

Allergy-Related Symptoms Are Poorly Predicted by IgE and Skin Prick Testing in Early Life

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Keywords

Aeroallergen · Allergen-specific IgE · Dietary allergen · Sensitization · Skin prick test

Abstract

Introduction: In childhood, the so-called allergic march involves progression from IgE sensitization to allergy-related symptoms. Both IgE sensitization and relevant clinical symptoms are required for the diagnosis of allergy, but concordance between test results and clinical symptoms varies greatly, creating challenges for the diagnostics and for the prediction of outcomes. We assessed the prevalence of IgE sensitization and allergy symptoms, concordance between 2 IgE sensitization testing methods, and predictive value of these tests in relation to clinical symptoms in young Finnish children. **Methods:** The current study included 2 series of children: a birth cohort, in which the participants were followed prospectively from birth up to 3 years, and a young children cohort observed from 3 to 5 years of age. They were regularly monitored for sensitization by measuring serum

allergen-specific IgEs (sIgEs) and performing skin prick tests (SPTs). The emergence of atopic dermatitis, wheezing, and symptoms associated with food allergies was recorded. **Results:** Over the first 5 years of life, the prevalence of sIgE sensitization was 46%, while it was 36% for positive SPTs. Disease prevalence was 26% for atopic dermatitis, 25% for wheezing, and 19% for symptoms associated with food allergies. Concordance between sIgE and SPT results was good for aeroallergens, but poor for dietary allergens. The association between clinical symptoms and sensitization was stronger at 5 years than at 3 years of age. The proportion of children with concordant combinations of allergy symptoms and sensitization markers in contrast to those with discordant combinations increased from 3 to 5 years. **Conclusion:** In early childhood, testing for IgE sensitization predicts allergy-related symptoms in an age-dependent manner, but not particularly well. Tests predict symptoms caused by aeroallergens clearly better than those caused by dietary allergens. The clinical relevance of sensitization testing in early life is therefore limited in the prediction of true allergy.

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Introduction

Allergic diseases affect children worldwide, especially in the Western world, where the prevalence of atopic diseases has been rising rapidly over the last decades [1, 2]. The prevalence of allergic diseases in Finland is among the highest in Europe, and a remarkable difference in their prevalence exists between Finland and its neighbouring areas in Russia [3]. Instigators that promote rapid increase in the prevalence of immune-mediated diseases, including allergies, are still poorly understood, but combined with genetics, environmental factors appear to strongly influence the development of these disorders [4].

The so-called allergic march describes disease progression starting in infants with atopic dermatitis, sensitization to dietary allergens, and clinical food allergies, advancing to wheezing and aeroallergen sensitization during the toddler years, and continuing to allergic rhinitis and asthma later in childhood [5, 6]. Early sensitization has been shown to increase the risk of future allergic diseases, asthma in particular [7]. Children with maternal and paternal history of allergy have an increased risk to develop allergies [8]. Other known risk factors are male gender and birth by caesarean section [9, 10].

Diagnosis of allergic disease requires relevant symptoms combined with appropriate IgE sensitization, indicated by the appearance of allergen-specific IgE (sIgE) in the serum or a positive skin prick test (SPT). Neither test alone, without clinical symptoms, is, however, diagnostic for allergic diseases. These indicators are often used interchangeably despite their inconsistent comparability; some studies have indicated good [11–13] and others poor concordance [13–17]. Both methods have their advances: sIgE testing is often easily available and is independent of the assessed person's medication or skin condition, while SPTs are fast, inexpensive, and require no blood samples. However, to avoid misinterpretation, SPTs should be performed only by well-trained medical staff [18].

The aim of this study was to evaluate how well IgE sensitization predicts early-life allergy-related symptoms such as atopic dermatitis, symptoms associated with food allergies, and wheezing in childhood. In addition, we examined childhood sensitization patterns in Finland and assessed the concordance of the results obtained by sIgE and SPT methods.

Materials and Methods

Study Design and Cohorts

As a part of the prospective DIABIMMUNE study, 1961, Finnish children born between 2006 and 2010 were included in the current analyses [19]. All included children had at least one of the following data available: sIgE measurements, SPT, or allergy questionnaires answered. The local ethics committee (Ethics committee, Helsinki and Uusimaa Hospital District) had approved the study before starting any study procedures. The parents of the children gave their written informed consent to their child's participation in the study.

In the birth cohort (BC), 386 children carrying human leukocyte antigen (HLA)-conferred susceptibility to type 1 diabetes (T1D) were observed from birth up to the age of 3 years. HLA genotypes were assessed from cord blood, and all BC children participating in the follow-up carried haplotypes conferring a strong or moderate risk for T1D, that is, a combination of DR3-DQ2 ([DR3]-DQA1*05-DQB1*02) and DR4-DQ8 (DRB1*04:01/02/04/05/08-DQA1*03-DQB1*03:02/4) haplotypes indicating a strongly increased risk or alternatively DR4-DQ8/X (X = DR4-DQ8 or a neutral haplotype) or DR3-DQ2/Y (Y = DR3-DQ2 or a neutral haplotype) indicating moderately increased risk [20, 21]. Children visited the study centre at the age of 3, 6, 12, 18, 24, and 36 months for clinical examination, blood sampling, and evaluation of the study diary and questionnaires [22].

In the young children's cohort (YCC), 1,575 children representing the general population were followed from 3 to 5 years of age. They were HLA genotyped at the age of 3 years, but no selection for follow-up was based on the HLA genotypes. Five percent of the subjects in the YCC did not have reliable HLA data available (no results [$n = 3$] and inconclusive results [$n = 73$]). Children visited the study centre at the age of 3 and 5 years. Children who at the 3-year visit tested positive for T1D- and/or coeliac disease-associated antibodies and/or showed at least 2 positive sIgE results (≥ 0.35 kU/L) against common allergens were re-examined with their controls at the age of 4 years. Cases and controls were matched for age, gender, HLA genotype, and time of the 3-year visit. However, this subcohort was not analyzed within its case-control setting in this study.

Allergy Symptom Evaluation

The prevalence of allergy-related symptoms was evaluated by using a modification of the standardized questionnaire by the International Study of Asthma and Allergies in Childhood (ISAAC) [23]. For the BC children, the questionnaire was filled out by their parents at the age of 24 and 36 months, and for the YCC children at the age of 4 and 5 years. In the current study, we focused on atopic dermatitis, wheezing, and symptoms associated with food allergies reported until the end of respective follow-up. Symptoms associated with food allergies were evaluated based on parental reports of urticaria, angioedema, flushing, pruritus, contact dermatitis, dermatitis herpetiformis, manifestation or worsening of atopic dermatitis, wheeze, abdominal pain, vomiting, diarrhoea/loose stool, or flatulency as reactions to certain foods.

IgE Measurements

Total and sIgE antibodies were analyzed from serum by using the ImmunoCAP® fluoroenzyme immunoassay, according to the manufacturer's instructions (Phadia Diagnostics, Thermo Fisher

Scientific, Waltham, MA, USA). All IgE measurements were performed in a blinded manner in relation to the clinical data. Values ≥ 110 kU/L for total IgE (tIgE) and ≥ 0.35 kU/L for sIgEs were considered positive. Serum IgE against 6 allergens (cat, egg, milk, birch, timothy, and dust mite [*Dermatophagoides pteronyssinus*]) was analyzed at the age of 6, 18, and 36 months in the BC. Peanut was added to the test panel for analyses performed at 18 and 36 months and dog at 36 months. Approximately 92% of this cohort had IgE analyses performed. In the YCC, IgE against all these 8 allergens was analyzed at 3 and 5 years of age and at the age of 4 in the subcohort for case-control comparison. tIgE was assessed at the age of 3 years in both cohorts. In the YCC, nearly all children (99%) had IgE analyses performed. Children positive for sIgE were further classified as positive to aeroallergens (cat, dog, dust mite, birch, and timothy) and/or positive to dietary allergens (egg, milk, and peanut).

Skin Prick Tests

At the age of 3 years in the BC and at the age of 4 and 5 years in the YCC, skin tests with 9 allergens (birch, timothy, cat, dog, dust mite, egg white, milk, peanut, and wheat flour) were performed by the prick technique utilizing commercial extracts (Stallergens; ALK Copenhagen). Histamine dihydrochloride (10 mg/mL) was used as the positive control and allergen solvent as the negative control. A skin wheal reaction 3 mm or more in diameter was considered positive, if the positive and negative controls gave relevant results. Children from both cohorts were further classified as positive to aeroallergens (birch, timothy, cat, dog, and dust mite) and/or dietary allergens (egg white, milk, peanut, and wheat flour). Around 71% ($n = 273$) of the BC children and 28% ($n = 447$) of the YCC children had SPTs performed.

Statistical Analyses

Analyses were conducted by using IBM SPSS Statistics, version 22.0 and 25.0 (IBM Corp., Armonk, NY, USA). Children with no data of allergy-related symptoms, or sIgE or SPT, were excluded from those analyses in question. Categorical variables were analyzed by using the χ^2 and Fisher's exact tests. Changes in prevalence rates were assessed by using the McNemar test for paired samples. The Mann-Whitney U test and the Kruskal-Wallis test were applied for non-parametric variables, and these are marked in the results with medians and interquartile range. The agreement between sIgE sensitization and SPT was tested with Cohen's kappa statistics (κ) for dichotomous variables and with correlations (Spearman's rho) for continuous variables. Logistic regression models were performed as multivariate models for each test at each age, when possible. The models were adjusted for gender, delivery route, and parental allergy symptoms and reported with odds ratios (OR) and 95% confidence intervals (95% CI). A p value < 0.05 was considered statistically significant.

Results

Cohort Description

The prevalence of sIgE positivity against at least one common specific allergen during the follow-up from birth to 3 years in the BC or from 3 to 5 years of age in the

Table 1. Prevalence (%) of allergy-related outcomes until the end of respective follow-up (from birth to 3 years in the BC and from 3 to 5 years in the YCC)

	BC	YCC	<i>p</i> value
sIgE sensitization, <i>n</i>	355	1,566	
Any allergen	45.6	46.0	0.954
Aeroallergen	18.9	30.7	<0.001
Dietary allergen	41.7	39.4	0.462
Sensitized to both	14.9	24.1	<0.001
Simultaneous sensitization for ≥ 2 allergens	21.7	24.5	0.290
SPT sensitization, <i>n</i>	273	447	
Any allergen	22.3	44.7	<0.001
Aeroallergen	14.7	41.6	<0.001
Dietary allergen	16.1	27.7	<0.001
Allergy symptoms, <i>n</i>	304	1,366	
Atopic dermatitis	27.6	26.2	0.662
Wheezing	29.9	24.5	0.056
Symptoms associated with food allergies	22.0	18.4	0.174
Any of these 3 allergy signs	53.0	46.4	0.045
All of these 3 allergy signs	5.9	5.1	0.674
Allergy symptoms and sensitization, <i>n</i>	304	1,366	
Symptoms and positive sIgE/SPT	30.6	28.8	0.591
Symptoms and negative sIgE/SPT	22.4	17.6	0.062
No symptoms and positive sIgE/SPT	21.4	19.3	0.462
No symptoms and negative sIgE/SPT	25.7	34.3	0.005

Significant p values are bolded. sIgE, allergen-specific IgE; SPT, skin prick test; BC, birth cohort; YCC, young children's cohort.

YCC was 28.5% for aeroallergens and 39.8% for dietary allergens, altogether 45.9%. A total of 22.4% of children were positive for both groups of allergens, while 24.0% showed positivity for at least 2 allergens simultaneously. The prevalence of positive SPT was somewhat higher for aeroallergens, 31.4%, compared to dietary allergens, 23.3%, altogether 36.3%. The prevalence of symptoms referring to allergy was 26.5% for atopic dermatitis, 25.4% for wheezing, and 19.1% for symptoms associated with food allergies. Almost 50% of the children had experienced at least one of the 3 main symptom categories and around 5% had experienced all 3 of them. Background characteristics of both cohorts can be seen in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000512109).

Children in the YCC had more often positive IgE antibodies to aeroallergens and to both dietary and aeroallergens as well as positive SPT during the follow-up, but slightly less symptoms (Table 1). At the age of 3 years, children in the BC tended to be more often sensitized to specific allergens when compared to children in the YCC,

Table 2. Comparisons between the BC and the YCC at the age of 3 years in prevalence for sIgE positivity and tIgE values

	BC	YCC	<i>p</i> value
sIgE, <i>n</i>	294	1,554	
Sensitized to any allergen, %	41.2	35.1	0.057
Sensitized to aeroallergen, %	20.4	15.5	0.045
Sensitized to dietary allergen, %	34.7	28.7	0.046
Sensitized to both, %	13.9	9.1	0.014
tIgE, <i>n</i>	297	1,556	
tIgE value, kU/L (median; IQR)	25.6; 11.1–75.1	24.6; 10.2–63.2	0.275

Significant *p* values are bolded. IQR, interquartile range; sIgE, allergen-specific IgE; tIgE, total IgE; BC, birth cohort; YCC, young children's cohort.

while tIgE levels were not different between these 2 cohorts (Table 2). The prevalence of sIgE and SPT sensitization for each allergen is shown in online suppl. Table 2.

In the YCC, sIgE sensitization increased from 35.1% at the age of 3 years to 39.3% at the age of 5 years ($p = 0.001$). This increase in prevalence was seen for aeroallergens (15.6 vs. 24.2%, $p < 0.001$) but not for dietary allergens (28.6 vs. 29.1%, ns). In SPT, no change in prevalence was observed between the age of 4 and 5 years (any allergen 42.6 vs. 41.4%, ns). Seventy-nine percent of those showing positive sIgE results at 3 years of age showed them also at 5 years. In SPTs, 85% of those positive at the age of 4 years were also positive at 5 years, but since the cohort at the age of 4 years was highly selected, this result is not directly comparable with the persistence of positive sIgEs.

Clinical Symptoms and Sensitization

A total of 29.2% of the children had experienced atopic dermatitis, wheezing, or symptoms associated with food allergies and were sensitized (sIgE or SPT), while 32.7% had neither clinical nor sensitization markers indicating allergies. The proportion of children having symptoms and negative sIgE/SPT results was 18.4%, while the proportion of children without symptoms but positive sIgE/SPT result was 19.7%. There were more symptom-free and sIgE/SPT-negative subjects in the YCC, compared to those in the BC (Table 1). The proportion of children with or without symptoms and with or without sensitization was approximately a fourth for each combination in the BC, but 2 years later in the YCC, the proportion of concordant combinations (symptoms and sensitization or neither) was clearly higher than the proportion of discordant combinations.

The specificity (range 50–95%) for sIgE and SPT to detect symptoms referring to allergy (atopic dermatitis, wheezing, and symptoms associated with food allergies) was in general higher than the sensitivity (range 13–87%),

indicating that negative sIgE/SPT results exclude allergy-related symptoms better than positive sIgE/SPT results which confirm such symptoms (Tables 3, 4). Compared to sIgE results, SPT tended to have higher sensitivity and specificity, especially at 3 years of age. Sensitivity was also higher at the age of 5 years than at the age of 3 years. Sensitivity and specificity of sIgE and SPT in the assessment of wheezing were only significant at the age of 5 years.

Children who experienced atopic dermatitis, wheezing, symptoms associated with food allergies, any of these 3 allergy signs, or all 3 of these allergy signs showed in general higher tIgE and sIgE and larger SPT wheal size at the age of 3 years (BC) and 5 years (YCC), compared to those without the symptom in question (online suppl. Table 3). These results were more significant at 5 years (YCC) than at 3 years (BC). In the BC, wheezing was not significantly associated with sIgE or SPT results at the age of 3 years.

In order to demonstrate how sensitization markers predict allergy-related symptoms in early life, logistic regression models adjusted for gender, route of delivery, and parental allergy symptoms were analyzed (Table 5). Sensitization tests predicted allergy symptoms better at the older age in the YCC than at the younger age in the BC. Among the allergy-related symptoms, sensitization tests were weakest at predicting wheezing, especially at a young age. Interestingly, sensitization to dietary allergens by SPTs seemed to predict symptoms associated with food allergies clearly better than with sIgE especially at 5 years of age (OR: 7.1, 95% CI: 3.7–13.5 vs. 1.9, 1.4–2.6).

Concordance of sIgE and SPT Results

The best concordance of sIgE and SPT results was observed for aeroallergens, as 87% of the results were compatible (shown in Fig. 1). For dietary allergens, 68% of the results were compatible and for any allergens 74%. The agreement between these 2 tests varied from fair to almost

Table 3. Sensitivity and specificity of serum sIgE and SPT sensitizations and positivity for both of them in the evaluation of allergy symptoms at 3 years of age in the BC

	Data available, <i>n</i>	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Atopic dermatitis			
sIgE**	304	63.1 (51.9–73.4)	54.5 (47.7–61.3)
sIgE aero***	304	36.9 (26.6–48.1)	84.1 (78.6–88.7)
sIgE dietary*	304	56.0 (44.7–66.8)	57.7 (50.9–64.3)
SPT***	273	38.7 (27.6–50.6)	83.8 (78.0–88.7)
SPT aero***	273	28.0 (18.2–39.6)	90.4 (85.4–94.1)
SPT dietary**	273	28.0 (18.2–39.6)	88.4 (83.1–92.5)
Both***	273	37.3 (26.4–49.3)	85.9 (80.2–90.4)
Both aero***	273	26.7 (17.1–38.1)	92.4 (87.8–95.7)
Both dietary**	273	26.7 (17.1–38.1)	88.9 (83.6–92.9)
Wheezing			
sIgE	304	51.6 (40.9–62.3)	50.2 (43.3–57.1)
sIgE aero	304	23.1 (14.9–33.1)	78.9 (72.8–84.2)
sIgE dietary	304	47.3 (36.7–58.0)	54.5 (47.5–61.3)
SPT	273	25.6 (16.8–36.1)	79.1 (72.6–84.7)
SPT aero	273	16.3 (9.2–25.8)	86.1 (80.3–90.7)
SPT dietary	273	19.8 (12.0–29.8)	85.6 (79.7–90.3)
Both	273	23.3 (14.8–33.6)	80.7 (74.4–86.1)
Both aero	273	12.8 (6.6–21.7)	87.2 (81.5–91.6)
Both dietary	273	18.6 (11.0–28.4)	86.1 (80.3–90.7)
Symptoms associated with food allergies			
sIgE**	304	65.7 (53.1–76.8)	54.0 (47.4–60.5)
sIgE aero***	304	43.3 (31.2–56.0)	84.4 (79.1–88.8)
sIgE dietary**	304	61.2 (48.5–72.9)	58.2 (51.7–64.6)
SPT***	273	46.7 (33.7–60.0)	84.5 (78.9–89.1)
SPT aero***	273	33.3 (21.7–46.7)	90.6 (85.9–94.2)
SPT dietary***	273	43.3 (30.6–56.8)	91.5 (87.0–94.9)
Both***	273	46.7 (33.7–60.0)	86.9 (81.6–91.1)
Both aero***	273	33.3 (21.7–46.7)	93.0 (88.7–96.0)
Both dietary***	273	43.3 (30.6–56.8)	92.5 (88.1–95.6)
Any of these 3 allergy signs			
sIgE*	304	56.5 (48.5–64.3)	56.6 (48.1–64.9)
sIgE aero***	304	29.8 (22.9–37.5)	87.4 (80.8–92.4)
sIgE dietary	304	50.9 (42.9–58.9)	59.4 (50.9–67.6)
SPT***	273	30.7 (23.4–38.7)	87.8 (80.7–93.0)
SPT aero**	273	21.3 (15.1–28.8)	93.5 (87.6–97.2)
SPT dietary***	273	23.3 (16.8–30.9)	92.7 (86.6–96.6)
Both***	273	29.3 (22.2–37.3)	90.2 (83.6–94.9)
Both aero***	273	19.3 (13.3–26.6)	95.1 (89.7–98.2)
Both dietary***	273	22.7 (16.2–30.2)	93.5 (87.6–97.2)
All of these 3 allergy signs			
sIgE	304	61.1 (51.7–70.5)	50.3 (44.4–56.3)
sIgE aero*	304	44.4 (35.5–53.3)	79.7 (74.6–84.2)
sIgE dietary	304	55.6 (46.7–64.5)	54.5 (48.6–60.4)
SPT**	273	53.3 (44.4–62.2)	79.5 (74.0–84.2)
SPT aero**	273	46.7 (37.8–55.6)	87.2 (82.5–91.0)
SPT dietary**	273	46.7 (37.8–55.6)	85.7 (80.8–89.7)
Both**	273	53.3 (44.4–62.2)	81.4 (76.1–86.0)
Both aero***	273	46.7 (37.8–55.6)	89.1 (84.7–92.7)
Both dietary**	273	46.7 (37.8–55.6)	86.4 (81.6–90.4)

The highest percentages for sensitivity and specificity for each allergy symptom category are bolded. sIgE, allergen-specific IgE; SPT, skin prick test; BC, birth cohort. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$ with χ^2 .

Table 4. Sensitivity and specificity of serum sIgE and SPT sensitizations and positivity for both of them in the evaluation of allergy symptoms at 5 years of age in the YCC

	Data available, <i>n</i>	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Atopic dermatitis			
sIgE***	1,366	66.2 (61.0–71.1)	58.9 (55.8–62.0)
sIgE aero***	1,366	50.0 (44.7–55.3)	73.8 (71.0–76.5)
sIgE dietary***	1,366	58.9 (53.6–64.1)	65.4 (62.3–68.3)
SPT***	429	64.9 (56.8–72.4)	66.5 (60.6–72.1)
SPT aero***	429	61.7 (53.5–69.4)	69.8 (64.0–75.2)
SPT dietary***	429	48.7 (40.6–56.9)	84.0 (79.1–88.1)
Both***	429	64.3 (56.2–71.8)	68.7 (62.9–74.2)
Both aero***	429	60.4 (52.2–68.2)	73.5 (67.8–78.6)
Both dietary***	429	47.4 (39.3–55.6)	85.5 (80.7–89.4)
Wheezing			
sIgE***	1,366	61.7 (56.2–66.9)	56.9 (53.8–59.9)
sIgE aero***	1,366	47.3 (41.8–52.8)	72.4 (69.5–75.1)
sIgE dietary***	1,366	55.1 (49.6–60.5)	63.6 (60.5–66.5)
SPT***	429	65.9 (56.9–74.1)	64.0 (58.3–69.4)
SPT aero***	429	62.7 (53.6–71.1)	67.3 (61.7–72.6)
SPT dietary***	429	46.0 (37.1–55.1)	79.9 (74.9–84.2)
Both***	429	65.1 (56.1–73.3)	66.0 (60.4–71.3)
Both aero***	429	58.7 (49.6–67.4)	69.6 (64.1–74.8)
Both dietary***	429	45.2 (36.4–54.3)	81.5 (76.7–85.7)
Symptoms associated with food allergies			
sIgE***	1,366	71.4 (65.4–76.9)	57.7 (54.8–60.6)
sIgE aero***	1,366	57.9 (51.6–64.1)	73.3 (70.6–75.9)
sIgE dietary***	1,366	62.7 (56.4–68.7)	63.9 (61.0–66.7)
SPT***	429	77.5 (68.6–84.9)	66.7 (61.2–71.8)
SPT aero***	429	71.2 (61.8–79.4)	68.9 (63.5–73.9)
SPT dietary***	429	64.9 (55.2–73.7)	85.2 (80.8–88.9)
Both***	429	76.6 (67.6–84.1)	68.6 (63.1–73.6)
Both aero***	429	69.4 (59.9–77.8)	72.0 (66.7–76.9)
Both dietary***	429	62.2 (52.5–71.2)	86.2 (81.9–89.8)
Any of these 3 allergy signs			
sIgE***	1,366	61.8 (57.9–65.6)	64.6 (61.0–68.1)
sIgE aero***	1,366	46.2 (42.3–50.2)	79.5 (76.4–82.4)
sIgE dietary***	1,366	54.7 (50.8–58.7)	70.9 (67.5–74.2)
SPT***	429	62.1 (55.7–68.3)	78.0 (71.3–83.7)
SPT aero***	429	58.0 (51.5–64.3)	80.1 (73.6–85.6)
SPT dietary***	429	42.8 (36.5–49.3)	91.9 (87.0–95.4)
Both***	429	61.3 (54.9–67.5)	80.6 (74.2–86.1)
Both aero***	429	55.6 (49.1–61.9)	83.3 (77.2–88.4)
Both dietary***	429	41.2 (34.9–47.6)	93.0 (88.3–96.2)
All of these 3 allergy signs			
sIgE***	1,366	77.1 (65.6–86.3)	53.9 (51.2–56.7)
sIgE aero***	1,366	70.0 (57.9–80.4)	69.6 (67.0–72.1)
sIgE dietary***	1,366	70.0 (57.9–80.4)	60.6 (57.9–63.2)
SPT***	429	87.2 (72.6–95.7)	59.5 (54.4–64.4)
SPT aero***	429	84.6 (69.5–94.1)	62.8 (57.8–67.6)
SPT dietary***	429	84.6 (69.5–94.1)	77.9 (73.5–82.0)
Both***	429	87.2 (72.6–95.7)	61.3 (56.2–66.1)
Both aero***	429	82.1 (66.5–92.5)	65.6 (60.7–70.3)
Both dietary***	429	84.6 (69.5–94.1)	79.5 (75.1–83.4)

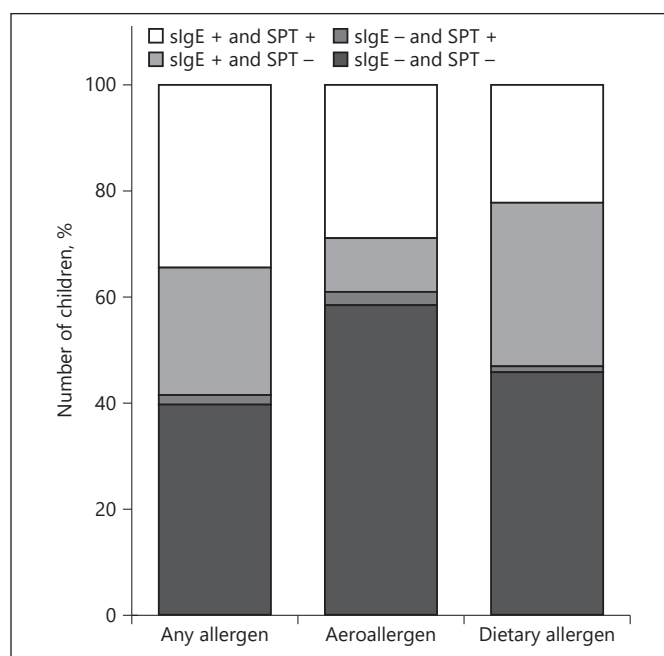
The highest percentages for sensitivity and specificity for each allergy symptom category are bolded. sIgE, allergen-specific IgE; SPT, skin prick test; YCC, young children's cohort. *** $p < 0.001$ with χ^2 .

Table 5. Logistic regression model predicting the likelihood of allergy-related symptoms by the age of 3 years in the BC and by the age of 5 years in the YCC

	Atopic dermatitis		Wheezing		Symptoms associated with food allergies		Any of these 3 allergy signs		All of these 3 allergy signs	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
BC										
<i>6 months</i>										
sIgE aero	4.3	0.7–26.8	2.1	0.4–11.0	1.9	0.3–12.5	na	na	2.3	0.2–25.3
sIgE dietary	3.5	1.7–7.0	1.3	0.6–2.6	8.5	4.0–18.3	5.5^a	2.3–13.1 ^a	3.2	1.1–9.6
<i>18 months</i>										
sIgE aero	2.6	0.9–7.1	0.6	0.2–1.9	1.7	0.6–4.9	0.9	0.3–2.6	4.9	1.2–20.0
sIgE dietary	2.2	1.2–3.9	1.8	1.0–3.1	4.1	2.2–7.7	3.2	1.8–5.6	2.0	0.7–6.0
<i>36 months</i>										
sIgE aero	3.0	1.5–5.8	1.0	0.5–2.0	3.3	1.7–6.5	2.7	1.4–5.3	3.2	1.0–9.9
sIgE dietary	1.1	0.6–1.9	1.0	0.6–1.8	1.5	0.8–2.8	0.9	0.5–1.6	1.3	0.4–3.9
SPT aero	2.9	1.3–6.5	1.0	0.4–2.2	2.0	0.8–4.8	2.5	1.0–6.1	3.9	1.0–15.4
SPT dietary	2.0	0.9–4.4	1.5	0.6–3.1	6.2	2.8–14.1	2.7	1.2–6.4	3.0	0.8–11.7
YCC										
<i>3 years</i>										
sIgE aero	1.6	1.2–2.3	1.7	1.2–2.3	1.7	1.2–2.4	2.1	1.5–2.9	2.0	1.1–3.5
sIgE dietary	2.2	1.7–2.9	1.7	1.3–2.3	2.6	1.9–3.5	2.3	1.8–3.0	2.7	1.6–4.5
<i>5 years</i>										
sIgE aero	2.6	1.9–3.5	1.9	1.4–2.6	3.4	2.5–4.7	2.9	2.2–3.9	3.9	2.2–6.9
sIgE dietary	1.7	1.3–2.3	1.5	1.1–2.0	1.9	1.4–2.6	2.0	1.5–2.5	2.7	1.6–4.8
SPT aero	2.2	1.3–3.8	1.8	1.0–3.2	2.1	1.1–4.0	2.8	1.6–4.8	2.0	0.6–6.8
SPT dietary	3.7	2.0–6.7	3.0	1.6–5.5	7.1	3.7–13.5	8.8	3.5–22.3	16.1	4.9–52.7

All models are adjusted for gender, delivery route, and parental allergy symptoms. Each multivariate logistic regression model is specific for testing age and test (sIgE/SPT). Significant odds ratios are bolded. BC, birth cohort; CI, confidence interval; OR, odds ratio; sIgE, allergen-specific IgE; SPT, skin prick test; YCC, young children's cohort. ^a Univariate logistic regression model due to unreliable results for sIgE aero.

Fig. 1. Proportion of children ($n = 720$) having concordant and discordant sIgE and SPT results during the follow-up from birth to 3 years or from 3 to 5 years of age. Allergens are divided as sensitization to any allergen, to aeroallergens (birch, timothy, cat, dog, and dust mite), and to dietary allergens (egg white, milk, peanut, and wheat flour; wheat flour was only tested with SPT). The cutoff for positivity was 0.35 kU/L for sIgE and 3 mm wheal size for SPT. sIgE, allergen-specific IgE; SPT, skin prick test.



perfect agreement ($\kappa = 0.37\text{--}0.87$), showing higher sIgE/SPT agreement for aeroallergens ($\kappa = 0.69\text{--}0.87$) than for dietary allergens ($\kappa = 0.37\text{--}0.43$; online suppl. Table 4). Overall, agreement between sIgE and SPT results was stronger at 5 than at 3 years of age.

When assessing the diagnostic tests based on continuous variables, values for sIgE and the SPT wheal size correlated positively for all allergens (online suppl. Table 5). The strongest correlations ($\rho > 0.60$) were seen for birch, timothy, cat, and peanut at the age of 5 years in the YCC. In the BC, tests for egg white showed the strongest correlation ($\rho = 0.51$). Children with positive SPT at 3 (BC) or 5 years (YCC) had higher tIgE and sIgE values at the age in question, compared to children with negative SPTs ($p < 0.001$ for all allergens).

Discussion

The overall prevalence of sIgE sensitization was high, with close to half of all children being sensitized during the follow-up, that is, from birth up to 3 years of age and from 3 to 5 years of age, agreeing with the prevalence rates reported in earlier studies in Finland [12, 24]. The prevalence of positive SPTs was slightly lower than the prevalence of sIgE sensitization, also agreeing with previous results from Finland [12, 25, 26]. The prevalence for allergy symptom, wheezing, and atopic dermatitis in particular was slightly higher in previous studies from Finland than in our study, most probably because these studies were carried out among school children [12, 26].

Our sensitization rates agree well with the principles of the so-called allergic march, with dietary allergen sensitization rates being higher at a young age while aeroallergen sensitization starts to increase after 3 years of age. Sensitization rates for sIgE increased from 3 to 5 years of age, while SPT positivity rates did not increase between 4 and 5 years. This is quite contrary to what was seen in Denmark, where sIgE positivity remained stable and SPT increased from 3 to 5 years [27]. In early childhood, the spectrum of allergy-related symptoms seems to be broader, more unspecific, and more difficult to interpret than at 5 years of age. For example, SPTs and sIgE for dietary allergens at 5 years of age seem to predict symptoms associated with food allergies and also other allergy-related symptoms better than at the age of 3. Wheezing in early life, when the respiratory tract is not yet fully developed, is often a sign of a virus infection, but can also be an IgE-mediated reaction to an allergen. However, wheezing in early life seems to be quite unspecific in relation to aller-

gies since it does not relate well to sensitization tests at all, especially before the age of 3 years. This shows how the allergic march and the development of true allergy are still dynamic at 3 years of age, but 2 years later, allergy symptoms and sensitization tests together give a more accurate profile of allergies. This could reflect on developmental processes in early childhood, for example, early production of antibodies in the intestinal mucosa that disappear due to the progression of tolerance and maturation. The persistence of sensitization, both in terms of sIgE and SPT, between 3 and 5 years of age was quite high.

The agreement between sIgE and SPT was good for aeroallergens but fair for dietary allergens, also seen previously in Finland [12]. Earlier studies in children from other countries have shown quite inconsistent results, with some recent studies indicating good concordance for dietary allergens [11], discordance for aeroallergens [14] and dietary allergens [15], and moderate agreement for aeroallergens together with variable agreement for dietary allergens [17]. Among the discordant results in our study, sIgEs were more frequently positive and SPTs negative than the other way around. The sensitivity and specificity for sIgE, SPT, or both of them varied greatly in identifying allergy-related symptoms. The specificities of the tests were in general higher than the sensitivities. Sensitivity at 3 years was usually low, but it increased up to 5 years of age. Surprisingly, by testing both sIgE and SPT compared to only one of them, the sensitivity and specificity for allergic symptoms did not increase remarkably. For symptoms associated with food allergies, SPT sensitization seemed to be more reliable than sIgE to predict symptoms both at 3 and 5 years of age according to the logistic regression models. Among all children with sIgE respective SPT dietary allergen sensitization, 28.4 and 60.1% had reported symptoms associated with food allergies, similar to a previous report [28]. At 5 years of age, children with positive SPTs for dietary allergens had a higher risk to have symptoms associated with food allergies than children with positive sIgE for dietary allergens. A negative allergy test result is in general more reliable than a positive result.

There seems to be an agreement that sIgE and SPT should be used complementary, not interchangeably, and they should preferably be quantified, not dichotomized [29, 30]. For almost all 3 allergy symptom categories we evaluated, values for tIgE, sIgE, and SPT diameters were higher in children with such a symptom. However, tIgE in children under 5 years should be interpreted with caution and preferable in relation to sIgE and age [17, 31]. Especially in older toddlers, aeroallergen sensitization tested by sIgE or SPT is accurate in the evaluation of

symptomatic allergies; neither test proved to be clearly superior to the other. However, when in suspicion of food allergies, sensitization tests are usually insufficient and should therefore be used together with controlled oral food challenges.

The aim of this study was not to evaluate the role of HLA genetics in the development of allergic diseases, but the cohort inclusion criteria are partly based on genetics. Since the younger children in the BC all carried an HLA-conferred risk for autoimmunity, and the older children in the YCC represented the general population, the results regarding the BC from birth up to the age of 3 years cannot be directly generalized to the general population. However, these HLA risk genotypes are common in the Finnish population, and only a fraction of people carrying them will eventually develop an autoimmune disease. In our earlier study [32], we showed that children with HLA-conferred susceptibility to autoimmunity are somewhat more frequently sensitized compared to the general population at the age of 3. According to this and in contrast to the Th1/Th2 paradigm, our observations indicate that children carrying HLA-conferred susceptibility to autoimmune disease have not a priori reduced frequency of atopic and allergic manifestations. One may speculate that the age-dependent differences we found in this study could be even more prominent within cohorts and during a longer follow-up. Unfortunately, the study design did not allow us to follow both cohorts simultaneously from birth up to 5 years of age.

Our study has also other limitations. In order to be able to evaluate sensitization patterns regarding sIgE as well as SPT more accurately in both cohorts and to compare those properly, it would have been useful to have each test performed more regularly and especially at 3 years of age in both cohorts. The study setting of the general population versus a selected cohort was interesting, but a proper case-control study with a similar follow-up timeline would have provided benefits. Controlled oral food challenges were not available for proper diagnostics of food allergies, but parental reports of symptoms associated with food allergies were utilized. Parental reports of allergy-related symptoms might allow subjectivity in the questionnaires. In order to identify those children at risk for allergies at an early age, future studies need to evaluate whether higher values of sensitization tests predict clinical allergy outcomes more reliable.

To conclude, the spectrum of allergy-related symptoms in young children is broad, and symptoms do not relate to allergy tests particularly well, indicating that the development of true allergies is still dynamic and under development in early childhood. The clinical relevance of

sensitization testing in early life is therefore limited. The agreement of sIgE and SPT was good for aeroallergens but fair for dietary allergens, and neither test alone proved to be clearly superior to the other to predict symptoms relevant to allergy.

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Statement of Ethics

The local ethics committee (Ethics committee, Helsinki and Uusimaa Hospital District; Decision No. 228/13/March 3, 2008) had approved the study before starting the study procedures. The parents of the children gave their written informed consent to the child's participation in the study.

References

- Platts-Mills TAE. The allergy epidemics: 1870–2010. *J Allergy Clin Immunol*. 2015; 136(1):3–13.
- Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733–43.
- Hahtela T, Laatikainen T, Alenius H, Auvinen P, Fyhrquist N, Hanski I, et al. Hunt for the origin of allergy: comparing the Finnish and Russian Karelia. *Clin Exp Allergy*. 2015;45(5): 891–901.
- Stelmach I, Bobrowska-Korzeniowska M, Smejda K, Majak P, Jerzynska J, Stelmach W, et al. Risk factors for the development of atopic dermatitis and early wheeze. *Allergy Asthma Proc*. 2014;35(5):382–9.
- Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003;112(6 Suppl):S118–27.
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol*. 1999;103(6):1173–9.
- Piippo-Savolainen E, Remes S, Korppi M. Does early exposure or sensitization to inhalant allergens predict asthma in wheezing infants? A 20-year follow-up. *Allergy Asthma Proc*. 2007;28(4):454–61.
- de Jong NW, Elbert NJ, Mensink-Bout SM, van der Valk JPM, Pasmans SGMA, Jaddoe VVW, et al. Parental and child factors associated with inhalant and food allergy in a population-based prospective cohort study: the Generation R Study. *Eur J Pediatr*. 2019; 178(10):1507–17.
- Koplin J, Allen K, Gurrin L, Osborne N, Tang ML, Dharmage S. Is caesarean delivery associated with sensitization to food allergens and IgE-mediated food allergy: a systematic review. *Pediatr Allergy Immunol*. 2008;19(8): 682–7.
- Huang S, Garshick E, Weschler LB, Hong C, Li J, Li L, et al. Home environmental and lifestyle factors associated with asthma, rhinitis and wheeze in children in Beijing, China. *Environ Pollut*. 2020;256:113426.
- Yang HJ, Park MJ, Youn SY, Yoo S, Min TK, Jeon YH, et al. Agreement between the skin prick test and specific serum IgE for egg white and cow's milk allergens in young infant with atopic dermatitis. *Allergol Int*. 2014;63(2): 235–42.
- Pekkarinen PT, von Hertzen L, Laatikainen T, Mäkelä MJ, Jousilahti P, Kosunen TU, et al. A disparity in the association of asthma, rhinitis, and eczema with allergen-specific IgE between Finnish and Russian Karelia. *Allergy*. 2007;62(3):281–7.
- Voor T, Julge K, Böttcher MF, Jenmalm MC, Duchén K, Björkstén B. Atopic sensitization and atopic dermatitis in Estonian and Swedish infants. *Clin Exp Allergy*. 2005;35(2):153–9.
- de Vos G, Nazari R, Ferastraoraru D, Parikh P, Geliebter R, Pichardo Y, et al. Discordance between aeroallergen specific serum IgE and skin testing in children younger than 4 years. *Ann Allergy Asthma Immunol*. 2013;110(6): 438–43.
- Mehl A, Niggemann B, Keil T, Wahn U, Beyer K. Skin prick test and specific serum IgE in the diagnostic evaluation of suspected cow's milk and hen's egg allergy in children: Does one replace the other? *Clin Exp Allergy*. 2012; 42:1266–72.
- Frith J, Fleming L, Bossley C, Ullmann N, Bush A. The complexities of defining atopy in severe childhood asthma. *Clin Exp Allergy*. 2011;41(7):948–53.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

This study was designed by M.K., H.S., and T.H. H.S. and M.K. were involved in the data collection. J.I. was responsible for the HLA genotyping of the study participants. O.N. was responsible for IgE testing. N.M. performed the data analysis and wrote the first version of the manuscript. All authors were involved in the editing and final approval of the manuscript.

- 17 Rø AD, Saunes M, Smidesang I, Storø O, Oien T, Moen T, et al. Agreement of specific IgE and skin prick test in an unselected cohort of two-year-old children. *Eur J Pediatr*. 2012; 171(3):479–84.
- 18 Sicherer SH, Wood RA. Allergy testing in childhood: using allergen-specific IgE tests. *Pediatrics*. 2012;129(1):193–7.
- 19 Simre K, Uibo O, Peet A, Tillmann V, Kool P, Hämäläinen AM, et al. Exploring the risk factors for differences in the cumulative incidence of coeliac disease in two neighboring countries: the prospective DIABIMMUNE study. *Dig Liver Dis*. 2016;48(11):1296–301.
- 20 Hermann R, Turpeinen H, Laine AP, Veijola R, Knip M, Simell O, et al. HLA DR-DQ-encoded genetic determinants of childhood-onset type 1 diabetes in Finland: an analysis of 622 nuclear families. *Tissue Antigens*. 2003; 62(2):162–9.
- 21 Peet A, Hämäläinen AM, Kool P, Ilonen J, Knip M, Tillmann V. Early postnatal growth in children with HLA-conferred susceptibility to type 1 diabetes. *Diabetes Metab Res Rev*. 2014;30(1):60–8.
- 22 Mustonen N, Siljander H, Peet A, Tillmann V, Härkönen T, Ilonen J, et al. Early childhood infections precede development of beta-cell autoimmunity and type 1 diabetes in children with HLA-conferred disease risk. *Pediatr Diabetes*. 2018;19(2):293–9.
- 23 Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483–91.
- 24 Ruokolainen L, von Hertzen L, Fyhrquist N, Laatikainen T, Lehtomäki J, Auvinen P, et al. Green areas around homes reduce atopic sensitization in children. *Allergy*. 2015;70(2): 195–202.
- 25 Kujansuu E, Kujansuu L, Paasilta M, Mustonen J, Vaarala O. Exposure to sewage water and the development of allergic manifestations in Finnish children. *Pediatr Allergy Immunol*. 2019;30(6):598–603.
- 26 von Hertzen L, Mäkelä MJ, Petäys T, Jousilahti P, Kosunen TU, Laatikainen T, et al. Growing disparities in atopy between the Finns and the Russians: a comparison of 2 generations. *J Allergy Clin Immunol*. 2006; 117(1):151–7.
- 27 Kjaer HF, Eller E, Andersen KE, Høst A, Bindslev-Jensen C. The association between early sensitization patterns and subsequent allergic disease. The DARC birth cohort study. *Pediatr Allergy Immunol*. 2009;20(8): 726–34.
- 28 Bergmann RL, Bergmann KE, Lau-Schadendorf S, Luck W, Dannemann A, Bauer CP, et al. Atopic diseases in infancy. The German Multicenter Atopy Study (MAS-90). *Pediatr Allergy Immunol*. 1994;5(6 Suppl):19–25.
- 29 Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol*. 2005;116(4):744–9.
- 30 Haahtela T, Burbach GJ, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, et al. Clinical relevance is associated with allergen-specific wheal size in skin prick testing. *Clin Exp Allergy*. 2014;44(3):407–16.
- 31 Sacco C, Perna S, Vicari D, Alfö M, Bauer CP, Hoffman U, et al. Growth curves of “normal” serum total IgE levels throughout childhood: a quantile analysis in a birth cohort. *Pediatr Allergy Immunol*. 2017;28(6):525–34.
- 32 Mustonen N, Siljander H, Peet A, Tillmann V, Härkönen T, Niemelä O, et al. Coeliac disease and HLA-conferred susceptibility to autoimmunity are associated with IgE sensitization in young children. *Allergy*. 2020;75(3): 692–4.

Supplementary Material

TABLE S1 Characteristics of children in the birth cohort and young children's cohort. Values are medians and interquartile ranges, if not otherwise indicated.

	Birth cohort n=386	Young children's cohort n=1575
Proportion of males (%)	50.5	52.0
Mother's age at delivery, years	30.9 (28.5–34.2)	31.8 (29.0–35.0)
Number of siblings at child's birth	0 (0–1)	1 (0–1)
Gestational age, weeks	40.3 (39.3–41.0)	40.0 (39.0–40.9)
Caesarean section (%)	9.6	20.8
Duration of breastfeeding, months	9.8 (4.7–12.2)	9.0 (6.0–12.0)
Birth weight, g	3578 (3258–3861)	3535 (3200–3890)
Birth length, cm	51 (49–52)	51 (49–52)
HLA risk group (%)		
DR3-DQ2 / DR4-DQ8	9.1	2.1
DR4-DQ8 / X ^a or DR3-DQ2 / Y ^b	90.9	21.1
Non-risk genotypes	–	76.9

^a X=DR4-DQ8 or a neutral haplotype

^b Y=DR3-DQ2 or a neutral haplotype

TABLE S2 Prevalence (%) of sIgE and SPT sensitisation for each allergen at 3 and 5 years. Prevalence of sIgE sensitisation for each allergen was compared between BC and YCC at the age of 3 year with Chi-square test (significant differences are bolded).

	BC		YCC	
	sIgE	SPT	sIgE	SPT
3 years				
Birch	15.0	7.3	11.3	NA
Timothy	5.3	5.1	3.1	NA
Cat	5.4	4.8	4.1	NA
Dog	7.3	5.9	4.4	NA
Dust mite	2.7	0.4	1.5	NA
Egg white	17.4	12.1	15.9	NA
Milk	32.0^a	3.7	21.9^a	NA
Peanut	5.9	7.0	4.6	NA
Wheat flour	NA	2.6	NA	NA
5 years				
Birch	NA	NA	18.1	29.6
Timothy	NA	NA	8.9	17.8
Cat	NA	NA	8.0	15.8
Dog	NA	NA	8.5	14.0
Dust mite	NA	NA	3.2	3.5
Egg white	NA	NA	14.3	10.0
Milk	NA	NA	20.8	3.0
Peanut	NA	NA	8.5	17.8
Wheat flour	NA	NA	NA	6.3

^a p<0.001 with Chi-square test

BC, birth cohort; sIgE, allergen-specific IgE; SPT, skin prick test; YCC, young children's cohort

TABLE S3 Relationship of IgE values and SPT diameters in children with clinical allergy symptoms. Results are marked with *P* values calculated with the Mann-Whitney U Test. All significant values (bolded) indicate that children with that allergy symptom show higher values of that particular allergy test, compared to children without that symptom.

	Atopic dermatitis	Wheezing	Symptoms associated with food allergies	Any of these three allergy signs	All of these three allergy signs
At 3 years (BC)					
tlgE	0.006	0.089	0.002	0.001	0.036
slgE cat	<0.001	0.322	<0.001	0.001	0.051
slgE dog	0.006	0.045	<0.001	<0.001	0.019
slgE egg	0.009	0.158	<0.001	0.001	0.158
slgE milk	0.653	0.447	0.266	0.470	0.493
slgE peanut	0.002	0.427	0.002	0.109	0.027
slgE birch	0.001	0.401	<0.001	0.001	0.002
slgE timothy	0.002	0.654	0.004	0.046	0.034
slgE dust mite	0.100	0.122	0.002	0.045	0.010
SPT cat	0.027	0.936	0.136	0.104	0.119
SPT dog	0.001	0.616	<0.001	0.001	0.016
SPT egg	<0.001	0.079	<0.001	<0.001	<0.001
SPT milk	0.002	0.570	<0.001	0.023	0.039
SPT peanut	0.043	0.309	0.001	0.082	<0.001
SPT birch	<0.001	0.403	<0.001	<0.001	<0.001
SPT timothy	0.046	0.737	<0.001	0.064	<0.001
SPT dust mite	0.538	0.498	0.596	0.269	0.809
SPT wheat flour	0.009	0.021	<0.001	0.016	<0.001
At 5 years (YCC)					
tlgE	<0.001	<0.001	<0.001	<0.001	<0.001
slgE cat	<0.001	<0.001	<0.001	<0.001	<0.001
slgE dog	<0.001	<0.001	<0.001	<0.001	<0.001
slgE egg	<0.001	<0.001	<0.001	<0.001	<0.001
slgE milk	<0.001	<0.001	<0.001	<0.001	<0.001
slgE peanut	<0.001	<0.001	<0.001	<0.001	<0.001
slgE birch	<0.001	<0.001	<0.001	<0.001	<0.001
slgE timothy	<0.001	<0.001	<0.001	<0.001	<0.001
slgE dust mite	<0.001	<0.001	<0.001	<0.001	<0.001
SPT cat	<0.001	0.003	<0.001	<0.001	<0.001
SPT dog	<0.001	<0.001	<0.001	<0.001	<0.001
SPT egg	<0.001	<0.001	<0.001	<0.001	<0.001
SPT milk	0.022	0.004	<0.001	0.015	<0.001
SPT peanut	<0.001	<0.001	<0.001	<0.001	<0.001
SPT birch	<0.001	<0.001	<0.001	<0.001	<0.001
SPT timothy	<0.001	0.006	<0.001	<0.001	<0.001
SPT dust mite	0.023	0.020	0.425	0.283	0.008
SPT wheat flour	<0.001	<0.001	<0.001	<0.001	<0.001

BC, birth cohort; slgE, allergen-specific IgE; SPT, skin prick test; tlgE, total IgE; YCC, young children's cohort

TABLE S4 Strength of agreement between allergen-specific IgE and skin prick test sensitisations. Significant *P* values are bolded.

Sensitisation to allergens	n	κ^a (95% CI)	<i>P</i>
During the follow-up (age 0–3 or 3–5 years)	720		
Any allergen		0.51 (0.46–0.54)	<0.001
Aeroallergen		0.73 (0.67–0.76)	<0.001
Dietary allergen		0.38 (0.34–0.40)	<0.001
At 3 years of age (BC)	264		
Any allergen		0.40 (0.29–0.48)	<0.001
Aeroallergen		0.69 (0.56–0.76)	<0.001
Dietary allergen		0.37 (0.25–0.45)	<0.001
At 5 years of age (YCC)	396		
Any allergen		0.65 (0.58–0.69)	<0.001
Aeroallergen		0.87 (0.80–0.92)	<0.001
Dietary allergen		0.43 (0.35–0.48)	<0.001

^a $\kappa=0.21$ – 0.40 indicates fair agreement, $\kappa=0.41$ – 0.60 moderate agreement, $\kappa=0.61$ – 0.80 substantial agreement, $\kappa=0.81$ – 1.00 almost perfect agreement
BC, birth cohort; CI, confidence interval; κ , Cohen's kappa coefficient; YCC, young children's cohort

TABLE S5 Correlations between SPT diameter and sIgE values for each allergen at 3 years in the BC and at 5 years in the YCC. Significant *P* values are bolded.

	3 years (BC)		5 years (YCC)	
	Spearman's rho	<i>P</i>	Spearman's rho	<i>P</i>
Birch	0.477	<0.001	0.763	<0.001
Timothy	0.376	<0.001	0.621	<0.001
Cat	0.403	<0.001	0.660	<0.001
Dog	0.387	<0.001	0.551	<0.001
Dust mite	0.108	<0.001	0.195	<0.001
Egg white	0.509	<0.001	0.442	<0.001
Milk	0.204	<0.001	0.180	<0.001
Peanut	0.341	<0.001	0.616	<0.001

BC, birth cohort; sIgE, allergen-specific IgE; SPT, skin prick test; YCC, young children's cohort