

The association of allergic symptoms with sensitization to inhalant allergens in childhood

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Although it is generally agreed that sensitization is an important risk factor for allergic diseases, the extent to which sensitization accounts for allergic symptoms in children is controversial. As part of the Aalst Allergy Study, this cross-sectional study investigated the prevalence of allergic symptoms and their association with sensitization in an unselected population of Flemish children aged 3.4–14.8 yr. Skin prick testing with the most common aeroallergens was performed and allergic symptoms were documented by a parental questionnaire. In the children older than 6 yr, a significant association of current wheezing, current dyspnea, airway hyperreactivity, rhinoconjunctivitis, and current eczema with sensitization was found, while in the pre-school children these associations were less pronounced. The association with sensitization was strongest for rhinoconjunctivitis and current respiratory symptoms – the association was less striking for children with current eczema. The impact of a positive family history of allergy on the association with sensitization was more important for eczema than for the other analyzed allergic symptoms. Persistent and late-onset wheezers were significantly more likely than non-wheezers and transient early wheezers to be associated with sensitization and a personal history of rhinoconjunctivitis. Late-onset wheezing was associated with a positive family history of allergy, while transient early wheezing was associated with day-care attendance. An association with eczema was found for all three childhood wheezing phenotypes. The association of allergic symptoms with sensitization is significant in the older but less pronounced in pre-school children and is more pronounced for current allergic symptoms. Diagnosis and disease definition of allergy symptoms remains difficult at pre-school age. The influence of a positive family history of allergy on the association of the respective allergic symptoms with sensitization was most important for eczema. Our data confirm the atopic characteristics of the different wheeze phenotypes.

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Over the last three to four decades a rise in the incidence and prevalence of allergic disorders – atopic dermatitis, asthma, allergic rhinitis, and conjunctivitis – has occurred (1–3), although recent data suggest that this increase may now be levelling off (4). The allergic disorders affect a

large percentage of the pediatric population. These children present or report symptoms such as itchy skin lesions, sneezing, a runny or blocked nose, itching, redness, and tearing of the eyes, cough, wheezing, and chest tightness. Although it is generally agreed that sensitization

is an important risk factor for allergic diseases, the extent to which sensitization accounts for these diseases is controversial (5, 6). When sensitization is presumed to be the cause in the vast majority of children, similar symptoms occur in non-atopic individuals. School children and especially pre-school children, often present nasal symptoms such as sneezing, runny or blocked nose, as well as cough and wheezing. A considerable part of the upper and lower respiratory tract symptoms may rely on viral infections. Therefore, particularly at this age diagnosis and disease definition may be difficult (7). Early diagnosis may facilitate effective prevention and treatment (8–12). Nevertheless, factors operating very early in life, such as antigen exposure and infections, are particularly important for the acquisition of childhood allergic diseases. On the other hand, we know from daily practice that many subjects sensitized to aero-allergens do not always experience allergic symptoms (13, 14).

Measurement of skin prick test reactivity to allergens is the golden standard for the assessment of allergic sensitization (15). The combination of a careful clinical history and skin prick testing may facilitate the diagnosis of an atopic disorder.

As a part of the Aalst Allergy Study, the aim of this study was to investigate the prevalence of allergic symptoms and their association with sensitization in an unselected population of Flemish children aged 3.4–14.8 yr.

Materials and methods

Study population

The study was performed from January 2004 to June 2005 in an unselected sample of children aged 3.4–14.8 yr (mean age, 9.3 yr) attending randomly selected nursery, primary, and secondary schools in the city of Aalst and the surrounding area. Aalst is a Belgian municipality situated 19 miles northwest of Brussels. It has a total population of 76,852 for a total area of 78.12 km², giving a population density of 983.83 inhabitants/km².

The parents of all 2674 children in the 2nd grade of nursery school, the 1st, 3rd, and 5th grade of primary school, and the 1st grade of secondary school were contacted, provided with a questionnaire (see below), and invited to participate in the study. The parents of 2021 children (75%) returned a completed questionnaire and provided written consent for skin prick testing to be performed in their child (see below).

Approval for the study was obtained from the local medical ethical committee.

Questionnaire

Parental questionnaires were distributed by the school doctors of the participating schools. The questions addressing respiratory and allergic disorders, i.e. rhinoconjunctivitis and asthma were adapted from the International Study of Asthma and Allergies in Childhood questionnaire (2) and also covered the items of the Brief Pediatric Asthma Screen Plus (BPAS+) score (16) (the scoring for the asthma component of the BPAS+ is a positive response to any of the following four items: wheeze, persistent cough, night cough, and response to change in air temperature). The presence of eczema, as well as the time of occurrence, was documented by parentally reported eczema. For the presence of the respiratory symptoms of wheezing and dyspnea in the past history of the child, the questionnaire distinguished four periods: before the age of 1 yr, between 1 and 2.5 yr, pre-school age and primary school age. The children older than 6 yr were classified into four wheezing categories based on the current and previous history of their wheezing symptoms (17–19): non-wheezers (no wheezing during the first 2.5 yr of life and no wheezing at pre-school or primary school age), transient early wheezers (wheezing during the first 2.5 yr of life, but no wheezing at pre-school or primary school age), late-onset wheezers (no wheezing during the first 2.5 yr of life, but wheezing in the previous 12 months) and persistent wheezers (wheezing during the first 2.5 yr of life and wheezing in the previous 12 months).

For eczema we distinguished between eczema in infancy, current eczema (in the last 12 months) and eczema ever.

In our study we defined current allergic symptoms as the presence of wheezing, dyspnea, airway hyperreactivity, rhinitis, conjunctivitis or eczema in the last 12 months. A positive family history of allergy was defined as the presence of one of the allergic symptoms in one of the parents or siblings.

The questionnaire also included questions about demographic characteristics (age, gender, nationality, maternal, and paternal profession), tobacco smoke exposure (pre- and post-natal), and other potential risk factors for sensitization, such as pre-maturity, feeding practices in the neonatal period, family history of allergy, number of siblings, frequency of childhood infections, vaccinations, place of residence (urban or rural), animal contacts, and housing characteristics (age

of building, heating, dampness, bedroom conditions etc).

Skin prick tests

Skin prick testing with the most common aeroallergens was performed by the same two experienced pediatricians (EG and DVG) to ensure uniformity in testing technique and interpretation. The allergen panel consisted of *Dermatophagoides pteronyssinus*, *Alternaria tenuis*, cat, dog, mixed grass pollens (orchardgrass, Kentucky bluegrass, perennial ryegrass, gramineae, and timothy), tree pollens (common alder, common birch, hazel, and European hornbeam) and *Blatella germanica* (cockroach); the concentration of allergen extracts was 100 I.R./ml (Stallergenes, Waterloo, Belgium). Histamine solution (10 mg/ml in distilled water), was used as a positive control and saline as a negative control. Each child was tested on the volar surface of the forearm using 1-mm prick lancets (Stallergenes). The skin reaction was recorded after 15 min by evaluating the skin response rate to inoculation of each allergen extract in comparison with the wheal given by the positive and the negative control. The size of each wheal was documented as the mean of the longest diameter and the diameter perpendicular to it. A positive test was defined as a mean wheal size, after subtraction of the negative control, of at least 3 mm. Use of H1 antihistamines was suspended at least 7 days before skin prick testing. Atopy was defined as at least 1 positive skin test to any of the seven allergens tested (15).

Statistical analysis

Descriptive statistical analysis methods were used to study the distribution of all covariates between the sensitized and non-sensitized children. Chi-squared test was used to study the univariate association between allergic symptoms and sensitization. Logistic regression analysis was used to study the association between co-variables and the outcome (sensitized or non-sensitized). In a univariate analysis, the association between each covariate and sensitization was studied. We then added one by one all risk factors for sensitization into the model. If any of these factors changed the estimate with more than 5%, these risk factors were entered into the final model.

For the analysis on the association between respiratory symptoms and sensitization, we only included those children with complete information on the specific topics. To check for the potential of 'confounding by missing variables',

the fact of having missing data was added as a dummy in the analysis.

A p-value of < 0.05 was considered as statistically significant. All analyses were done using spss 13.0 (SPSS Inc., Chicago, IL, USA).

Results

After returning a completed questionnaire and a written permission of their parents for skin prick testing, 2021 children (75% of all contacted children) were included in this study.

Table 1 shows the baseline characteristics of the study population. 1538 (76.1%) of all children had negative skin prick tests and 483 children (23.9%) had at least one positive skin prick test (20–22). We first analyzed the association of allergic symptoms (at present and in the past) with overall sensitization for the whole study population (Table 2). A positive association with sensitization was found for conjunctivitis (Odds_{adj} 7.3, 95% CI 4.5–11.9), rhinitis (Odds_{adj} 3.7, 95% CI 2.6–5.2), current wheezing (Odds_{adj} 3.6, 95% CI 2.0–6.4), current dyspnea (Odds_{adj} 3.4, 95% CI 1.8–6.6), airway hyper-reactivity (Odds_{adj} 1.7, 95% CI 1.1–2.5), current eczema (Odds_{adj} 1.9, 95% CI 1.2–3.0), and in general current allergic complaints (Odds_{adj} 2.9, 95% CI 2.1–4.0).

We stratified the whole study population for age and repeated the analyses for both the group of children younger than six and the group of children older than 6 yr at the time of participation in the study (Table 3). A significant association with overall sensitization was found for all investigated allergic symptoms in the older children – this association was less pronounced (and not statistically significant) in children younger than 6 yr. In this older age group as well we found that mainly children with current allergic symptoms, compared to children with allergic symptoms in the past, were sensitized.

The influence of a positive family history of allergy on the association of the respective allergic symptoms with sensitization was investigated as shown in Table 4. For current allergic symptoms, rhinitis, conjunctivitis, and current respiratory symptoms (wheezing and airway hyperreactivity) in particular, the impact of the presence of symptoms on the association with sensitization was stronger than the impact of a positive family history of allergy. In contrast, for current eczema, the impact of a positive family history of allergy on the association with sensitization was stronger than the impact of the presence of eczema itself. After stratification for age, the same effects of a positive family history

Table 1. Baseline characteristics of the study population

	Study population (n = 2021)		Odds ratio [95%CI]
	Not sensitized (n = 1538)	Sensitized (n = 483)	
Age (in yr)	3.4–14.8 (mean 9.0 ± 2.8)	3.9–14.0 (mean 10.0 ± 2.6)	
3.4–< 6 yr	301 (19.6%)	57 (11.8%)	1
6–< 8 yr	239 (15.5%)	39 (8.1%)	0.9 [0.6–1.3]
8–< 10 yr	240 (15.6%)	62 (12.8%)	1.4 [0.9–2.0]
10–< 12 yr	468 (30.4%)	198 (41.0%)	2.2 [1.6–3.1]
12–14.8 yr	290 (18.9%)	127 (26.3%)	2.3 [1.6–3.3]
Gender (male/female)	697/841	293/190	1/0.5 [0.4–0.7]
Current animal exposure (cat and dog)			
No	667 (43.4%)	222 (46.0%)	1
Yes	868 (56.4%)	259 (53.6%)	0.9 [0.7–1.1]
Missing	3 (0.2%)	2 (0.4%)	
Animal exposure at birth			
No	773 (50.3%)	269 (55.7%)	1
Yes	732 (47.6%)	211 (43.7%)	0.8 [0.7–1.0]
Missing	33 (2.1%)	3 (0.6%)	
Passive smoke exposure			
No	842 (54.7%)	294 (60.9%)	1
Yes	676 (44.0%)	184 (38.5%)	0.8 [0.6–0.96]
Missing	20 (1.3%)	5 (1.0%)	
Maternal smoking during pregnancy			
No	1255 (81.6%)	402 (83.2%)	1
Yes	239 (15.5%)	68 (14.5%)	0.9 [0.7–1.2]
Missing	44 (2.9%)	13 (2.7%)	
Prematurity			
No	1410 (91.7%)	457 (94.6%)	1
Yes	101 (6.6%)	21 (4.3%)	0.6 [0.4–1.0]
Missing	27 (1.8%)	5 (1.0%)	
Breastfeeding			
No	860 (55.9%)	268 (55.5%)	1
Yes	637 (41.4%)	203 (42.0%)	1.0 [0.8–1.3]
Missing	41 (2.7%)	12 (2.5%)	
Number of siblings			
One child	296 (19.2%)	113 (23.4%)	1
More than one child	1234 (80.2%)	367 (76.0%)	0.8 [0.6–0.96]
Missing	8 (0.5%)	3 (0.6%)	
Day-care attendance			
No	896 (58.3%)	294 (60.9%)	1
Yes	595 (38.7%)	178 (36.9%)	0.9 [0.7–1.1]
Missing	47 (3.1%)	11 (2.3%)	
Bedroom conditions			
Stuffed toys			
No	93 (6.0%)	46 (9.5%)	1
1–5	603 (39.2%)	227 (47.0%)	0.8 [0.5–1.1]
> 5	756 (49.2%)	198 (41.0%)	0.5 [0.4–0.8]
Missing	86 (5.6%)	12 (2.5%)	
Bedding material			
Synthetic	975 (63.4%)	349 (72.3%)	1
Duvet or non-synthetic	428 (27.8%)	103 (21.3%)	0.7 [0.5–0.9]
Missing	135 (8.8%)	31 (6.4%)	
Floor			
Wood or fitted carpet	1299 (84.5%)	416 (86.1%)	1
Smooth flooring	192 (12.5%)	47 (9.7%)	0.8 [0.6–1.1]
Missing	47 (3.1%)	20 (4.1%)	
Place of residence			
Urban	468 (30.4%)	139 (28.8%)	1
Rural	1034 (67.2%)	339 (70.2%)	1.1 [0.9–1.4]
Missing	36 (2.3%)	5 (1.0%)	
Family history of allergy			
No	502 (32.6%)	126 (26.1%)	1
Yes	685 (44.5%)	266 (55.1%)	1.5 [1.2–2.0]
Missing	351 (22.8%)	91 (18.8%)	

The right columns gives the odds ratio for the association between the different covariates and sensitization.

Statistically significant results ($p < 0.05$) are represented in bold.

Table 2. Association of allergic manifestations with overall sensitization for the whole study population

	Sensitized		Crude OR [95%CI]	Odds _{adj} [95%CI]
	No n = 1538 (100%)	Yes n = 483 (100%)		
Wheezing				
No wheezing	1219 (82.0%)	321 (66.6%)	1	1
In the past	194 (13.1%)	79 (16.9%)	1.5 [1.2–2.1]	1.2 [0.8–1.8]
Current	73 (4.9%)	68 (14.5%)	3.5 [2.5–5.0]	3.6 [2.0–6.4]
Dyspnea				
No dyspnea	1333 (89.5%)	374 (80.1%)	1	1
In the past	102 (6.9%)	36 (7.7%)	1.3 [0.8–1.9]	0.8 [0.4–1.5]
Current	54 (3.6%)	57 (12.2%)	3.8 [2.5–5.6]	3.4 [1.8–6.6]
Airway hyperreactivity	178 (11.6%)	105 (21.7%)	2.1 [1.6–2.8]	1.7 [1.1–2.5]
Rhinitis	220 (14.3%)	195 (40.4%)	4.1 [3.3–5.2]	3.7 [2.6–5.2]
Conjunctivitis	73 (4.7%)	132 (27.3%)	7.6 [5.6–10.4]	7.3 [4.5–11.9]
Eczema				
No eczema	1208 (79.8%)	321 (67.9%)	1	1
In the past	156 (10.3%)	69 (14.6%)	1.7 [1.2–2.3]	1.4 [0.9–2.2]
Current	149 (9.8%)	83 (17.5%)	2.1 [1.6–2.8]	1.9 [1.2–3.0]
Current allergic complaints	474 (30.8%)	295 (61.1%)	3.6 [2.9–4.5]	2.9 [2.1–4.0]

Crude OR, crude odds ratio; OR_{adj}, adjusted odds ratio; 95% CI, 95% confidence interval.

Odds ratio adjusted for all factors that changed the crude OR with more than 5% for the specific research item (checked factors: age, gender, passive smoke exposure, housing conditions now and at birth, maternal smoking during pregnancy, prematurity, breastfeeding, day care attendance, domestic pets at present and at birth, family history of allergy, number of siblings, and birth order). Information on specific factors that were entered in each multivariate analysis can be provided upon request.

Statistically significant results ($p < 0.05$) are represented in bold.

of allergy on the association with overall sensitization was observed for all analyzed allergic symptoms in the older children and could not be documented in the children younger than 6 yr (data not shown).

In the subset of children older than 6 yr with available data on their history of wheezing ($n = 1450$) we described prevalences and characteristics of the distinct childhood wheezing phenotypes, as defined by the Tucson Children's Respiratory Cohort Study (17). Eighty nine point five percent ($n = 1298$) of our children older than 6 yr were assigned as never wheezers, 4.6% ($n = 67$) as transient early wheezers, 2.6% ($n = 38$) as persistent and 3.2% ($n = 47$) as late-onset wheezers (Table 5). Forty seven point four percent ($n = 18$) of the persistent wheezers were atopic.

Persistent and late-onset wheezers were significantly more likely than non-wheezers to be associated with sensitization and a personal history of rhinitis and conjunctivitis. Late-onset wheezing was significantly associated with a positive family history of allergy while for persistent wheezing, significance was lost after adjustment (Table 5). Transient early wheezing was associated with day-care attendance. An association with eczema was found for all three childhood wheezing phenotypes. No further associations of gender, passive smoke exposure,

maternal smoking during pregnancy, pre-maturity, breastfeeding, housing conditions, and the presence of domestic pets at present and at birth, number of siblings and chronological position of the child in the family with any of the wheezing phenotypes was found (data not shown).

Discussion

A total of 483 children (23.9%, 95% CI 22.1–25.8%) had evidence of allergic sensitization. The age standardized prevalence rate was 20.5% (95% CI 17.9–23.2%) (20).

This paper investigated the association of allergic symptoms in infancy and childhood with sensitization to inhalant allergens. All investigated current allergic symptoms were positively associated with sensitization. The association was strongest for rhinoconjunctivitis and stronger for respiratory allergic symptoms than for eczema. After stratification of the whole study population into children younger than or older than 6 yr, we found that the associations of any of the investigated allergy symptoms with overall sensitization were limited to the children older than 6 yr (Table 3). No significant association could be documented in the group of children younger than six. Apart from the smaller number of children in this group, this might be due to the overlap of the 'allergic-like' symptoms with viral

Table 3. Association of allergic manifestations with overall sensitization for the whole study population, stratified for age: < 6 yr compared to ≥ 6 yr

	Sensitized			
	No n = 301 (100%)	Yes n = 57 (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]
< 6 yr				
Wheezing				
No wheezing	214 (73.3%)	31 (59.6%)	1	1
In the past	47 (16.1%)	9 (17.3%)	1.3 [0.6–3.0]	1.3 [0.4–5.0]
current	31 (10.6%)	12 (23.1%)	2.7 [1.2–5.7]	1.4 [0.2–9.6]
Dyspnea				
No dyspnea	250 (86.2%)	42 (77.8%)	1	1
In the past	22 (7.6%)	5 (9.3%)	1.4 [0.5–3.8]	–
current	18 (6.2%)	7 (13.0%)	2.3 [0.9–5.9]	–
Airway hyperreactivity	50 (16.6%)	16 (28.1%)	1.9 [1.0–3.6]	0.8 [0.2–3.5]
Rhinitis	69 (22.9%)	23 (40.4%)	2.2 [1.2–4.0]	0.6 [0.2–2.1]
Conjunctivitis	17 (5.6%)	7 (12.3%)	2.3 [1.0–5.9]	0.9 [0.1–11.8]
Eczema				
No eczema	234 (79.1%)	30 (56.6%)	1	1
In the past	28 (29.5%)	6 (11.3%)	1.7 [0.6–4.4]	2.7 [0.5–14.1]
Current	34 (11.5%)	17 (32.1%)	3.9 [1.9–7.8]	1.8 [0.4–7.3]
Current allergic complaints	135 (44.9%)	38 (66.7%)	2.5 [1.3–4.5]	0.4 [0.1–1.3]
	Sensitized			
	No n = 1237 (100%)	Yes n = 426 (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]
≥ 6 yr				
Wheezing				
No wheezing	1005 (84.2%)	290 (69.7%)	1	1
In the past	147 (12.3%)	70 (16.8%)	1.7 [1.2–2.3]	1.1 [0.7–1.8]
current	42 (3.5%)	56 (13.5%)	4.6 [3.0–7.0]	4.0 [2.1–7.6]
Dyspnea				
No dyspnea	1083 (90.3%)	332 (80.4%)	1	1
In the past	80 (6.7%)	31 (7.5%)	1.3 [0.8–1.9]	0.9 [0.5–1.7]
Current	36 (3.0%)	50 (12.1%)	4.5 [2.9–7.1]	4.3 [2.1–8.8]
Airway hyperreactivity	128 (10.3%)	89 (20.9%)	2.3 [1.7–3.1]	1.7 [1.1–2.7]
Rhinitis	151 (12.2%)	172 (40.4%)	5.0 [3.9–6.5]	4.5 [3.1–6.5]
Conjunctivitis	56 (4.5%)	125 (29.3%)	8.9 [6.3–12.5]	7.9 [4.8–13.2]
Eczema				
No eczema	974 (80.0%)	291 (69.3%)	1	1
In the past	128 (10.5%)	63 (15.0%)	1.6 [1.2–2.3]	1.4 [0.8–2.2]
current	115 (9.4%)	66 (15.7%)	1.9 [1.4–2.7]	1.8 [1.1–3.0]
Current allergic complaints	339 (27.4%)	257 (60.3%)	4.1 [3.3–5.2]	3.5 [2.5–5.0]

Crude OR, crude odds ratio; OR_{adj}, adjusted odds ratio; 95% CI, 95% confidence interval.

Odds ratio adjusted for all factors that changed the crude OR with more than 5% for the specific research item (checked factors: gender, passive smoke exposure, housing conditions now and at birth, maternal smoking during pregnancy, prematurity, breastfeeding, day care attendance, domestic pets at present and at birth, family history of allergy, number of siblings, and birth order).

Statistically significant results ($p < 0.05$) are represented in bold.

induced symptoms, which have a high prevalence in the younger age group. Tables 2 and 3 illustrate that many children without sensitization still had identifiable ‘allergic-like’ symptoms, confirming the observation that the development of allergic symptoms is not solely attributable to allergic sensitization and highlighting the need to further investigate the role of atopic sensitization in ‘allergic-like’ symptoms (23–27).

Investigating the influence of a positive family history of allergy on the association of the respective allergic symptoms with sensitization,

we found that the impact was more important for eczema than for rhinitis, conjunctivitis, and current respiratory symptoms (Table 4). This observation is in line with data, suggesting that atopic dermatitis may follow a different risk pattern than asthma and rhinoconjunctivitis (28, 29).

In the Tucson Children’s Respiratory Cohort Study (17, 30) Martinez et al. demonstrated that distinct wheezing phenotypes exist during the first 6 yr of life. In this study we have employed a similar phenotypic approach in the subset of

Table 4. Influence of family history of allergy on the association of allergic symptoms with sensitization

	Sensitized		Crude odds [95%CI]	Odds _{adj} [95%CI]
	No	Yes		
<i>Family history of allergy and current allergic symptoms</i>	n = 1146 (100%)	n = 384 (100%)		
Negative history & no symptoms	371 (32.4%)	63 (16.4%)	1	1
Positive history & no symptoms	403 (35.2%)	77 (20.1%)	1.1 [0.8–1.6]	1.5 [1–2.4]
Negative history & symptoms	109 (9.5%)	60 (15.6%)	3.2 [2.1–4.9]	3.6 [2.0–6.4]
Positive history & symptoms	263 (22.9%)	184 (47.9%)	4.1 [3.0–5.7]	3.9 [2.5–6.2]
<i>Family history of allergy and current wheezing</i>	n = 1170 (100%)	n = 384 (100%)		
Negative history & no symptoms	486 (41.5%)	114 (29.7%)	1	1
Positive history & no symptoms	631 (53.9%)	214 (55.7%)	1.4 [1.1–1.9]	1.6 [1.2–2.2]
Negative history & symptoms	8 (0.7%)	10 (2.6%)	5.3 [2.1–13.8]	8.0 [2.5–25.9]
Positive history & symptoms	45 (3.8%)	46 (12.0%)	4.4 [2.8–6.9]	4.3 [2.3–8.0]
<i>Family history of allergy and airway hyperreactivity</i>	n = 1168 (100%)	n = 388 (100%)		
Negative history & no symptoms	456 (39.0%)	99 (25.5%)	1	1
Positive history & no symptoms	571 (48.9%)	202 (52.1%)	1.6 [1.2–2.1]	1.8 [1.3–2.6]
Negative history & symptoms	40 (3.4%)	26 (6.7%)	3.0 [1.7–5.1]	2.6 [1.2–5.5]
Positive history & symptoms	101 (8.6%)	61 (15.7%)	2.8 [1.9–4.1]	2.5 [1.4–4.3]
<i>Family history of allergy and rhinitis</i>	n = 1168 (100%)	n = 382 (100%)		
Negative history & no symptoms	442 (37.8%)	81 (21.2%)	1	1
Positive history & no symptoms	553 (47.3%)	142 (37.2%)	1.4 [1.0–1.9]	1.6 [1.1–2.3]
Negative history & rhinitis	48 (4.1%)	43 (11.3%)	4.9 [3.0–7.9]	4.8 [2.6–9.0]
Positive history & rhinitis	125 (10.7%)	116 (30.4%)	5.1 [3.6–7.2]	5.3 [3.3–8.5]
<i>Family history of allergy and conjunctivitis</i>	n = 1169 (100%)	n = 383 (100%)		
Negative history & no symptoms	483 (41.3%)	99 (25.8%)	1	1
Positive history & no symptoms	627 (53.6%)	175 (45.7%)	1.4 [1.0–1.8]	1.4 [0.9–2.0]
Negative history & conjunctivitis	9 (0.8%)	26 (6.8%)	14.1 [6.4–31.0]	17.7 [5.5–56.7]
Positive history & conjunctivitis	50 (4.3%)	83 (21.7%)	8.1 [5.4–12.2]	7.9 [4.4–14.2]
<i>Family history of allergy and current eczema</i>	n = 1174 (100%)	n = 386 (100%)		
Negative history & no symptoms	463 (39.4%)	112 (29.0%)	1	1
Positive history & no symptoms	596 (50.8%)	206 (53.4%)	1.4 [1.1–1.9]	1.5 [1.1–2.1]
Negative history & symptoms	32 (2.7%)	9 (2.3%)	1.2 [0.5–2.5]	1.5 [0.6–3.7]
Positive history & symptoms	83 (7.1%)	59 (15.3%)	2.9 [2.0–4.4]	2.9 [1.7–4.8]

Crude OR, crude odds ratio; OR_{adj}, adjusted odds ratio; 95% CI, 95% confidence interval.

Odds ratio adjusted for all factors that changed the crude OR with more than 5% for the specific research item (checked factors: age, gender, passive smoke exposure, housing conditions now and at birth, maternal smoking during pregnancy, prematurity, breastfeeding, day care attendance, domestic pets at present and at birth, number of siblings, and birth order).

Statistically significant results ($p < 0.05$) are represented in bold.

children older than 6 yr to examine the characteristics of the different childhood wheezing phenotypes. Our prevalences of persistent and late-onset wheezers are consistent with the Italian data reported by De Sario et al. (18) and Rusconi et al. (31). Our lower prevalence of early transient wheezers may be due to recall bias due to the larger age range of our included children. Our data, as well as the data reported by De Sario et al. (18) and Rusconi et al. (31) show a lower percentage of wheezers in comparison with the data of Martinez et al., probably due to a different study approach, a different geographical area and different environmental and genetic factors.

Compared with non-wheezers and transient early wheezers, the persistent and late-onset wheezing types were more associated with atopy and the presence of concomitant allergic symp-

toms (rhinitis, conjunctivitis, and eczema). Transient early wheezing was significantly associated with day-care attendance, suggesting an important role of viral induced upper and lower respiratory tract infections in early childhood (32). Only the late-onset wheezers showed a significant association with a positive family history of allergy. These results are in line with the data from literature, demonstrating that distinct wheeze phenotypes have different clinical characteristics and risk factors in terms of respiratory health and atopic status (18, 33, 34). An association with eczema was found for all three childhood wheezing phenotypes and is consistent with the findings of Rusconi et al. (31).

No other risk factors (gender, passive smoke exposure, maternal smoking during pregnancy, pre-maturity, breastfeeding, housing conditions,

Table 5. Characteristics of early transient, persistent, and late-onset wheezers in the children older than 6 yr

	Overall sensitization				Day-care attendance			
	No n = 1098 (100%)	Yes n = 352 (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]	No n = 877 (100%)	Yes n = 539 (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]
Total (n = 1450)								
No wheezing (n = 1298)	1008 (91.8%)	290 (82.4%)	1	1	799 (91.1%)	468 (86.8%)	1	1
Transient early (n = 67)	54 (4.9%)	13 (3.7%)	0.9 [0.5–1.6]	0.7 [0.3–1.5]	26 (3.0%)	39 (7.2%)	2.6 [1.5–4.3]	3.5 [1.7–7.2]
Persistent (n = 38)	20 (1.8%)	18 (5.1%)	3.1 [1.6–6.0]	2.6 [1.1–6.1]	19 (2.2%)	19 (3.5%)	1.7 [0.9–3.3]	2.2 [0.9–5.3]
Late-onset (n = 47)	16 (1.5%)	31 (8.8%)	6.7 [3.6–12.5]	14.9[4.1–53.6]	33 (3.8%)	13 (2.4%)	0.9 [0.6–1.3]	0.8 [0.4–1.4]
	Rhinitis				Conjunctivitis			
	No (n = 116) (100%)	Yes (n = 261) (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]	No (n = 1289) (100%)	Yes (n = 141) (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]
No wheezing	1080 (92.6%)	198 (75.9%)	1	1	1177 (91.3%)	103 (73.0%)	1	1
Transient early	51 (4.4%)	16 (6.1%)	1.7 [1.0–3.1]	2.6 [1.2–5.5]	61 (4.7%)	6 (4.3%)	1.1 [0.5–2.7]	1.0 [0.3–3.2]
Persistent	17 (1.5%)	20 (7.7%)	6.4 [3.3–12.5]	7.2 [2.9–17.9]	24 (1.9%)	13 (9.2%)	6.2 [3.1–12.5]	5.5 [1.9–15.4]
Late-onset	18 (1.5%)	27 (10.3%)	8.2 [4.4–15.1]	8.8 [3.3–23.7]	27 (2.1%)	19 (13.5%)	8.0 [4.3–15.0]	10.1 [3.5–28.9]
	Eczema				Positive family history of allergy			
	No (n = 1130) (100%)	Yes (n = 307) (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]	No (n = 484) (100%)	Yes (n = 662) (100%)	Crude odds [95%CI]	Odds _{adj} [95%CI]
No wheezing	1040 (92.0%)	247 (80.5%)	1	1	449 (92.8%)	570 (86.1%)	1	1
Transient early	41 (3.6%)	25 (8.1%)	2.6 [1.5–4.3]	2.5 [1.2–5.1]	23 (4.8%)	35 (5.3%)	1.2 [0.7–2.1]	1 [0.5–1.8]
Persistent	24 (2.1%)	14 (4.6%)	2.5 [1.3–4.8]	2.9 [1.2–7.1]	7 (1.4%)	25 (3.8%)	2.8 [1.2–6.6]	2.4 [0.9–6.3]
Late-onset	25 (2.2%)	21 (6.8%)	3.2 [2.1–4.7]	3.4 [1.9–6.3]	5 (1.0%)	32 (4.8%)	3.1 [1.8–5.2]	3.4 [1.8–6.4]

Crude OR, crude odds ratio; OR_{adj}, adjusted odds ratio; 95% CI, 95% confidence interval.

Odds ratio adjusted for all factors that changed the crude OR with more than 5% for the specific research item (checked factors: age, gender, passive smoke exposure, housing conditions now and at birth, maternal smoking during pregnancy, prematurity, breastfeeding, day care attendance, domestic pets at present and at birth, number of siblings, and chronological position of the child in the family).

Statistically significant results ($p < 0.05$) are represented in bold.

and domestic pets at present and at birth, number of siblings, and chronological position of the child in the family) were associated with any of the wheezing phenotypes.

As for all observational research, our data need to be interpreted with caution.

First of all, this is a cross-sectional study implicating that we measured risk factors and outcome (allergic symptoms and sensitization) at the same time. This implicates that we cannot disentangle the chronological order of exposure and manifestation of allergic sensitization.

In addition information on risk factors, the presence of allergic symptoms and the family history of allergy was retrieved from the completed parental questionnaires and no clinical examination or pulmonary lung function tests were done. This method can not rule out the danger of a recall bias by the parents. One could well imagine that recall of symptoms in children from families with positive family history of allergy is higher compared to recall of symptoms in children from families without positive family history of allergy. Other epidemiological studies

however, collected their data in a comparable way. Children were only eligible to participate in the study if parents consented to perform skin prick tests and completed the questionnaire. One could imagine that selection bias might have occurred as parents of children with a positive family history of allergy will be more willing to consent. However, selection bias is probably not substantial in this study as our prevalence rates on sensitization are in line with other published data (2, 35) and our response rate was rather high (75%).

In conclusion, the association of allergic symptoms with sensitization to inhalant allergens is significant in the older but less pronounced in pre-school children and is more pronounced for current allergic symptoms than for symptoms in the past. Diagnosis and disease definition of allergy symptoms remains difficult at pre-school age. The influence of a positive family history of allergy on the association of the respective allergic symptoms with sensitization was most important for eczema. Our data confirm the atopic characteristics of the different wheeze phenotypes.

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