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The predictive value of allergen skin prick tests and IgE tests at pre-school age: The PACT study

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Keywords
allergic rhinoconjuncitivitis; asthma; atopic eczema; birth cohort; prediction; prevalence; receiver operating characteristic; sensitization; skin prick test; specific IgE

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Abstract

Background: Sensitization toward allergens, as determined by skin prick test (SPT) or specific IgE (sIgE), is a predictor for the later presence of allergy-related disease (atopic eczema, allergic rhinoconjuctivitis and asthma). However, it is not known whether SPT or sIgE should be the preferred test. The aim of this study was to compare the predictive ability of SPT and sIgE when performed in a general population of 2-yr-old children.

Methods: In a prospective, longitudinal population-based study of children aged 2–6 yr, SPT and sIgE for nine common allergens were performed at 2 yr. Allergy-related disease was evaluated by clinical examination and questionnaire at 2 and 6 yr of age (n = 199).

Results: Skin prick test or sIgE was positive in 10.6% and 21.1% in the 2-yr-old children, respectively. The prevalence of allergy-related disease was 25.6% at 2 yr and 25.1% at 6 yr. Half of the cases at 2 yr were transient. Both SPT and sIgE were statistically significant predictors for later allergy-related disease, OR = 6.5 (95% CI 2.3–18.6) and OR = 4.1 (95% CI 1.9–9.0), respectively. Receiver operating characteristic analysis showed that SPT and sIgE had comparable predictive ability for atopic eczema, asthma or any allergy-related disease, but sIgE had better ability to predict later allergic rhinoconjunctivitis.

Conclusion: Sensitization at 2 yr may be useful predictors of allergy-related disease later in childhood. The predictive ability of SPT and sIgE were mainly comparable; however, it may be that sIgE is the preferred choice in young children when the aim is to predict allergic rhinoconjunctivitis.

In Norway, 21% of the children are allergy-tested before 2 yr of age (1). Sensitization toward allergens early in life, especially before the age of 2, is a predictor for later allergy-related disease (atopic eczema, asthma and allergic rhinoconjuncitivitis) and may precede the onset of symptoms by several years (2–11). Early identification of children at risk provides the opportunity to take preventive measures (12).

Both skin prick testing (SPT) and specific IgE (sIgE) immunoassays are used for assessing sensitization. SPT and sIgE are different tests of a biological diverse phenomenon. SPT reflects allergen-sIgE bound to the mast cell in the skin, whereas sIgE immunoassays detect the level of allergen-sIgE in serum. The allergen extracts used are not the same, and the results do not show perfect agreement (13, 14). It is uncertain whether SPT or sIgE is the best predictor of allergy-related disease, as only a few longitudinal studies in general populations include both tests. Furthermore, sensitization is usually considered categorically (positive/negative), even though using quantitative measures may improve the predictive value of the tests (8, 15, 16).

Our hypothesis was that SPT and sIgE are equally useful in predicting allergy-related disease. The aim of this study was to compare the usefulness of SPT and sIgE at 2 yr of age in a general population as predictors for allergy-related disease at 6 yr of age, evaluating both the dichotomous and the quantitative values of the tests.

Materials and methods

Population

The Prevention of Allergy among Children in Trondheim (PACT) study is a large prospective birth cohort intervention study aiming to reduce the incidence of allergy-related disease among children (17). Participants in two substudies of the PACT study, the 'Immunology and Microbial study in PACT' (IMPACT) and 'The Probiotic study in PACT' (Pro-PACT), were included in this study. The original substudies are described in detail elsewhere (17, 18). Briefly, 720 pregnant women were recruited to the IMPACT study from March 2001 to September 2002. When their offspring were 2 yr of age, 390 children attended a clinical examination and structured interview during which the parents provided details regarding the presence of allergy-related disease. In the ProPACT study, 415 pregnant women were included from September 2003 to 2005 and 278 of their children attended a clinical examination at 2 yr. The current study population thus consisted of 668 children. At 2 yr of age, SPT was performed in 542 and sIgE in 422 children. Both tests could not be completed in all children, as only one attempt at SPT and venipuncture was permitted to avoid too much discomfort. At 6 yr of age, the children were invited to a clinical examination and structured interview identical to the examination at 2 yr. Complete data for SPT and sIgE at 2 yr, and clinical data at 2 and 6 yr were available for 199 children (Fig. 1). Additionally, prior to the clinical examination, the parents completed a detailed questionnaire regarding the child's health.

Disease outcome

At both 2 and 6 yr, the 12-month prevalence and severity of atopic eczema were assessed using a structured clinical interview and skin inspection for the presence of eczematous lesions, while the 12-month prevalence of asthma and the cumulative incidence of allergic rhinoconjunctivitis were assessed using questions only. Atopic eczema was defined according to the UK working party's criteria, and the severity was assessed with the Nottingham Eczema Severity Score (19, 20). In brief, the UK working party's criteria demands the presence of an itchy skin condition in the last 12 months plus 3 or more of the following minor criteria: onset below age 2, history of flexural involvement, history of dry skin, personal history of other atopic disease or visible flexural dermatitis. The first minor criteria: onset before age 2 was not used when the child was 2 yr. Current asthma was defined as an answer of 'yes' to both of the following questions: 'Has the child ever had doctor-diagnosed asthma?' and 'Has the child been treated with tablets, inhalation medicine or other treatment for wheezing, tightness in the chest or asthma during the last 12 months?' Allergic rhinoconjunctivitis was defined as an answer of 'yes' to the question 'Has the child ever had hay fever or allergic rhinoconjunctivitis?' The child was considered having 'any allergy-related disease' if at least one of the three allergy-related diseases were present.

The questions concerning asthma and allergic rhinoconjunctivitis in the questionnaire completed by the parents were identical to those used in the structured interview conducted as part of the clinical examination at 2 and 6 yr. Questions concerning atopic eczema in the questionnaire were 'Has your

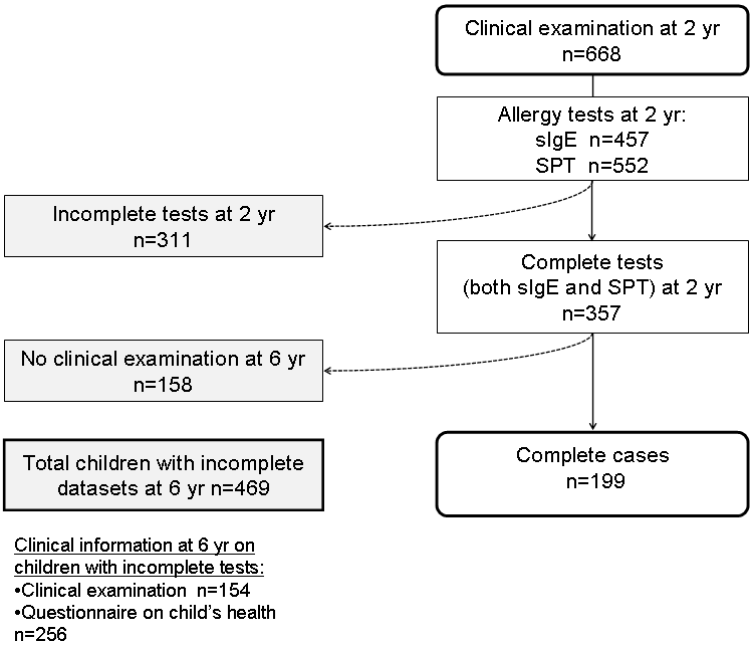

Figure 1 Inclusion of participants. The children were included as complete cases only if all data for both SPT and sIgE at 2 yr, and clinical examination and questionnaires at both 2 and 6 yr were available. sIgE, specific Immunoglobulin E; SPT, skin prick test.

child ever had eczema?' and 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' Answers provided in the questionnaire completed by the parents were used in the absence of clinical examination results for the multiple imputation analyses described below. The answers provided in the questionnaire showed very good agreement with the answers given during clinical examination. In cases where responses were conflicting, the answer from the clinical examination was used for analysis.

Allergen-specific tests

Allergen-specific SPT and sIgE were evaluated for nine common allergens in our geographic area. Food allergens included egg white (F1), milk (F2), fish (F3), peanut (F13), and hazelnut (F17). Inhalant allergens included dog (E5), cat (E1), birch (T3), and timothy (G6). sIgE was analyzed using the Immulite 2000 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). IgE concentrations of 0.35 kU/l or above were considered positive. For SPT allergen, extracts from Soluprick (ALKAbello, Copenhagen, Denmark) were used, except for milk where undiluted fresh skimmed milk was used, as this was the routine method of milk SPT at the Department of Pediatrics, Trondheim University Hospital, Norway. The SPT was performed according to the ISAAC II procedure (21). Parents were asked to stop antihistamine medication and to avoid steroid creams on the forearms of their children 1 wk prior to testing. The tests were read after 15 min. Histamine 10 mg/ml and diluent (NaCl) were used as positive and negative controls, respectively. A positive SPT was defined as a mean wheal diameter at least 3 mm greater than the negative control. A child was considered to be sensitized if any of the SPT or sIgE tests were positive.

The maximum quantitative value (sIgE value and SPT wheal diameter) for any of the tested allergens for each child was calculated. For instance, if a child had an sIgE value of 3.5 kU/l for cat, and lower value for the rest of the sIgE tests, her maximum quantitative value for sIgE would be 3.5 kU/l. Likewise, for the SPT, if the largest wheal were 9 mm, then this would be considered the maximum SPT value.

Statistics

Statistical analyses were performed using STATA (version 12.1; College Station, TX, USA). In tables, the data are presented as percentages or means with 95% confidence interval. Confidence intervals for proportions were calculated by the 'proportion' command in STATA. Differences between groups were analyzed by the chi-square test or Fisher's exact test for categorical data and *t*-test for continuous data. Logistic regression was conducted to assess the dichotomous values of SPT and sIgE in predicting allergy-related disease at 6 yr. The analysis was performed separately for SPT and sIgE. The predictive value of the quantitative values of SPT and sIgE was further assessed by comparing areas under the curve (AUC) of receiver operating characteristics (ROC) curves from the maximum quantitative values. The equality of the AUC of the ROC curves was tested by chi-square with the 'roccomp' procedure. Logistic regression and ROC comparison analyses were performed in the total population and as a subgroup analysis with only children without allergy-related disease at 2 yr included. Possible confounding factors were identified by *a priori* knowledge, and their influence on the presence of any allergy-related disease at 6 yr was individually evaluated using univariate logistic regression analyses. Due to the study size, only the most influential confounders were included, being allergy-related disease at 2 yr and allergy-related disease in first-degree relatives.

As sensitivity analyses, we used multiple imputations to evaluate the impact of missing data. Multiple imputations ($m = 50$) were performed using chained equations under the assumption that the data was missing at random, given the observed data (22). The imputation model included the following predictor variables from both 2 and 6 yr: atopic eczema, asthma, allergic rhinoconjunctivitis from clinical examination and questionnaire, SPT, sIgE, and gender and atopic disease in first-degree relatives. Logistic regression was conducted on the imputed data separately for SPT and sIgE and adjusted for the same variables as for the complete cases.

Ethics

The study was performed according to the Helsinki declaration. Written informed consent was signed by the parents. The study was approved by the Regional Committee for Medical Research Ethics (Ref 097-03) and by the Norwegian Data Inspectorate to process personal health data. The current Controlled Trials number is ISRCTN28090297.

Results

Baseline characteristics of the children with complete (n = 199) and incomplete data at 6 yr (n = 469) are shown in Table 1. The children with complete data had a statistically significant higher frequency of first-degree relatives with allergy-related disease (p = 0.001), and atopic eczema at 2 yr (p = 0.04). Otherwise the baseline characteristics were comparable between the children with and without complete data. Atopic eczema-affected children had mild to moderate disease with NESS score below 11. Sensitization status for children with complete tests at 2 yr is shown in Table 2. Statistically significant higher frequencies of positive SPTs for any allergens (p = 0.016), for food allergens (p = 0.049), inhalation allergens (p = 0.003), and of sIgE for inhalation allergens (p = 0.008) were observed among the children with complete compared to children with incomplete clinical data at 6 yr.

The prevalence of any allergy-related disease at 2 yr was 25.6% (Table 1). For a substantial proportion of the children, allergy-related disease was transient. Half the children (26/51) with allergy-related disease at 2 yr did not have allergy-related disease at 6 yr, and half (25/51) had persistent allergy-related disease at 6 yr. The incidence of children with newly developed allergy-related disease at 6 yr of age was 17% (25/148). At 6 yr, the total prevalence of atopic eczema was 36/199 (18.1%), asthma 7/199 (3.5%), and allergic rhinoconjuncitivitis 18/199

Table 1 Baseline characteristics and prevalence of allergy-related diseases at 2 yr (n = 668)

	Children with complete data (n = 199)		Children with incomplete data (n = 469)		p-value
	%	95% CI	%	95% CI	
Gender (male)	50.2	43.2–57.2	49.4	44.5–53.6	0.78
Born >2 wk before term	8.0	4.2–11.9	8.8	6.2–11.4	0.74
Sibling(s)	67.3	60.7–74.0	62.1	57.6–66.5	0.2
Allergy-related disease in first-degree relatives	83.4	78.2 –88.6	71.1	67.0–75.3	**0.001**
Cat indoors	11.6	7.1–16.1	9.0	6.4–11.6	0.31
Dog indoors	6.1	2.7–9.4	8.0	5.5–10.4	0.39
Mother smoking	10.7	6.3–15.1	12.0	9.0–15.0	0.63
Father smoking	11.1	6.6–15.6	11.0	8.0–14.0	0.96
Any allergy-related disease*	25.6	19.5–31.7	20.3	16.6–23.9	0.12
Atopic eczema	21.1	15.3–26.8	14.7	11.4–17.9	**0.04**
Asthma	4.5	1.6–7.4	6.4	4.2–8.6	0.35
Allergic rhinoconjunctivitis	1.0	0–2.4	1.7	0.5–2.9	0.73
	Mean	95% CI	Mean	95% CI	p-value
Birth weight (g)	3638	3567–3706	3635	3587–3683	0.96
Education, father (yr)	14.6	14.1–14.9	14.7	14.4–14.9	0.81
Education, mother (yr)	15.2	14.9–15.5	15.3	15.1–15.5	0.64

Differences between groups were analyzed by chi-square test or Fisher's exact test for categorical data and *t*-test for continuous data. Significant p-values in bold.
*Any allergy-related disease was defined as presence of at least one of the three diseases: atopic eczema, asthma, and allergic rhinoconjuncitivitis..

(9.0%), and 50 of 199 children (25.1%) had any allergy-related disease.

Predictors for allergy-related disease at 6 yr

Children sensitized at 2 yr had increased risk of allergy-related disease at 6 yr. Univariate analyses of potential confounders showed allergy-related disease at 2 yr of age, OR: 4.7 (95% CI: 2.4–9.5), and disease in first-degree relatives, OR: 2.1 (0.8–5.7), to be the most influential independent risk factors for allergy-related disease at 6 yr (Table 3). The odds for having an allergy-related disease at 6 yr given a positive test at 2 yr were higher for SPT than sIgE, both in crude and adjusted estimates (Tables 4 and 5). In the subgroup of children without an allergy-related disease at 2 yr, positive SPT or sIgE at 2 yr was associated with any allergy-related disease and allergic rhinoconjunctivitis at 6 yr. The presence of atopic eczema at 6 yr

Table 2 Prevalence of sensitization for children with complete tests at 2 yr (n = 357)

Sensitization at 2 yr	Children with complete clinical data at 6 yr (n = 199)			Children with incomplete clinical data at 6 yr* (n = 158)			p-value
	n	%	95% CI	n	%	95% CI	
SPT							
Any allergen†	21	10.6	6.2–14.9	6	3.8	0.8–6.8	0.016
Food allergens	18	9.0	5.0–13.1	6	3.8	0.8–6.8	0.049
Inhalation allergens	10	5.0	2.0–8.1	0	0	–	0.003
sIgE							
Any allergen†	42	21.1	15.4–26.8	23	14.6	9.0–20.1	0.111
Food allergens	31	15.6	10.5–20.7	22	13.9	8.5–19.4	0.662
Inhalation allergens	21	10.6	6.2–14.9	5	3.1	4.1–5.9	0.008

SPT, skin prick test; sIgE, specific Immunoglobulin E.
Differences between groups were analyzed by chi-square test or Fisher's exact test for categorical data and *t*-test for continuous data.
*Both tests (SPT and sIgE) were complete, but clinical data at 6 yr were incomplete.
†Positive to at least one of the tested allergens.

Table 3 Effect of potential risk factors for presence of any allergy related-disease at 6 yr (complete cases, n = 199)

	OR	95% CI
Gender (male)	1.1	0.6–2.1
Born >2 wk before term	0.4	0.1–1.8
Sibling(s)	0.7	0.3–1.7
Allergy-related disease in first-degree relatives	2.1	0.8–5.7
Cat indoors	0.3	0.0–2.1
Dog indoors	0.8	0.3–2.4
Mother smoking	1.8	0.7–5.1
Father smoking	1.6	0.6–4.2
Any allergy-related disease at 2 yr*	4.7	2.4–9.5
Birth weight (g)	1.0	1.0–1.0
Education, father (yr)	1.0	0.9–1.1
Education, mother (yr)	1.0	0.9–1.2

Odds ratio (OR) calculated by univariate logistic regression.
*Any allergy-related disease was defined as presence of at least one of the three diseases: atopic eczema, asthma, and allergic rhinoconjuncitivitis.

was only associated with a positive SPT at 2 yr in this subgroup (Table 5). Analyses performed on imputed datasets (n = 668, $m = 50$) gave comparable results (Tables 4 and 5).

Positive SPT at 2 yr had 28% sensitivity, 95% specificity, positive predictive value of 67%, and negative predictive

Table 4 Associations between sensitizations at 2 yr and prevalence of allergy-related disease at 6 yr of age (total population)

	Complete cases n = 199		Imputed datasets, *m* = 50 n = 668	
	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Any allergy-related disease†				
SPT	7.9 (3.0–21.0)	6.5 (2.3–18.6)	9.2 (4.0–21.2)	7.3 (2.9–18.3)
sIgE	4.4 (2.1–9.1)	4.1 (1.9–9.0)	3.9 (2.2–6.8)	3.3 (1.8–6.1)
Atopic eczema				
SPT	6.7 (2.5–17.5)	7.0 (2.7–18.3)	7.1 (3.2–15.7)	5.3 (2.2–12.6)
sIgE	3.1 (1.4–6.7)	3.1 (1.4–6.9)	2.8 (1.5–5.1)	2.1 (1.1–4.2)
Asthma				
SPT	3.6 (0.7–20.1)	na	5.9 (2.0–16.9)	na
sIgE	5.4 (1.2–25.2)	na	1.6 (1.7–14.2)	na
Allergic rhinoconjunctivitis				
SPT	4.0 (1.3–12.6)	4.2 (1.3–13.4)	5.3 (2.3–12.3)	3.4 (1.4–8.4)
sIgE	5.8 (2.1–15.9)	6.2 (2.2–17.1)	4.9 (2.4–10.1)	3.9 (1.8–8.4)

SPT, skin prick test; sIgE, specific Immunoglobulin E; OR, odds ratio; na, not applicable due to few cases.
The association between sensitization at 2 yr and allergy-related disease at 6 yr of age was analyzed separately for SPT and sIgE. The same analyses were performed on imputed datasets (n = 668, *m* = 50).
*Adjusted OR: OR adjusted for any allergy-related disease at 2 yr and allergy-related disease in first-degree relatives.
†Any allergy-related disease was defined as presence of at least one of the three allergy diseases: atopic eczema, asthma, and/or allergic rhinoconjuncitivitis.

Table 5 Subgroup analysis of associations between sensitizations at 2 yr and prevalence of allergy-related disease at 6 yr of age in children without any allergy-related disease at 2 yr

	Complete cases n = 148		Imputed datasets *m* = 50 n = 522	
	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Any allergy-related disease†				
SPT	5.9 (1.5–22.2)	6.3 (1.6–24.3)	6.7 (2.2–21.0)	6.9 (2.2–21.6)
sIgE	2.7 (1.0–7.3)	2.8 (1.1–7.6)	3.0 (1.4–6.3)	3.0 (1.4–6.3)
Atopic eczema				
SPT	6.4 (1.6–25.7)	6.7 (1.6–27.2)	6.8 (2.1–22.6)	6.9 (2.1–23.0)
sIgE	2.2 (0.7–6.8)	2.2 (0.7–7.0)	2.2 (0.8–5.3)	2.1 (0.8–5.3)
Asthma				
SPT	na	na	4.2 (0.5–34.0)	na
sIgE	2.4 (0.2–27.5)	na	4.1 (0.9–19.7)	na
Allergic rhinoconjunctivitis				
SPT	5.5 (1.0–31.7)	5.9 (1.0–35.1)	4.2 (0.9–19.6)	4.3 (0.9–19.9)
sIgE	5.4 (1.2–23.1)	5.7 (1.3–24.7)	5.5 (1.7–18.4)	5.5 (1.6–18.4)

SPT, skin prick test; sIgE, specific Immunoglobulin E; OR, odds ratio; na, not applicable due to few cases.
The association between sensitization at 2 yr and allergy-related disease at 6 yr of age was analyzed separately for SPT and sIgE. The same analyses were performed on imputed datasets (n = 668, *m* = 50).
*Adjusted OR: OR adjusted for allergy-related disease in first-degree relatives.
†Any allergy related disease was defined as presence of at least one of the three allergy diseases: atopic eczema, asthma and/or allergic rhinoconjuncitivitis.

value of 80% for predicting allergy-related disease at 6 yr. Positive sIgE had 42% sensitivity, 86% specificity, positive predictive value of 50%, and negative predictive value of 82%.

Comparisons of AUC in ROC curves utilizing the maximum quantitative results of SPT and sIgE as predictors for allergy-related disease at 6 yr are shown in Fig. 2. There was no statistically significant difference between SPT and sIgE for predicting any allergy-related disease at 6 yr when all three diseases were combined. However, when differentiating between the three diseases, sIgE predicted allergic rhinoconjuncitivitis at 6 yr statistically significantly better than SPT

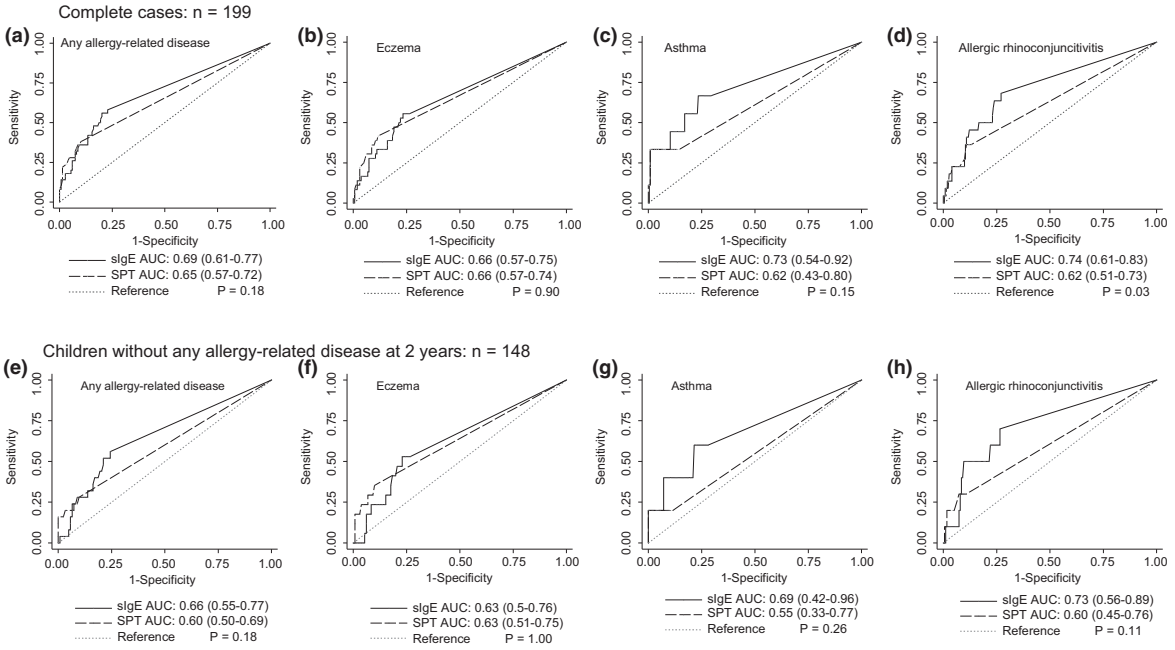

Figure 2 Comparison of specific Immunoglobulin E (sIgE) and SPT for prediction of allergy-related disease. Maximum quantitative values of SPT and sIgE at 2 yr for any of the nine allergens were used as predictors for allergy-related disease at 6 yr for any allergy-related disease and for the separate diseases. ROC comparisons were performed on total population of complete cases (n = 199) (a–d), and subgroup analysis were performed on the children without allergy-related disease at 2 yr (n = 148) (e–h). SPT, skin prick test.

($\chi^2(1) = 4.85$, $p = 0.03$). No statistical differences were found between the performance of SPT or sIgE in the subgroup of children without allergy-related disease at 2 yr. There was no statistically significant difference between food and inhalant sensitization as predictors (data not shown).

Discussion

At 2 yr of age, 10.6% had a positive SPT and 21.1% had a positive sIgE. The prevalence of allergy-related disease was 25.6% at 2 yr and 25.1% at 6 yr. Half of the cases at 2 yr were transient. We found early sensitization indicated by SPT and sIgE to be statistically significant predictors for presence of allergy-related disease at 6 yr, both in children with and without allergy-related disease at 2 yr of age, consistent with the findings of prior studies (2–11). In this study, a positive test at 2 yr would correctly predict presence of allergy-related disease at 6 yr in 50–67% of the children. The Danish Allergy Research Centre (DARC) study reported that children with early sensitization to food allergens had increased risk of allergic disease at 6 yr, whereas children early sensitized to inhalant allergens did not (3). We did not find a similar difference. The discrepancy may be a result of the study size, as the DARC study had sIgE values for twice as many children.

In our study, positive SPT seemed to be more strongly associated with later allergy-related disease than sIgE with higher odds ratios, with the exception of allergic rhinoconjunctivitis. However, the difference was not statistically significant, with wide and overlapping confidence intervals (Tables 4 and 5). Many studies have evaluated sensitization as predictor of allergy-related diseases either by SPT or sIgE, and the reported odds ratios for SPT are generally higher than for sIgE (2, 3, 8, 15, 23). These estimates are not directly comparable as the tests are not performed in the same population. A few studies performed both SPT and sIgE, but even in these studies, SPT and sIgE were evaluated separately, as few children were tested with both methods (3, 8). In the present study, a large number of children were allergy-tested with both SPT and sIgE. We were therefore able to make a direct comparison on the same population for both tests. As far as we know, this is the first study performing such direct comparison.

The quantitative value of sIgE levels and SPT wheal diameters and ROC analysis offer more information and better demonstrate the predictive value of tests than dichotomised (positive/negative) test results and the odds ratio from logistic regression analyses (8, 15, 24, 25). Comparing the AUCs for the ROC analysis of the quantitative values, sIgE had slightly better ability to predict later allergic rhinoconjuncitivitis. There was also a tendency for sIgE to be better at predicting asthma; however, this difference was not statistically significant due to few cases. The resolution in lower levels was better for sIgE compared to SPT, and this increased sensitivity may be of particular importance when the aim is to predict

allergies with airway symptoms. Another explanation could be that this difference is related to the young age of the children as it is known that SPT should be interpreted with caution in young children (12).

The strengths of this study are that it is a prospective cohort study of young children with long follow-up time, recruited from a general population, and that a large number of children were allergy-tested with both SPT and sIgE.

A potential limitation of the study is the frequency of missing data leading to reduced power and the possibility of selection bias. Indeed, the children with complete data reported a higher frequency of allergy-related disease among first-degree relatives compared to the children with incomplete data and the prevalence of allergy-related disease was slightly higher among complete compared to incomplete cases at 2 yr. This selection bias may have influenced our findings. However, disease prevalence and frequency of positive tests were comparable to other studies performed in general populations and the results from sensitivity analyses using multiple imputations were comparable to the complete case analyses (3, 15). Therefore, we consider that the missing values did not substantially influence our results. Another limitation is the low frequency of positive test results and allergy-related disease at 6 yr which limits the number of possible confounders one can adjust for without over-fitting the model. However, lower disease prevalence is a known trade-off when the participants are recruited from a general population, as opposed to a hospital-based study.

Another limitation of this study is that for allergic rhinoconjuncitivitis and asthma, we relied on accurate parental reporting, and not clinical examination. The question: 'Has the child ever had doctor-diagnosed asthma?' showed very good agreement with the occurrence of more than two obstructive episodes as found in the children's medical records (26). The symptoms of allergy-related diseases may be intermittent. The diagnosis of asthma and allergic rhinoconjunctivitis in 2-yr-old children is complex, and the ISAAC questions are not as suitable for 2-yr-old children as for older children. We chose to use doctor's diagnose as this would include earlier and current symptoms and exclude differential diagnosis. To ensure consistency, the same questions were used at 2 and 6 yr of age.

A confident diagnosis of asthma in 2 yr-old children is particularly difficult in many cases, as up to 50% of all infants and children below the age of 3 yr will have at least one episode of wheezing. Thus, differential diagnoses should be excluded (27). In this study, we used doctor's diagnosis of asthma in combination with treatment for the last 12 months as diagnostic criteria. The question: 'Has the child ever had doctor-diagnosed asthma?' showed very good agreement with the occurrence of more than two obstructive episodes as found in the children's medical records (26). This strict definition limited the number of children with asthma, but the diagnosis was relatively certain.

Conclusion

Both SPT and sIgE at 2 yr may be clinically useful as predictors of allergy-related disease later in childhood. Utilizing quantitative values of sIgE and SPT improved the predictive performance. The predictive capability of SPT and sIgE were mainly comparable; however, it may be that sIgE is the preferred choice in very young children when the aim is to predict allergic rhinoconjunctivitis.

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