms of rhinitis, 8 individuals (17%) had asthma, and 33 individuals (70%) had eczema during the study period. Of the 148 individuals participating in all examinations, 10 individuals lost sensitization during the study; of these, 3 individuals (30%) had rhinitis, 1 individual (10%) had asthma, and 5 individuals (50%) had eczema (Table 4). In this desensitization group, a large number of individuals lost their symptoms of allergic diseases during the study period; 2 individuals (67%) lost symptoms of rhinitis, 1 individual (100%) lost symptoms of asthma, and

Table 1
Characteristics of the 983 Study Participants From the Copenhagen Cohort Who Provided Data on SPT Reactivity From the 4 Examinations

Characteristic	Year				Complete data (n = 148)
	1986 (n = 519)	1992 (n = 662)	1998 (n = 525)	2006 (n = 297)	
Sex, M/F, No.	258/261	321/341	229/296	130/167	62/86
Age for M/F, mean (SD), y	12.1 (2.8)/12.3 (2.9)	18.5 (2.8)/18.7 (2.9)	23.9 (2.9)/23.9 (3.0)	33.2 (2.9)/33.3 (3.0)	21.9 (2.8)/21.9 (2.9)
SPT completed, %	98	100	99	100	100

Abbreviation: SPT, skin prick test.

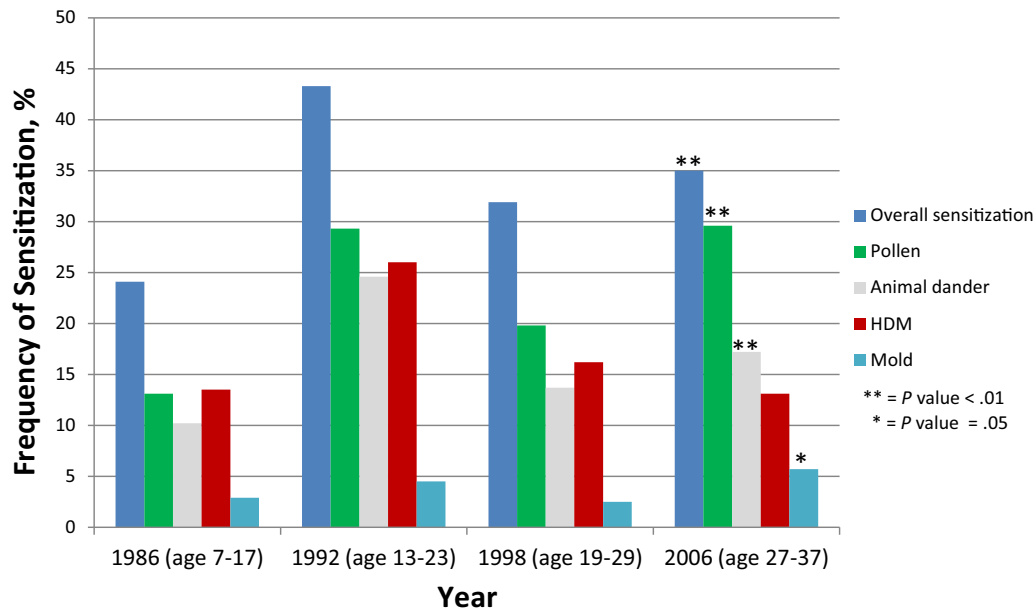


Figure 1. Prevalence of positive skin prick tests at the 4 examinations in 1986, 1992, 1998, and 2006 grouped into overall sensitization to any allergen and sensitization to pollen, animal dander, house dust mites, and mold. The listed *P* values show the difference in prevalence from 1986 to 2006.

2 individuals (40%) lost their symptoms of eczema. Only 3 individuals had symptoms of rhinitis before developing sensitization.

Discussion

Overall Prevalence of Sensitization

To our knowledge, this is the first follow-up study of a randomly selected population sample of children and adolescents followed up during a 20-year period. The study reveals an increasing prevalence of sensitization through puberty, with a peak in late puberty to early adulthood and a subsequent decline as the cohort ages. These results are consistent with the findings detailed in the existing literature. For instance, Nissen et al¹⁵ found, in a randomly selected group of infants tested 5 times with IgE blood samples until the age of 26 years, that sensitization to aeroallergens peaked at 15 to 26 years of age, with 32% overall sensitization in that age group. Two separate cross-sectional studies of healthy individuals^{16,17} ($n = 2,327$ and $n = 8,344$) found that sensitization is more frequent in young adults than in older age groups and that allergy peaks in puberty and decreases later in life. These findings are somewhat different than the present findings. Furthermore, a study by Park et al.¹⁸ of a randomly selected group of individuals with allergic symptoms indicated that young individuals

(≤ 30 years old) had a higher prevalence of positive SPT result than individuals in older age groups.

Results indicating that sensitization to pollen allergens is the most frequent allergy are supported by Barbee et al¹¹ in a general population study and Åslund et al¹⁹ in a study of sensitized persons. In addition, results indicating that animal dander and house dust mites are the second and third most common allergens, respectively, and mold is the rarest allergen are reported in several cross-sectional studies.^{2,20,21} We performed analyses in which we excluded the American house dust mite (*D. farinae*), and it did not change the overall results.

Longitudinal Changes in Sensitization

We found that during this study from childhood and teenage years into adulthood more individuals developed sensitization than lost sensitization, which is comparable to cross-sectional studies indicating that sensitization peaks in early adulthood^{16,21,22} and longitudinal studies following up individuals from childhood to adolescence.^{12,13}

Peat et al¹³ found a 16% increase in sensitization in a 4-year longitudinal study in children 8 to 10 years old to 12 to 16 years old ($n = 380$). We found a 24% increase in our youngest age group

Table 2
Distribution of Sensitization to Specific Allergens in 1986, 1992, 1998, and 2006

Allergen	Prevalence by year, %				<i>P</i> value ^a
	1986 ($n = 519$)	1992 ($n = 662$)	1998 ($n = 525$)	2006 ($n = 297$)	
Birch	7	13	9	15	<.001
Grass	7	23	15	23	<.001
Mugwort	5	9	6	9	.03
Horse	4	4	3	3	.26
Dog	7	18	8	13	.005
Cat	6	18	12	13	<.001
<i>Dermatophagoides pteronyssinus</i>	14	23	15	12	.52
<i>Dermatophagoides farinae</i>	NA	20	12	11	NA
<i>Alternaria</i>	3	4	2	4	.31
<i>Cladosporium</i>	1	1	1	3	.04
Overall sensitization	24	43	32	35	<.001

Abbreviation: NA, not applicable.

^a*P* value for change in prevalence from 1986 to 2006.

Table 3

Longitudinal Changes in Skin Prick Test Reactivity During 20 Years for Individuals Tested 2 or More Times

Group	No. (%) of patients
Never sensitized	326 (52)
Always sensitized	133 (22)
Development of sensitization	96 (16)
Desensitization	55 (9)
Total	592 (100 ^a)

^aPercentage does not total because of rounding.

followed up for 6 years, although this age group consisted of both teenagers and children, which might contribute to the higher sensitization rate. Kuehr et al¹² reported an increase in sensitization in a population aged 7 to 16 years followed up for 2 years. In addition, the duration of these studies is much shorter than the duration of our study. In contrast to these findings, Kaleyias et al²³ found no change in sensitization in a group of children followed up through puberty.

To our knowledge, no studies have reexamined the same population more than 3 times. Our study found an increase in sensitization from 20% to 32% in the group tested at all 4 sessions (Fig 2). The possible outcomes for the skin prick test in the group of individuals tested at all 4 examinations are shown in eTable 1. We performed nonresponder analysis that revealed no difference in the response rate for individuals who tested positive vs negative at their first examination ($P = .29$). Development of sensitization occurred predominantly between the first 2 examinations ($n = 35$), suggesting development of sensitization is more frequent in puberty. Unexpectedly, on the basis of the cross-sectional findings of this study, a smaller number of individuals ($n = 16$) became sensitized during the final 2 study sessions. Desensitization peaked between examinations 2 and 3 at ages 13 to 23 years and 19 to 29 years, suggesting sensitization is unstable in puberty and early

adulthood. The results indicate that more than a half of the individuals who develop sensitization in puberty are desensitized later in the study, predominantly between the second and third examinations.

Our study has a number of strengths. First, it focuses on a large randomly selected study sample. Second, a 20-year follow-up period is, to our knowledge, the longest reported in the literature. Third, the same SPT kit was used at each examination. Fourth, double testing was performed at each examination.

This study also has some limitations. First, a positive SPT result was defined as a wheal of 3 mm or larger, which excludes individuals with sensitization with a wheal smaller than 3 mm, although this is a widely used definition of a positive SPT result. Second, the study involved several physicians who performed and interpreted the SPT results, which can result in interobserver variability. Repeated measurements of SPTs are associated with a repeatability that ranges from 70% (positive SPT result) to 90% (negative SPT result).²⁴ However, because we used double testing, the variability in SPT results is reduced. Third, the 24-hour restriction of oral antihistamine use might have resulted in some false-negative results. We have no data on the exact number of participants who used oral antihistamine within 24 to 72 hours before testing. However, only 8% to 10% of the participants used antihistamine when they experienced symptoms. Fourth, the study has a large dropout rate, with only 15% completing all 4 examinations. Analyses revealed no difference in dropout rate between sensitized and nonsensitized individuals. The most likely reason for the high dropout rate is that the participant grew into adulthood and moved to other parts of Denmark.

Conclusion

To our knowledge, this is the largest and longest study of sensitization to common airborne allergens over time in a randomly selected population of children and adolescents. The

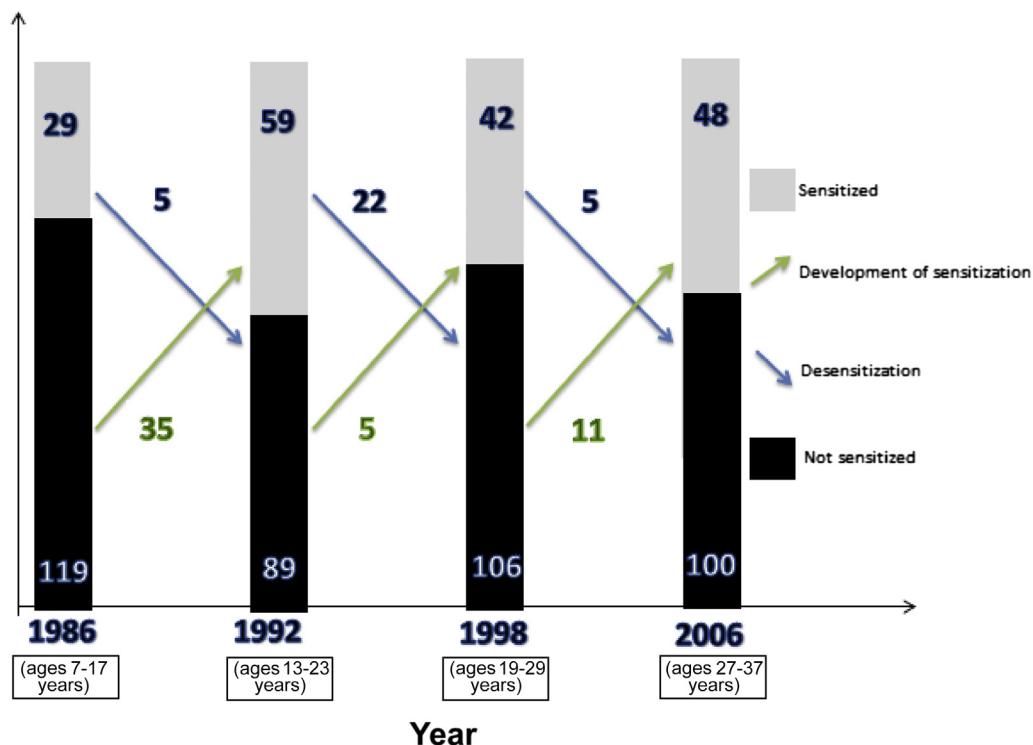


Figure 2. Longitudinal changes in skin prick test reactivity for the group of individuals ($n = 148$) with complete data on skin prick tests performed at all 4 examinations. Individuals are grouped into sensitized (gray) and not sensitized (black). Green arrows indicate development of sensitization; blue arrows, desensitization.

Table 4

Distribution of Rhinitis, Asthma, and Eczema in the 148 Participants Tested at All 4 Examinations

Study group	No. (%) of patients		
	Rhinitis	Asthma	Eczema
Never sensitized (n = 72)	10 (14)	4 (5)	8 (11)
Always sensitized (n = 19)	19 (100) ^a	7 (36) ^a	19 (100) ^a
Development of sensitization (n = 47)	26 (55) ^a	8 (17) ^b	33 (70) ^a
Desensitization (n = 10)	3 (30) ^c	1 (10) ^c	5 (50) ^a

^aP < .01 for the difference in the distribution of rhinitis, asthma, and eczema in the study groups.^bP < .05 for the difference in the distribution of rhinitis, asthma, and eczema in the study groups.^cP values is nonsignificant.

findings of this study confirm that sensitization is common, but the prevalence in individuals is variable over time. We found that through puberty and early adulthood a large number of individuals develop sensitization and a smaller number of individuals become desensitized. These findings further support earlier findings that sensitization to allergens can change over time. Furthermore, we found that symptoms of rhinitis rarely preceded sensitization.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.05.001>.

References

- [1] Rönmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundbäck B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol*. 2009;124:357–363.
- [2] Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy*. 1995;25:815–881.
- [3] Linneberg A, Jørgensen T, Nielsen NH, Madsen F, Frølund L, Dirksen A. The prevalence of skin-test-positive allergic rhinitis in Danish adults: two cross-sectional surveys 8 years apart. *Allergy*. 2000;55:767–772.
- [4] Baiardini I, Braido F, Brandi S, Canonica GW. Allergic disease and their impact on quality of life. *Ann Allergy Asthma Immunol*. 2006;97:419–428.
- [5] Bousquet J, Gaugris S, Kocavar VS, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy. *Clin Exp Allergy*. 2005;36:723–727.
- [6] Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol*. 2000;105(6, pt 2):S605–S609.
- [7] Werfel T, Heratizadeh A, Niebuhr M, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol*. 2015;136:96–103.
- [8] Darsow U, Vieluf D, Ring J. Atopy Patch Test Study Group. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double-blind multicenter study. *J Am Acad Dermatol*. 1999;40(2, pt 1):187–193.
- [9] Zuberbier T, Lötval J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. *Allergy*. 2014;69:1275–1279.
- [10] Fornadley JA. Skin testing for inhalant allergy. *Int Forum Allergy Rhinol*. 2014;4(suppl 2):s41–s45.
- [11] Barbee RA, Lebowitz MD, Thompson HC, Burrows B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med*. 1976;84:129–133.
- [12] Kuehr J, Karmaus W, Frischer T, et al. Longitudinal variability of skin prick test results. *Clin Exp Allergy*. 1992;22:839–844.
- [13] Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol*. 1990;85(pt 1):65–74.
- [14] Barbee RA, Kaltenbom W, Lebowitz MD, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol*. 1987;79:16–24.
- [15] Nissen SP, Kjaer HF, Høst A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. *Pediatr Allergy Immunol*. 2013;24:549–555.
- [16] Kerkhof M, Dubois AE, Postma DS, Schouten JP, de Monchy JG. Role and interpretation of total serum IgE measurements in the diagnosis of allergic airway disease in adults. *Allergy*. 2003;58:905–911.
- [17] Wüthrich B, Schindler C, Medici TC, Zellweger JP, Leuenberger P. SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team. IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. *Int Arch Allergy Immunol*. 1996;111:396–402.
- [18] Park HJ, Lim HS, Park KH, Lee J, Park JW, Hong CS. Changes in allergen sensitization over the last 30 years in Korea respiratory allergic patients: a single-center trial. *Allergy Asthma Immunol Res*. 2014;6:434–443.
- [19] Aslund N, Thomsen SF, Mølgaard E, Nolte H, Backer V. Changes in skin test reactivity among adults with atopic disease: a 3-year prospective study. *Ann Allergy Asthma Immunol*. 2008;101:524–528.
- [20] Gergen PJ, Turkeltaub PC, Kovar MG. The prevalence of allergic skin test reactivity to eight common aeroallergens in the U.S. population: results from the second National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 1987;80:669–679.
- [21] Cline MG, Burrows B. Distribution of allergy in a population sample residing in Tucson, Arizona. *Thorax*. 1989;44:425–431.
- [22] Lee JE, Ahn JC, Han DH, et al. Variability of offending allergens of allergic rhinitis according to age: optimization of skin prick test allergens. *Allergy Asthma Immunol Res*. 2014;6:47–54.
- [23] Kaleyias J, Papaioannou D, Manoussakis M, Syrigou E, Tapratzi P, Saxonipapageorgiou P. Skin-prick test findings in atopic asthmatic children: a follow-up study from childhood to puberty. *Pediatr Allergy Immunol*. 2002;13:368–374.
- [24] Bodtger U, Jacobsen CR, Poulsen LK, Malling HJ. Long-term repeatability of the skin prick test is high when supported by history or allergen-sensitivity tests: a prospective clinical study. *Allergy*. 2003;58:1180–1186.

eTable 1Possible Outcomes of the 4 Skin Prick Tests^a

Possible outcome	No. (%) of individuals
1-1-1-1	72 (48.6)
1-1-1-2	7 (4.7)
1-1-2-1	1 (0.7)
1-1-2-2	4 (2.7)
1-2-1-1	15 (10.1)
1-2-1-2	2 (1.4)
1-2-2-1	4 (2.7)
1-2-2-2	14 (9.5)
2-1-1-1	5 (3.4)
2-2-1-1	3 (2.0)
2-2-1-2	2 (1.4)
2-2-2-2	19 (12.8)
Total	148 (100)

^aTest results for the individuals participating in all 4 examinations: 1, negative skin prick test result; 2, positive skin prick test result.