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High incidence and persistence of airborne allergen sensitization up to age 19 years

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Short title: Incidence and persistence of allergic sensitization

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ABSTRACT

Background: Longitudinal population-based studies about the natural history of allergic sensitization are rare. The aim was to study incidence and persistence of airborne allergen sensitization up to young adulthood, and risk factors for early and late onset of sensitization.

Methods: All children aged 7-8 years in two municipalities in Northern Sweden were invited to a parental questionnaire and skin prick tests (SPT) to ten airborne allergens, and 2,148 (88%) participated. The protocol was repeated at age 11-12 and 19 years, and 1,516 participated in all three examinations.

Results: Prevalence of any positive SPT increased from 20.6% at age 7-8y to 30.6% at 11-12y, and 42.1% at 19y. Animals were the primary sensitizers at age 7-8y, 16.3%, followed by pollen, 12.4%. Mite and mold sensitization was low. Mean annual incidence of any positive SPT varied between 2.8-3.4/100/year, decreased by age for animal and was stable for

pollen. Sensitization before age 7-8y was independently associated with family history of allergy, OR 2.1(95%CI 1.6-2.8), urban living, OR 1.9(95%CI 1.2-2.9), and male sex, OR 1.3(95%CI 1.0-1.7), and negatively associated with birth order, OR 0.8(95%CI 0.7-1.0) and furry animals at home, OR 0.7(95%CI 0.7-0.9). Incidence after age 11-12y was associated only with family history of allergy. Multi-sensitization at age 19y was significantly associated with early age at sensitization. Remission of sensitization was uncommon.

Conclusion: The increasing prevalence of allergic sensitization by age was explained by high incidence and persistence. After age 11-12y the factors urban living, number of siblings and male sex lost their importance.

Key Words: Allergic sensitization, epidemiology, longitudinal study, prevalence, risk factors

INTRODUCTION

Development of IgE-mediated sensitization often starts early in life, and studies provide a uniform picture of an increasing prevalence of allergic sensitization to common airborne allergens by increasing age up to young adulthood¹⁻³, but thereafter the prevalence decreases by age⁴⁻⁷. The point prevalence of a condition is a function of the incidence, persistence and the remission of the condition which cannot be estimated by cross-sectional studies. In contrast to cross-sectional studies, longitudinal studies of allergic sensitization measured by objective methods based on large representative samples are rare^{1,2,8-12}. Knowledge about its natural history is essential as sensitization is the first step in development of clinical allergy.

As most of the current literature regarding risk factors is based on cross-sectional studies, it is not clear if the risk factor patterns reflect early or late onset of allergic sensitization. This may contribute to the inconsistency of reported risk factor patterns between different studies. For asthma, different risk factor patterns for early onset asthma compared to late onset asthma have been found¹³⁻¹⁴. This aspect of allergic sensitization has not been studied in a cohort followed longitudinally.

The only consistent risk factor for allergic sensitization is a history of allergy in the family^{5,7,9,15-17}. Some studies report sex differences with higher prevalence in males^{8,10,15-17}, while others report no sex differences⁴. Urban living has been reported to be a risk factor in several studies^{5,16-19}. Growing up on a farm and having several siblings have been associated with a decreased risk for allergic sensitization^{11,20}. Living in a home with cat or dog has also been associated with a decreased risk for sensitization^{11,21}, but the debate of this topic is ongoing²².

From a large longitudinal cohort study, recruited in 1996 within the Obstructive Lung Disease in Northern Sweden (OLIN) Studies, we have previously reported about prevalence^{17,23} and incidence¹¹ of allergic sensitization in early school age. The cohort has now been followed up at the age of 19 years^{14,24}. The aim of the present study was to assess the natural history, including prevalence, incidence and remission, of allergic sensitization to airborne allergens measured by skin prick test from age 7-8 until 19 years. Further, we studied the effect of childhood risk factors in relation to childhood and adolescent onset of sensitization.

METHODS

Study population

Within the OLIN studies, a prospective cohort study about asthma and allergy started in 1996. All children enrolled in the first and second grades of primary schools in three municipalities in Northern Sweden were invited to a parental questionnaire study¹⁷. The children in two of the areas, Kiruna and Luleå (n=2,454), were also invited to skin prick testing (SPT). The cohort was followed-up in 2000 at age 11-12 years¹¹, and in 2006-2007 at age 19 years^{14,24}. The participation rate in SPT was 88% at age 7-8 years (n=2,148), 83% at age 11-12 (n=2,027), and 76% at age 19 years (n=1,868), and 1,516 subjects participated at all three occasions, 71% of those who participated at age 7-8 years. The participation rate was similar in the two areas and in girls and boys.

Consent for SPT at age 7-8 and 11-12 years was obtained from the parents, and by the subjects themselves at age 19 years. The studies were approved by the regional ethical review board at Umeå University, Sweden.

Skin prick tests

The SPT were carried out at the schools between February and April at each survey and by a limited number of trained personnel. The SPT was performed on the volar aspects of the forearm using lancets, and the specific allergens tested were birch, timothy, mugwort, dog, cat, horse, *Dermatophagoides farinae*, *D. pteronyssinus*, cladosporium and alternaria (Soluprick, ALK, Hørsholm, Denmark). The potency of the extracts was 10 HEP, except the

two molds, which were 1:20 w/v. Histamine 10mg/ml was used as positive control and glycerol as negative control. A positive reaction was recorded if the mean weal was 3 mm or more after 15 minutes ²⁵. The skin prick tests have been validated against specific IgE and showed very good agreements ^{11,26}.

Questionnaire

The questionnaire included the International Study of Asthma and Allergy in Childhood (ISAAC) core questionnaire with additional questions about symptoms and diagnoses.

Questions for an extensive screening of possible risk factors were added including family history of allergic diseases, past or present pets at home, parental smoking, house dampness, birth order, number of siblings, and respiratory infections ¹⁷.

Definitions

Any positive SPT: A positive SPT to at least one of the allergens tested.

Any pollen: A positive SPT to any of birch, timothy or mugwort.

Any animal: A positive SPT to any of cat, dog or horse.

Any mite: A positive SPT to any of *D. farina* or *D. pteronyssinus*,

Any mold: A positive SPT to any of cladosporium or alternaria.

Incidence of sensitization: A negative SPT to any allergen in the initial test, and foregoing test if applicable, but a positive SPT in the follow-up.

Remission of sensitization: A positive SPT in the initial test, and forgoing test if applicable, but a negative SPT in the follow-up.

Multi-sensitization: A positive SPT to ≥ 4 allergens.

Analyses

Statistical analyses were performed by using the Statistical package for the Social Sciences (SPSS) for Windows, Version 22.0. The analyses of prevalence were based on all children who participated at each test occasion. The longitudinal analyses of incidence and remission were based on the n=1516 children who participated at all three test occasions. The cumulative incidence from birth to 7-8 years, from 7-8 to 11-12 years, and from 11-12 to 19 years was calculated for any positive SPT, for positive SPT for each specific allergen, and for the allergen groups. In these calculations, the population at risk was those with a negative SPT to all allergens. The mean annual incidence was estimated by dividing the cumulative incidence with the number of observation years, i.e 7.5 years, 4.0 years, and 6.5 years, respectively. For testing differences in proportions, the Chi-square test was used, and if more than two groups the Mantel-Haenszel's test for trend was used, and $p < 0.05$ was considered as statistically significant. Risk factors for sensitization during different age periods, i.e. incidence from birth to age 7-8 years, from 7-8 to 11-12 years, and from 11-12 to 19 years were analyzed by multinomial logistic regression analyses with the subjects with negative SPT at all occasions as reference category. In addition, risk factors for prevalence of sensitization at age 19 years was analyzed by binary logistic regression analysis. The risks were expressed as odds ratios (OR) with 95% confidence intervals (CI). Factors significantly

associated with allergic sensitization at age 7-8 years in bivariate analyses were included in the multivariate models. Data regarding risk factors in early childhood were collected at age 7-8 years and included a family history of allergy (rhinitis), urban versus rural living at age 7-8 years, birth order, ever having had cat or dog at home at age 7-8 years, breast feeding <3 months, birth weight, maternal smoking during the first two years of life and severe respiratory infections before the age of 7-8 years. A consistency pattern, for the SPT readings (positive SPT =P and negative SPT=N) across all three test occasions is also presented.

RESULTS

The prevalence of allergic sensitization

The prevalence of *any positive SPT* increased significantly by age; from 20.6% at age 7-8 years, to 30.6% at age 11-12 years, and to 42.1% at age 19 years. At age 7-8 years, sensitization to *any animal* was most common, 16.3%, followed by *any pollen*, 12.4%, while at age 19 years the prevalence were of similar magnitude, 32.8% and 34.3%, respectively. Sensitization to *any mite* and *any mold* was low at all ages, 1-3% (Figure 1).

The prevalence of *any positive SPT* was higher among boys than girls at all ages, however significantly so only at age 11-12 and 19 years. This difference by sex was true for the major pollen allergens, birch and timothy, at all ages. The prevalence of positive SPT to the animal allergens, cat, dog and horse, was significantly higher among boys than girls at age 11-12 and 19 years, while at age 7-8 years this was found only for sensitization to horse (Table 1).

The prevalence of allergic sensitization, allergic conditions and potential risk factors at age 7-8 years was close to identical among the subjects who participated at all three examinations as it was in those participating in the initial examination at 7-8 years (data not shown).

The incidence of allergic sensitization

The mean annual incidence rate of *any positive SPT* was 2.9/100/year from birth to age 7-8 years, 3.4/100/year from 7-8 to 11-12 years, and 2.8/100/year from 11-12 to 19 years. The incidence rate of sensitization to *any animal* was highest from birth to age 7-8 years, 2.2/100/year, and it decreased by age, 1.9/100/year from 7-8 to 11-12 years, and 1.4/100/year from 11-12 to 19 years. No consistent pattern in the mean annual incidence rate of sensitization to *any pollen* was found. The incidence rate of sensitization to *any mite* was low but tended to increase by age to 0.3/100/year from 11-12 to 19 years (Table 2). The cumulative incidence of *any positive SPT* and positive SPT to the most common specific allergens was higher among boys compared to girls until the age of 11-12, while from age 11-12 to 19 years, no significant sex difference was found (data not in table).

Consistency of the SPT results in the longitudinal setting

The pattern of sensitization at an individual level across the observation period taking the three test occasions into account is presented in Table 3. Of the cohort, 55.7% showed a negative SPT to all allergens at all three test occasions (NNN), and 20.4% showed a positive test at all occasions (PPP). In general, once a subject had become sensitized, sensitization

remained (PPP, NPP) while only a few subjects showed inconsistent or remission patterns (PPN, PNN, PNP, NPN). The corresponding consistency patterns for sensitization to the specific allergen groups were similar.

Pattern of sensitization in relation to age at first reading of any positive SPT

Of those with *any positive SPT* at age 19 years (n=653), 47.5% had their first reading of *any positive SPT* at age 7-8 years, 23.4% at age 11-12, and 29.1% at age 19 years. The number of positive reactions at age 19 years was strongly associated with the age at the first reading of being sensitized. Of those with positive reactions to six or more allergens at age 19 years, 96.4% had their first reading of *any positive SPT* at age 7-8 years. In contrast, among those with only one positive reaction at the age of 19 years, 8.7% had their first positive reading at age 7-8 years, while 73.9% had their first positive reading at the age of 19 years (Figure 2). In a multivariate analysis, early sensitization, OR 19.5 (10.9-34.9), and first sensitization at age 12 years, OR 4.1 (2.2-7.9), were strongly associated with multi sensitization at age 19 years compared with first sensitization at age 19 years. Of those with onset of allergic sensitization before age 7-8 years, 66.1% were multi-sensitized at age 19 versus 28.8% among those with onset between 7-8 to 11-12 years, and 9.2% among those with onset after 11-12 years ($p<0,001$).

Risk factors for allergic sensitization

Risk factors for incidence of allergic sensitization during different age periods were analyzed by multinomial logistic regression, using subjects with a negative SPT at all three occasions

as reference. In unadjusted analyses, the incidence of *any positive SPT* from birth to 7-8 years was positively associated with family history of allergy (OR 2.1 (95%CI 1.6-2.7)), growing up in urban area (OR 2.0 (95%CI 1.3-3.0)), and male sex (OR 1.4 (95%CI 1.1-1.8)), and negatively associated with birth order (OR 0.9 (95%CI 0.8-1.0)) and furry animals at home (OR 0.6 (95%CI 0.4-0.8)). In adjusted analysis, the risk estimates remained on similar level (Table 4). The incidence of *any positive SPT* from 7-8 to 11-12 years was significantly associated with male sex (OR 1.5 (95%CI 1.1-2.1)), while family history of allergy was borderline associated in the unadjusted and adjusted analyses. In the unadjusted analysis, the incidence of *any positive SPT* from 11-12 to 19 years, was associated with a family history of rhinitis (OR 1.6 (95% CI 1.2-2.2)), and cat or dog at home (OR 0.7 (95%CI 0.5-0.9)), while in the adjusted analysis only a family history of rhinitis reached statistical significance (Table 4).

In a multivariate binary logistic regression analysis, the variables male sex (OR 1.3 (95%CI 1.1-1.6)), family history of allergy (OR 1.9 (95%CI 1.5-2.3)), urban living (OR 1.4 (95%CI 1.0-1.9)) were significantly associated with *any positive SPT* at age 19 years, while furry animal at home was borderline significant (OR 0.8 (95%CI 0.7-1.0)).

DISCUSSION

This longitudinal population-based study reports both a high incidence and a high persistence of allergic sensitization to airborne allergens during childhood and adolescence explaining the increasing prevalence of allergic sensitization by age to young adulthood. A

main finding is that once sensitized, the sensitization remains. Multi-sensitization at age 19 was strongly associated with early onset of allergic sensitization. The mean annual incidence of sensitization to furred animals decreased by age, while the incidence of sensitization to pollen was stable. Having a family history of allergy was consistently positively associated with the incidence of allergic sensitization during both childhood and adolescence. A novel finding was that the association with male sex lost significance with increasing age and the associations with environmental factors weakened and lost significance.

Besides our study, there are only a few population-based studies reporting data on persistence, incidence and remission of allergic sensitization to airborne allergens from birth to young adulthood^{1,2}. Previous longitudinal studies assessing incidence and remission are mainly focused on early childhood and primary school age^{8,27}. In line with our previously published results from primary school age¹¹, these studies also found a high incidence of sensitization both before and after school start. In accordance with our results, the large Isle of Wight-study found a high incidence and persistence of allergic sensitization throughout childhood and adolescence¹. Others report an increasing prevalence of allergic sensitization by age among adolescents without calculating the incidence or remission^{2,28}. A study from New Zealand reported a low remission of sensitization to airborne allergens among adolescents, but data regarding incidence was not presented²⁹. The remission of allergic sensitization was very low in our study, a result consistent with findings from the neighbouring Finland³⁰. These studies confirm the external validity of our study. Thus, there is strong evidence for high incidence and persistence of sensitization to airborne allergens during childhood and to young adulthood.

We assessed the stability of allergic sensitization by taking three SPT measurements into account. The very few remittent cases may be true remission, but it may also be a result of misclassification. Irrespective of this explanation, our study clearly verifies that remission of allergic sensitization is indeed very low and hardly exists before adulthood. In adults however, the pattern is the inverse with high remission and low incidence ⁹.

The incidence of allergic sensitization was high to all major specific allergens, especially timothy, cat, dog and birch. A German study found a higher incidence of elevated specific IgE for outdoor allergens like pollen, compared to indoor allergens such as mite and furry pets during the first six years of life ³. In our study however, the incidence of sensitization to any animal was highest before the age of seven. This is in line with results of the Tucson-study, which suggest a higher incidence and also an earlier age of onset as well as persistence of sensitization to perennial allergens, while sensitization to seasonal allergens occurred more often later in childhood ³¹. Regarding sensitization to the perennial allergen mite, both the prevalence and incidence was low in our study despite an increasing trend.

This was an expected result, as the study area is lacking mite due to the dry and cold climate

³².

Early onset of allergic sensitization was associated with multi-sensitization at age 19 years. Of those with positive SPT to at least six allergens, 96% were sensitized already at age seven, and of those multi-sensitized at age 19 years, 29.5% were multi-sensitized at age 7. Thus, the majority developed multi sensitization over time. This is a result of low remission and

further sensitization to specific allergens among subjects already sensitized at earlier age^{1,11}.

Having a family history of allergy was consistently associated with both childhood and adolescent allergic sensitization, in line with several studies^{5,7,15-17}. Male sex has been positively associated with onset of allergic sensitization among children in several studies^{8,15}. This association was found also in our study, but interestingly it lost its significance when the children reached adolescence. Also a Belgian study reports a significantly higher prevalence of allergic sensitization in boys up to the age of eight years thereafter the boy-to-girl ratio decreased³³. The reason for the male dominance in childhood is not clear, but complex hormonal mechanisms may be involved.

The hygiene hypothesis was launched by Strachan et al. in 1989 when a negative association between the number of siblings and hay fever was described³⁴. The theory was that infections in early childhood, which are more common in larger families, would prevent development of allergic sensitization. This protective effect has been confirmed also in adults³⁵, and having older siblings was negatively associated with sensitization also in our cohort¹¹. However, the association was only present for incidence of sensitization before the age of seven. This is an interesting result and may be related to a not fully developed immune system in early life.

Living in an urban area was significantly associated with onset of allergic sensitization before the age of seven and border-line significant for later onset. Several other studies have also reported urban living to be a risk factor for allergic sensitization^{5,16-19}, and in particular sensitization to pollen⁷. Today, there is evidence that the allergenicity of pollen is influenced by air pollutants common in urban areas such as diesel³⁶ and ozone³⁷.

Several studies have found a negative association between allergic sensitization and having cat or dog at home^{22,23}, including a previous more detailed analysis from our cohort¹¹. In the current study only sensitization before the age of seven reached significance although a similar trend was found for development of sensitization later during adolescence. The mechanism of the protective effect is unclear but may be related to development of tolerance³⁸, however, the debate continues as not all studies found this protective effect^{22,39}.

To the best of our knowledge, we are the first to present differences in risk factor pattern depending on age at onset of sensitization. Several risk factors were associated only with incidence of sensitization in early childhood and not during adolescence. Cross-sectional studies lack the ability to differentiate subjects with early and late onset of sensitization, why the risk factor patterns reflect a mixture of risk factors for early and late onset. This may explain why cross-sectional studies within different age-spans present varying risk factor patterns. In order to better understand the risk factors for allergic sensitization, longitudinal studies allowing analyses of late onset sensitization must be performed and the impact of exposures also later in life should be evaluated in detail.

Several factors support the validity of this study. All skin prick tests were performed with the same method and at the same time of the year, and a limited number of personnel performed all tests. The participation rate was high at all examinations, and the individuals studied longitudinally were representative for the entire cohort. Furthermore, the same standardized allergen was used, although not the same batch. However, a recent study has showed that use of different batches may interfere with the results ⁴⁰, but in the current cohort the correlation between the skin tests and *in vitro* IgE assays at age 7-8 and at age 11-12 years ^{11,26} was good.

In conclusion, the high incidence and persistence of allergic sensitization to airborne allergens from birth to young adulthood together with a very low remission explain the increasing prevalence by age. Early sensitization predicted multi-sensitization at age 19 years. The risk factor pattern for incidence of allergic sensitization differed between early and late onset; male sex, number of siblings, living in an urban area, and having a family history of allergy was significantly associated with incidence of allergic sensitization before age seven, while only family history of allergy was associated with onset during adolescence.

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Author contribution

ER designed the study, participated in data collection and interpretation of data, drafted and revised the manuscript. KW participated in data analysis and interpretation of data, drafted and revised the manuscript. AB participated in data collection and revised the manuscript. HB participated in data analysis and interpretation of data, and revised the manuscript. LH participated in data collection, interpretation of data, and revised the manuscript. BL participated in study design, interpretation of data, and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

None of the authors have any conflicts of interest related to this work.

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Legends to figures

Figure 1. The prevalence (%) of allergic sensitization measured by skin prick test at age 7-8 years, 11-12 years, and 19 years, respectively. Difference by age were tested with the Mantel-Haenszel's test for trend, and were significant for all allergens and allergen groups, $p=0.027$ for any mould, and $p<0.001$ for all other allergens and allergen groups.

Figure 2. Age at first reading of any positive skin prick test (SPT) in relation to number of positive SPT reactions at age 19 years.

Table 1. Prevalence (%) of allergic sensitization at age 7-8, 11-12 and 19 years, by sex

	Age 7-8 years (n=2148)			Age 11-12 years (n=2027)			Age 19 years (n=1868)		
	Girls	Boys	p-value	Girls	Boys	p-value	Girls	Boys	p-value
Birch	6.7	9.2	0.036	12.9	16.0	0.051	20.2	24.9	0.016
Timothy	5.2	8.1	0.007	12.7	18.2	0.001	23.5	31.6	<0.001
Mugwort	0.8	1.0	0.649	2.8	3.4	0.486	5.3	6.6	0.235
Any Pollen	10.3	14.5	0.004	19.0	25.5	<0.001	30.9	37.7	0.002
Cat	12.2	14.6	0.107	17.1	23.0	0.001	23.9	30.0	0.003
Dog	8.1	9.3	0.343	14.8	19.8	0.003	22.2	30.6	<0.001
Horse	4.8	7.4	0.011	9.1	11.9	0.037	12.6	16.2	0.026
Any animal	15.5	17.1	0.306	20.1	26.4	0.001	29.3	36.4	0.001
D.pteronyssinus	0.2	0.8	0.033	0.7	1.4	0.110	2.7	4.1	0.080
D.farinae	0.0	1.3	<0.001	0.6	1.3	0.133	1.4	2.6	0.059
Any mite	0.2	1.7	<0.001	1.0	1.8	0.121	3.0	4.4	0.093
Cladosporium	0.7	1.5	0.096	0.6	1.2	0.188	1.5	2.5	0.119
Alternaria	0.3	0.9	0.078	0.0	0.6	0.031	0.7	1.3	0.231
Any mold	0.8	1.9	0.037	0.6	1.3	0.132	1.6	2.9	0.052
Any allergen	19.0	22.3	0.059	26.8	34.2	<0.001	38.8	45.6	0.003

P-value =Chi square test for difference in proportions between girls and boys

Table 2. Incidence (%) of allergic sensitization from birth up to age 19 years.

	From birth to 7-8 years		From 7-8 to 11-12 years		From 11-12 to 19 years	
	Cumulative incidence	Mean annual incidence	Cumulative incidence	Mean annual incidence	Cumulative incidence	Mean annual incidence
Birch	8.3	1.1	3.4	0.9	5.5	0.8
Timothy	6.8	0.9	5.9	1.5	8.2	1.3
Mugwort	1.1	0.1	0.7	0.2	1.6	0.2
Any Pollen	12.8	1.7	8.4	2.1	11.4	1.8
Cat	14.2	1.9	5.4	1.4	6.2	1.0
Dog	8.7	1.2	4.7	1.2	5.6	0.9
Horse	6.4	0.9	1.8	0.5	1.7	0.3
Any animal	16.8	2.2	7.4	1.9	9.3	1.4
D.pteronyssinus	0.7	0.1	0.4	0.1	1.8	0.3
D.farinae	0.7	0.1	0.3	0.1	0.4	0.1
Any mite	1.1	0.1	0.7	0.2	1.7	0.3
Cladosporium	1.3	0.2	0.1	0.0	0.4	0.1
Alternaria	0.5	0.1	0.0	0.0	0.1	0.0
Any mold	1.5	0.2	0.1	0.0	0.5	0.1
Any positive SPT	21.5	2.9	13.5	3.4	17.9	2.8

Among n=1516 subjects participating at all three occasions, i.e. at 7-8 years, 11-12 years and 19 years of age
SPT=skin prick test

Table 3. Consistency of results from skin prick tests (SPT) at 7-8, 11-12 and 19 years of age

SPT Consistency			Any allergen		Any pollen		Any animal		Any mite		Any mold	
7-8y	11-12y	19y	n	%	n	%	n	%	n	%	n	%
N	N	N	845	55.7	983	64.8	976	64.5	1428	94.9	1446	96.1
P	P	P	310	20.4	188	12.4	239	15.8	3	0.2	2	0.1
N	N	P	184	12.1	182	12.0	163	10.8	44	2.9	26	1.7
N	P	P	153	10.1	154	10.2	107	7.1	6	0.4	4	0.3
N	P	N	8	0.5	3	0.2	13	0.9	10	0.7	7	0.5
P	N	N	8	0.5	4	0.3	10	0.7	10	0.7	15	1.0
P	N	P	6	0.4	1	0.1	4	0.3	3	0.2	3	0.2
P	P	N	2	0.1	1	0.1	1	0.1	0	0.0	2	0.1
All	All	All	1516	100.0	1516	100.0	1513	100.0	1504	100.0	1505	100.0

P=Positive reaction to skin prick test

N=Negative reaction to skin prick test

Among n=1516 subjects participating at all three occasions, i.e. at 7-8 years, 11-12 years and 19 years of age

Table 4. Early life risk factors in relation to the incidence of allergic sensitization to any allergen, expressed as odds ratios with 95% confidence intervals.

Risk factor	Incidence of any positive SPT from birth to 7-8 years, n=310		Incidence of any positive SPT from 7-8 to 11-12 years, n=153		Incidence of any positive SPT from 11-12 to 19 years, n=184	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Order among siblings*	0.8 (0.7-1.0)	0.007	1.0 (0.9-1.1)	0.871	0.9 (0.8-1.1)	0.239
Cat or dog in childhood	0.7 (0.5-0.9)	0.008	0.8 (0.6-1.2)	0.340	0.8 (0.5-1.1)	0.098
Urban area in childhood	1.9 (1.2-2.9)	0.007	0.7 (0.5-1.1)	0.144	1.7 (1.0-2.9)	0.066
Family history of allergy	2.1 (1.6-2.8)	<0.001	1.4 (1.0-1.9)	0.090	1.6 (1.1-2.3)	0.006
Male sex	1.3 (1.0-1.7)	0.031	1.5 (1.1-2.1)	0.021	1.0 (0.7-1.4)	0.984

Analyzed by multiple multinomial logistic regression with negative reactions to all allergens at all measurements as reference category (NNN), n= 845

*=numeric variable, with value 1 for being the first child and value 3 for being the third child, etc.

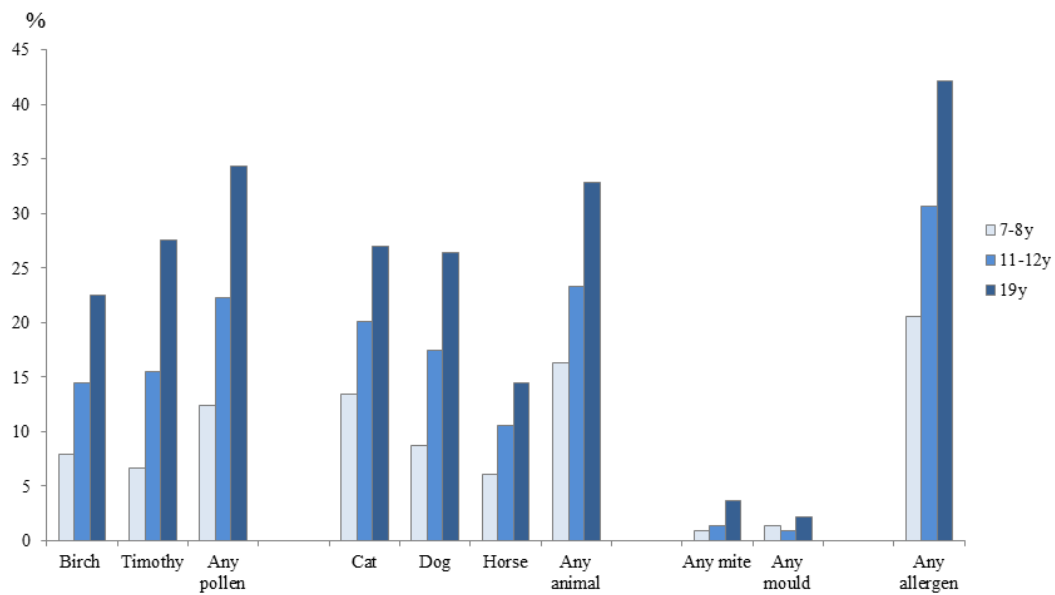


Figure 1

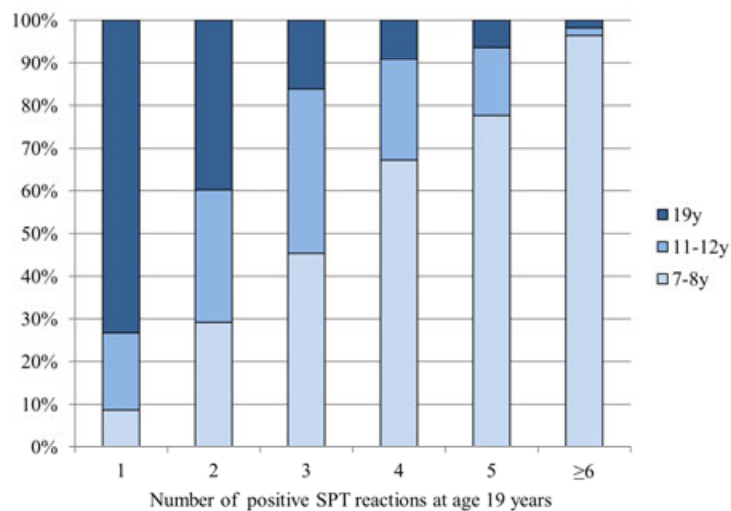


Figure 2.