Wheezing in childhood:
Incidence, longitudinal patterns and factors predicting persistence

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Abstract

Background  Childhood asthma is frequently perceived as a disease with uniform clinical pathways. This perception might be an oversimplification.

Objective  To investigate the incidence and natural course of wheeze over the first 13 years of life and analyse the risk factors predicting wheeze at 11 to 13 years of age.

Methods  The Multi-centre Allergy Study (MAS), a German birth cohort, recruited 1314 children in 1990. Physical examinations, interviews on atopic diseases, IgE and lung function tests were performed up to 13 years of age.

Results  Complete data on the course of wheeze was available for 441 children. Incidence of wheezing declined with age. The first wheezing episode was reported by 29%, 9% and 9% of participants at ≤3 (early wheezers), 3-6 (late wheezers), and >6 (very late wheezers) years of age, respectively. Wheezing at the age of 13 was associated with parental atopy, and with IgE sensitisation to common allergens, elevated total IgE and exposure to high levels of indoor allergens in early life. All these associations were remarkably stronger among early wheezers than among early non-wheezers.

Conclusion  The relevance of an early expression of atopy as a predictor of wheezing at age 13 years declines with increasing age at wheezing onset.

Author Keywords: wheezing; asthma; atopic dermatitis; IgE; children; epidemiology; prediction of persistence
Introduction

Asthma and other wheezing disorders are among the most common childhood diseases.[1] Understanding of the genetic, environmental and developmental factors of childhood asthma is essential to develop tools to predict and, hopefully, prevent recurrence of wheezing episodes and subsequent deficits in airway function growth.[2,3] Algorithms to predict asthma in wheezing children have been developed on the basis of observational longitudinal studies [4-7], with the most popular algorithm targeted to predict asthma in children who start wheezing before 3 years of age.[4] However, many children start wheezing only after age 3; if atopy and other risk factors for asthma in these children are different from those predicting asthma among early wheezers, then additional algorithms should be formulated. The airways of children with early wheezing may be more susceptible to the negative consequences of an early sensitization and exposure to allergens. We therefore hypothesized that atopy and other risk factors may have a different impact on the natural history of wheezing disorders in children according to their propensity to wheeze. To test this hypothesis, we analysed the data from the German Multi-centre Allergy Study (MAS), a prospective observational birth cohort study followed up to 13 years of age.[8] On the basis of our findings, we provide here first a description of the natural course of wheezing up to 13 years of life in the MAS cohort and then a comparative analysis of the risk factors predicting wheeze at age 11 to 13 years in children both wheezing and not wheezing in the first three years of life.

Methods

Study population

The German Multi-centre Atopy Study (MAS), a prospective observational birth cohort study, recruited 1314 infants born in 1990 in 6 German obstetric departments in 5 German cities. A detailed description of the stratified sampling scheme and study subjects is given elsewhere.[8] Briefly, 499 newborns with presumed risk factors for atopy (increased cord blood IgE \( \geq 0.9 \text{ kU/L} \), at least 2 atopic family members, or both) and 815 newborns with none of these risk factors were included in the cohort. All children were followed-up at ages 1, 3, 6, 12, 18, and 24 months and from then on yearly within 4 weeks of the child's birthday up to the age of 13 years. The study was approved by the hospital’s ethics committee. Each child's parents gave written informed consent at the time of enrolment.
Parental questionnaires and interviews

At each follow-up visit, parents gave structured interviews to a study physician or completed postal questionnaires (at age 8, 9, 11, and 12 years). The main topics of these interviews were asthmatic and atopic symptoms and disease; questions on diet, development, and psychological aspects were also included. From age 5 years onwards, questions relating to wheeze corresponded to the International Study of Asthma and Allergies in Childhood (ISAAC) core questions.[9] Foremost interest was in atopic symptoms and diseases. Furthermore, symptoms and diagnoses of other illnesses were assessed at every follow-up, as was maternal breast-feeding and feeding practices up to age 2 years. Parental smoking habits were assessed at age 1 month, and pet keeping was assessed at age 3 months. Furthermore, the use of medication was assessed at every follow-up. Children regularly visited a physician independent of the study team.

Definitions

Wheeze was defined as any parent-reported wheezing in the past 12 months at any of the follow-ups. We used the definition “early wheezers” and “late wheezers” to describe the children starting wheezing before 3 years of age and between 3 and 6 years of age [10]. Children who started wheezing only after 6 years of age were defined as “very late wheezers”. Early wheezers were further classified on the basis of the recurrence of wheezing between 4 and 13 years of age: they were defined “early persistent wheezers” if they continued to wheeze every year up to the age of 13y, “early intermittent wheezers”, if they wheezed in some years but not in others between 3y and 13y of age; or “early remittent wheezers” if they did not wheeze anymore from 3y up to the age of 13y. For the purposes of the univariate and multivariate analyses children not wheezing before the age of 3 years were defined “early non-wheezers”. Parental atopy was defined as any reporting of asthma, hay fever, or AD ever. Early AD was defined as present if the parents reported at least one of the following, applied up to the age of 2 years: (1) reported diagnosis by the family physician, (2) parental reporting of symptoms of AD, and (3) visible AD at the time of follow-up. In order to exclude very mild cases of AD, only children with parental reports of self-scratching were included in the definition of AD.[11]. Lower respiratory tract infections in the first 3 years of life were defined on the basis of parental reports of symptoms and diagnoses.[12]

Cord blood, total, and specific IgE
Serum samples were obtained from the children at birth and at 1, 2, 3, 5, 6, 7, and 10 years of age. Cord blood IgE, total IgE, and specific IgE antibodies to food allergens (cow's milk, egg white, soy bean, and wheat) and inhalant allergens (house dust mite [*Dermatophagoides pteronyssinus*], cat dander, mixed grass, and birch pollen) were determined by using the ImmunoCAP (Phadia, Freiburg, Germany). Sensitisation to a specific allergen was defined as a concentration of 0.70 kU/L or greater of the respective specific IgE (ImmunoCAP class 2). This cut-off was chosen to constitute a stronger atopic effect than would have been by merely choosing evidence of any detectable specific IgE, i.e. ImmunoCAP class 1. Increased cord blood IgE was defined as a concentration of 0.9 kU/L or greater, and increased total IgE at age 3 years was defined as a concentration of 30.0 kU/L or greater. This cut-off was based on the upper standard deviation limit of an equivalent-aged normal infant population. [13]

**Assessment of indoor allergen exposure**

At the ages of 6 and 18 months and 3, 4, and 5 years, Der p 1, Der f 1, and Fel d 1 allergens were extracted from dust samples collected by parents from the carpet and analysed with a sandwich ELISA (ALK, Copenhagen, Denmark).[14,15] High level of exposure to a specific allergen at a specific age was defined as a measured value above the third quartile of the respective distribution in the total population.

**Statistical analysis**

Chi-squared tests were used to compare prevalence between groups and Mantel-Haenszel tests were used for analysing trends over categories. Generalised estimation equation (GEE) models were used in order to adjust for repeated measures in the analysis of the effect of early childhood factors on wheezing at age 11, 12 and 13 years. Results are presented as odds ratios and 95% confidence intervals (CI). All factors significant in univariate analysis were included in a stepwise procedure to elicit a final model. In order to take the stratified sampling scheme and a possible participation bias into account all multivariate models were adjusted for parental atopy. Furthermore, sensitivity, specificity and positive/negative predictive values of various early life factors were calculated for the outcome of wheezing at the age of 11, 12, or 13 years. SAS software (version 9.1) was used for statistical analyses. For analyses on the incidence and natural course of wheeze over time all children with complete data on wheeze up to the respective time point of analysis were included in the analyses. For all other analyses, all children with data on early wheeze were included.
Results

Study population and response rates
Of the 1314 enrolled children, 441 (33.6%) had information on wheeze for every year of the follow-up until age 13 years (Figure 1). For 391 (88.7%) of these children data on specific IgE in the first three years of life was available. To assess potential participation bias the study population of 441 children was compared to children with incomplete data on the course of wheeze based on data collected at birth (Table 1). No significant differences were found with respect to parental history of atopy, gender, cord-blood IgE, older siblings, or parental education. However, children in the study population were more likely to have non-smoking parents (p<0.001). Furthermore, the study population of 441 children was compared to children with complete data up to the age of 3 years and incomplete data thereafter, based on data collected in the first years of life. No significant differences were found with respect to early atopic dermatitis, early wheeze and early atopic sensitisation. However, children in the study population were more likely to be breastfed for at least 4 weeks (p=0.020). A detailed description of the population sample is reported elsewhere.[16]

Incidence of first wheezing episode from birth to 13 years of age
Almost 1 out of 5 (80/441, 18%) children wheezed in the first year of life. The incidence of new wheeze sharply declined in the second (33/361, 9%) and third year of life (13/328, 4%). Overall 126/441 (29%) of the children in the MAS cohort started wheezing in their first three years of life (“early wheezers”). The incidence of new wheezing disorders was stable thereafter up to 7 years of age at around 4% (range 3.5-5.0%). Then the incidence further declined to <1% at 10-12 years and abruptly rose again at 13 years of age to about 4% (Figure 2). Overall, 40/441 (9%) of the population sample started wheezing between 3 and 6 years of age (“late wheezers”) and another 42/441 (9%) started wheezing after 6 years of age (“very late wheezers”) (Figure 1).

The natural course of wheezing
We distinguished six different longitudinal patterns of wheezing in the population sample (Figure 1). Among early wheezers, remission of symptoms after early childhood was very high, as 79/126 (63%) did not wheeze anymore after the age of 3, (“early remittent wheezers”); 43/126 (34%) continued to wheeze after the age of 3 but not every year (“early intermittent wheezers”); only 4/126 (3%) of the early wheezers kept on wheezing every single
year from birth up to age 13 years. Among children who never wheezed before the age of 3, 233/315 (74\%) also did not wheeze up to the age of 13 (“never wheezers”); 40/315 (13\%) started wheezing between the age of 3 and the age of 6 (“late wheezers”); 42/315 (13\%) started wheezing after the age of 6 (“very late wheezers”) (Figure 1). Overall, the prevalence of children wheezing at age 11, 12, or 13 years was 22\% (28/126) among early wheezers and only 10\% (31/315) among early non-wheezers. Among these 59 children wheezing at age 11-13, 28 (47\%) of them were early wheezers, 6 (10\%) were late wheezers and 25 (42\%) were very late wheezers.

We analysed the frequency of an atopic family background, early sensitization and current sensitization in relation to the six different longitudinal patterns of wheezing (table 2). The prevalence of atopy at 3 years of age was very low among never wheezers (12\%), low among early remittent wheezers and very late wheezers (both 19\%), intermediate among late and early intermittent wheezers (32 and 36\%, respectively) and high among early persistent wheezers (75\%). The prevalence of atopy at 10 years of age was low among never and early remittent wheezers (27\% and 30\%, respectively), intermediate among late and very late wheezers (45\% and 53\%, respectively) and maximal among early intermittent and early persistent wheezers (69\% and 75\%, respectively). Interestingly, among very late onset wheezers, the prevalence of early sensitisation is relatively low (18.7\%), whereas sensitisation at age 10 years is moderately high (53.1\%) (Table 2).

**Different patterns of risk factors for wheezing at the age of 13 years**
We examined the association of early atopic sensitization (and related risk factors) with wheezing at 11-13 years of age in children wheezing or not wheezing before three years of age (table 3). In the MAS cohort, cat/mite exposure and sensitisation are strongly linked [16] and their concurrence contributes to a reduced lung function at school age [17]; therefore we accounted for their interaction in the multivariate analysis. In the univariate analysis, the spectrum of early-life risk factors associated with wheezing at the age of 13 years was remarkably broader in early wheezers than in early non-wheezers: indeed, among early wheezers, wheezing at puberty was associated with parental asthma, hay fever and atopic dermatitis, allergic sensitisation against food or airborne allergens, elevated total IgE and early atopic dermatitis. Among early non-wheezers, by contrast, wheezing at puberty was associated significantly only with parental hay fever and asthma, sensitisation to indoor allergens, and early atopic dermatitis. In addition, the strength of the associations observed and their statistical significance was much stronger among early wheezers than among early
non-wheezers. This trend was maintained in the multivariate analyses: perennial sensitisation to indoor (mites, cat, dog) allergens persisted as a very strong predictor of wheezing at age 11 to 13 years among early wheezers, but no longer showed a significant association among early non-wheezers; the association of wheezing at age 11 to 13 years with parental atopy was three times stronger among early wheezers (adjusted OR 8.32, 2.74-25.20) than among early non-wheezers (aOR 2.48, 1.01-6.09). However, whereas atopic dermatitis early in life remained a significant predictor for wheezing at age 11 to 13 years among early non-wheezers, it was no longer significant in the group of children with early wheeze. In contrast, in the group of early wheezers, male gender emerged as a significant predictor for wheezing at age 11 to 13 years. All other analysed early life factors (i.e., cord blood IgE, sibs, breast feeding, parental smoking, parental education, early pets, early allergen exposure, early infections) did not show a significant association with wheezing at 11-13 years in both groups (data not shown).

In a model including the whole population, wheezing at 11 to 13 years of age was thus best described by the following factors in early life: early wheeze (aOR=1.87, 95%-CI 0.98-3.54, p=0.056) parental atopy (aOR=3.22, 95%-CI 1.54-6.72, p=0.002), early indoor (mites, cat, dog) sensitisation (aOR=4.04, 95%-CI 1.87-8.73, p=<0.001) and early AD (aOR=2.99, 95%-CI 1.52-5.88, p=0.002).

**Prediction of wheezing at 11 to 13 years of age**

Table 4 shows sensitivity, specificity, positive and negative predictive values of early-life factors for wheezing at 11 to 13 years of age. Best overall values for all prediction parameters were observed for early sensitisation to indoor (mites, cat, dog) allergens (PPV 57%). When early wheeze was a factor, prediction was even improved to some extent, with a positive predictive value of 75%. Thus, a child with sensitisation to indoor (mites, cat, dog) allergens as well as at least one episode of wheezing before the age of three years had a probability as high as 75% to still be wheezing at 13 years of age. The PPV increased to 83% when a child with early wheezing and early sensitization against indoor allergens was also exposed to high concentrations of indoor allergens in his/her first three years of life.

**Discussion**

In the present analysis of the German MAS cohort we found that the natural course of wheezing is highly heterogeneous. In the attempt to analyse and classify this heterogeneity,
we have described here six different longitudinal patterns of wheezing between birth and the age of 13 years. Our findings add further complexity to the previous classification, which was based on three longitudinal patterns (early, late and persistent wheezers) and covered only the period between birth and six years of age. We also found that the relative role of early atopic sensitization and of related risk factors for the long-term prognosis of wheezing change according to the age of wheezing onset. Taken together, our results support the concept that childhood asthma is more a syndrome, rather than a single, uniform disease.[18]

The incidence of wheezing was quite high in the first three years of life. However, the long-term prognosis of early wheezing was in most cases excellent. The vast majority of “early wheezers” either wheezed no more after the age of 3 years (“early remittent wheezers”) or only in some years (“early intermittent wheezers”) up to the age of 13 years. Only a very small fraction of early wheezers kept on wheezing every single year up to the age of 13 (“early persistent wheezers”) (figure 1). The major question here was “How to identify at 3 years of age, among early wheezers, those at risk for long-term, persistent wheezing?” In keeping with outcomes from previous birth cohort studies [4-7], we found that a strong predisposition to atopy (a positive family history, early IgE sensitisation) is the strongest factor predicting whether children wheezing early in life will keep on wheezing up to puberty (tables 3 and 4). We had previously shown that lung function at 7 years of age is compromised in children with early wheezing combined with early atopic sensitization.[19]

The long-term natural course of wheezing was highly heterogeneous also among children who did not wheeze in the first 3 years of life. Most of them remained free from wheeze up to the age of 13 years, while a minority started wheezing between the age of 3 and 6 (“late wheezers”) or after the age of 6 (“very late wheezers”). Here again, the question was “How to identify at 3 years of age, among early non-wheezees, those who will start wheezing later up to the age of 13 years?” The spectrum of early life, atopy-related risk factors associated with wheezing at puberty was remarkably smaller both qualitatively and quantitatively in early non-wheezees, compared to early wheezees (Table 3). In a consistent proportion of children, both atopy and wheeze started after 3 or after 6 years of age. In particular, among very late onset wheezers, the prevalence of sensitisation at 10 years of age was 3 times higher than in the first 3 years of life, suggesting that this wheezing pattern is associated with later development of sensitisation. This trend is likely to be maintained at older ages, as new atopic
sensitisation acquired at school age is also a significant independent predictor of unremitting asthma after puberty.[20,21]

By testing just a couple of parameters (sensitisation to indoor allergens: mites, cat, dog; high exposure to the same allergens), at three years of age we could identify a subset of wheezing children with an extremely high probability of wheezing up to age 13 (table 4). In the Tucson cohort study, wheeze by three years of age was also used to predict outcomes at 13 years [4]. We used most of the “loose” criteria of that algorithm (i.e. wheeze at any stage in the first 3 years plus other factors)[4] but found comparable sensitivities, specificities and negative predictive values to the “stringent” criteria of the same algorithm [4], and even more favourable positive predictive values (table 4). The additional inclusion in our algorithm of allergen exposure may have contributed to this outcome. The age-dependent variation of risk factors for wheezing at age 11-13 suggests that multiple, distinct algorithms are required to predict persistence of wheezing starting at different ages. This is also in line with other studies suggesting that we should aim at phenotype-specific strategies to predict and prevent asthma in children. [22,23]

We have to acknowledge some limitations of our study. First, the population study is enriched with infants at high risk for atopy, so the results may not be relevant to the general population. Losses in follow-up may have further limited a general value of our conclusions. Unfortunately, objective evaluation of viral infections on swabs was not available in the MAS. Others have found direct evidence of RSV and rhinovirus infection in infancy to be associated with persistence of asthma in teenagers [24,25].

Recent trials have provided evidence that prolonged anti-inflammatory treatment has an impact on infant wheeze but not on its natural history.[26-27] Generalized, aggressive intervention for secondary and tertiary prevention of wheezing cannot therefore be suggested on the basis of our findings. However, we observed that a small subset of children with early wheezing, early sensitization and high exposure to indoor allergens, showed a very high PPV+ (83.3%) for wheezing at the age of 11-13 years. More studies are necessary to ascertain whether this small, peculiar subset of early wheezers might benefit from preventive strategies yet to be identified.
In conclusion, our data support the concept that the natural course of wheezing disorders in childhood is quite heterogeneous and that prediction of long-term outcomes may take advantage not only of early diagnosis but also of algorithms based on the age of wheezing onset.

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References


Legend to figures

Fig. 1
Response rates, drop-out and longitudinal pattern of wheezing in the MAS cohort.

Fig. 2
Incidence of wheezing up to the age of 13 in the MAS cohort.
Fig. 1

Children enrolled in MAS birth cohort
N=1,314

Participation in each follow-up up to 13 years of age
441/1314 (33.6%),
of these 391/441 (88.7%) with IgE testing ≤3 years
and 345/441 (78.2%) with IgE testing at 10 years

"Early wheezers"
(Wheezing in the first 3 years of life)
126/441 (28.6%)

"Early remittent wheezers"
(No wheeze 4-13 years)
79/126 (62.7%)

"Early intermittent wheezers"
(Wheezing only in some but not every year up to the age of 13y)
43/126 (34.1%)

"Early persistant wheezers"
(Wheezing every year up to age 13y)
4/126 (3.2%)

"Early non-wheezers"
(non wheezing in the first 3 years of life)
315/441 (71.4%)

"Never wheezers"
(No wheezing up to age 13y)
233/315 (74.0%)

"Late wheezers"
(Starting wheezing between 3 and 6 years of age)
40/315 (12.7%)

"Very late wheezers"
(Starting wheezing after the age of 6)
42/315 (13.3%)
Fig. 2

![Bar chart showing incidence in percentage for different age groups. The x-axis represents age in years, ranging from 1 to 13. The y-axis represents incidence in percentage, ranging from 0 to 20. The chart indicates that the highest incidence is at age 1, followed by age 2, with a significant drop after age 7.](image-url)
Table 1 – Characteristics at birth and in the first years of life in children with complete data on the course of wheeze from birth to age 13yrs (study population, N=441) compared to children with incomplete data on the course of wheeze.

<table>
<thead>
<tr>
<th>Data collected at birth:</th>
<th>Children with complete data on the course of wheeze from birth to age 13yrs (study population)</th>
<th>Children with incomplete data on the course of wheeze from birth to age 13yrs</th>
<th>Children with complete data on the course of wheeze up to age 3 years, but with incomplete data on the course thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=441</td>
<td>N=873</td>
<td>N=515</td>
</tr>
<tr>
<td>Parental history of atopy</td>
<td>240 / 440 (54.5%)</td>
<td>443 / 867 (51.1%)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>234 / 441 (53.1%)</td>
<td>450 / 873 (51.5%)</td>
<td></td>
</tr>
<tr>
<td>Elevated cord-blood IgE (≥0.9 kU/l)</td>
<td>75 / 421 (17.8%)</td>
<td>166 / 840 (19.8%)</td>
<td></td>
</tr>
<tr>
<td>≥1 older siblings</td>
<td>194 / 441 (44.9%)</td>
<td>399 / 872 (45.8%)</td>
<td></td>
</tr>
<tr>
<td>Parental smoking</td>
<td>161 / 403 (39.9%)</td>
<td>411 / 787 (52.2%)**</td>
<td></td>
</tr>
<tr>
<td>Higher level of parental education</td>
<td>240 / 422 (56.9%)</td>
<td>423 / 807 (52.4%)</td>
<td></td>
</tr>
<tr>
<td>Data collected in the first years of life:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early AD ≤2yrs</td>
<td>108 / 441 (24.5%)</td>
<td></td>
<td>104 / 515 (20.2%)</td>
</tr>
<tr>
<td>Early wheeze ≤3 yrs</td>
<td>126 / 441 (28.6%)</td>
<td></td>
<td>173 / 515 (33.6%)</td>
</tr>
<tr>
<td>Atopic sensitization age 2 yrs (CAP I)</td>
<td>67 / 283 (23.7%)</td>
<td></td>
<td>87 / 318 (27.4%)</td>
</tr>
<tr>
<td>Breastfed ≥4 wks</td>
<td>347 / 439 (79.0%)</td>
<td></td>
<td>370 / 510 (72.5%) *</td>
</tr>
</tbody>
</table>

* p<0.05 compared to children with complete data on the course of wheeze up to age 13yrs

** p<0.001 compared to children with complete data on the course of wheeze up to age 13yrs
Table 2 – Parental atopy, gender and atopy in children with different longitudinal patterns of wheezing from birth to age 13y

<table>
<thead>
<tr>
<th></th>
<th>Parental atopy</th>
<th>Male gender</th>
<th>Atopy ≤ 3 yrs</th>
<th>Atopy 10 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
</tr>
<tr>
<td>Early wheezers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>126</td>
<td>77/125</td>
<td>61.6</td>
<td>74/126</td>
</tr>
<tr>
<td>remittent</td>
<td>79</td>
<td>41/78</td>
<td>52.6</td>
<td>48/79</td>
</tr>
<tr>
<td>intermittent</td>
<td>43</td>
<td>32/43</td>
<td>74.4</td>
<td>23/43</td>
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<td>persistant</td>
<td>4</td>
<td>4/4</td>
<td>100.0</td>
<td>3/4</td>
</tr>
<tr>
<td>Late wheezers</td>
<td>40</td>
<td>24/40</td>
<td>60.0</td>
<td>23/40</td>
</tr>
<tr>
<td>Very late wheezers</td>
<td>42</td>
<td>28/42</td>
<td>66.7</td>
<td>19/42</td>
</tr>
<tr>
<td>Never wheezers</td>
<td>233</td>
<td>111/233</td>
<td>47.6</td>
<td>118/233</td>
</tr>
</tbody>
</table>
Table 3 – Risk factors for wheezing at age 11 to 13 yrs by age at onset: results of unadjusted and adjusted* GEE.

<table>
<thead>
<tr>
<th></th>
<th>Children with no wheeze before age 3 yrs</th>
<th></th>
<th>Children with wheeze before age 3 yrs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%-CI) p aOR* (95%-CI) p</td>
<td>OR (95%-CI) p aOR* (95%-CI) p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>0.88 (0.40-1.97) 0.764</td>
<td>2.24 (0.91-5.47) 0.078</td>
<td>2.80 (1.08-7.28) 0.034</td>
<td></td>
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<tr>
<td>Any parental atopy</td>
<td>2.72 (1.12-6.61) 0.027 2.48 (1.01-6.09) 0.047$</td>
<td>8.99 (3.03-26.70) &lt;0.001</td>
<td>8.32 (2.74-25.20) &lt;0.001$</td>
<td></td>
</tr>
<tr>
<td>Parental asthma</td>
<td>2.42 (1.00-5.85) 0.050</td>
<td>2.50 (1.05-5.94) 0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental hay fever</td>
<td>2.67 (1.16-6.14) 0.021</td>
<td>4.09 (1.58-10.56) 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental atopic dermatitis</td>
<td>0.81 (0.17-3.93) 0.792</td>
<td>2.68 (0.96-7.45) 0.059</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any sensitisation (≤3yrs)</td>
<td>2.48 (0.95-6.44) 0.063</td>
<td>4.70 (1.93-11.42) &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food sensitisation (≤3yrs)</td>
<td>1.57 (0.45-5.49) 0.484</td>
<td>2.82 (1.08-7.33) 0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perennial sensitisation (≤3yrs)</td>
<td>4.86 (1.23-19.25) 0.024</td>
<td>7.44 (2.82-19.60) &lt;0.001</td>
<td>6.23 (2.41-16.09) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Seasonal sensitisation (≤3yrs)</td>
<td>3.31 (0.91-12.01) 0.069</td>
<td>3.00 (1.07-8.41) 0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated total IgE (3yrs)</td>
<td>0.76 (0.27-2.17) 0.610</td>
<td>2.94 (1.03-8.41) 0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early AD (≤2yrs)</td>
<td>3.71 (1.51-9.13) 0.004 3.35 (1.34-8.33) 0.009</td>
<td>3.19 (1.32-7.71) 0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High allergen exposure$ ≤(3yrs)</td>
<td>0.47 (0.21-1.05) 0.065</td>
<td>1.88 (0.75-4.69) 0.176</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interaction of sensitisation / exposure$ ≤(3yrs):

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No sensitisation to cat/mite</td>
<td>- $</td>
<td>-</td>
<td>-</td>
<td>$</td>
</tr>
<tr>
<td>Sensitisation to cat/mite + low allergen exposure</td>
<td>- $</td>
<td>-</td>
<td>6.22 (2.02-19.18) 0.001</td>
<td></td>
</tr>
<tr>
<td>Sensitisation to cat/mite + high allergen exposure</td>
<td>- $</td>
<td>-</td>
<td>9.70 (2.73-34.55) &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Mutually adjusted for each of the listed factors.
$§ Mutually adjusted as potential confounder.
† Exposure to cat or mite allergen ≤3yrs in the upper quartile of the respective distribution in the total MAS population.
‡ Sensitisation to cat or mite ≤3yrs and/or concurrent exposure to the respective allergen in the upper quartile of the distribution in the total MAS population.
$ No results due to zero cell: 0/3 children with no early wheeze, with sensitisation to cat or mite and with low concurrent exposure to the respective allergen had any wheezing episode in puberty.

The following factors were not significantly associated with wheezing at puberty in the univariate analysis: cord blood IgE, siblings, breast feeding, parental smoking, parental education, early exposure to pets, early infections.

The model for the total population resulted in the following mutually adjusted odds ratios: early wheeze (≤3yrs) aOR=1.87 (0.98-3.54), p=0.056; parental atopy aOR=3.22 (1.54-6.72), p=0.002; early perennial sensitisation (≤3yrs, CAP II) aOR=4.04 (1.87-8.73), p=<0.001; and early AD (≤2yrs) aOR=2.99 (1.52-5.88), p=0.002.
Table 4 – Predictive value of early-life factors to predict wheezing at age 11 to 13 yrs.

<table>
<thead>
<tr>
<th>Early life factors</th>
<th>SP  (%)</th>
<th>SE (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Combination with early wheeze (≤3yrs)</th>
<th>SP  (%)</th>
<th>SE (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze (≤3yrs)</td>
<td>74.3</td>
<td>47.5</td>
<td>22.2</td>
<td>90.2</td>
<td>Wheeze + male gender</td>
<td>85.6</td>
<td>32.2</td>
<td>25.7</td>
<td>89.1</td>
</tr>
<tr>
<td>Male gender</td>
<td>47.4</td>
<td>55.9</td>
<td>14.1</td>
<td>87.4</td>
<td>Wheeze + parental atopy</td>
<td>86.1</td>
<td>40.7</td>
<td>31.2</td>
<td>90.4</td>
</tr>
<tr>
<td>Any parental atopy</td>
<td>49.3</td>
<td>79.7</td>
<td>19.6</td>
<td>94.0</td>
<td>Wheeze + parental asthma</td>
<td>92.9</td>
<td>20.3</td>
<td>30.8</td>
<td>88.3</td>
</tr>
<tr>
<td>Parental asthma</td>
<td>80.8</td>
<td>35.6</td>
<td>22.3</td>
<td>89.0</td>
<td>Wheeze + parental hay fever</td>
<td>89.2</td>
<td>33.9</td>
<td>32.8</td>
<td>89.7</td>
</tr>
<tr>
<td>Parental AD</td>
<td>90.5</td>
<td>15.2</td>
<td>20.0</td>
<td>87.3</td>
<td>Wheeze + parental AD</td>
<td>97.4</td>
<td>11.9</td>
<td>41.2</td>
<td>87.6</td>
</tr>
<tr>
<td>Any sensitisation (≤3yrs)</td>
<td>84.9</td>
<td>43.4</td>
<td>31.1</td>
<td>90.5</td>
<td>Wheeze + any sensitisation (≤3yrs)</td>
<td>95.3</td>
<td>28.3</td>
<td>48.4</td>
<td>89.4</td>
</tr>
<tr>
<td>Food sensitisation (≤3yrs)</td>
<td>89.7</td>
<td>23.6</td>
<td>27.1</td>
<td>87.9</td>
<td>Wheeze + food sensitisation (≤3yrs)</td>
<td>97.1</td>
<td>16.4</td>
<td>47.4</td>
<td>87.8</td>
</tr>
<tr>
<td>Any inhalant sensitisation (≤3yrs)</td>
<td>92.1</td>
<td>33.3</td>
<td>40.0</td>
<td>89.8</td>
<td>Wheeze + inhalant sensitisation (≤3yrs)</td>
<td>96.8</td>
<td>22.2</td>
<td>52.2</td>
<td>88.8</td>
</tr>
<tr>
<td>Perennial sensitisation (≤3yrs)</td>
<td>97.4</td>
<td>22.2</td>
<td>57.1</td>
<td>88.8</td>
<td>Wheeze + perennial sensitisation (≤3yrs)</td>
<td>99.1</td>
<td>16.7</td>
<td>75.0</td>
<td>88.3</td>
</tr>
<tr>
<td>Seasonal sensitisation (≤3yrs)</td>
<td>93.9</td>
<td>20.0</td>
<td>34.4</td>
<td>88.0</td>
<td>Wheeze + seasonal sensitisation (≤3yrs)</td>
<td>97.4</td>
<td>12.7</td>
<td>43.7</td>
<td>87.5</td>
</tr>
<tr>
<td>Elevated total IgE (3yrs)</td>
<td>59.8</td>
<td>45.9</td>
<td>15.0</td>
<td>87.7</td>
<td>Wheeze + elevated total IgE (3yrs)</td>
<td>89.5</td>
<td>27.0</td>
<td>28.6</td>
<td>88.8</td>
</tr>
<tr>
<td>Atopic dermatitis (≤2yrs)</td>
<td>86.9</td>
<td>35.6</td>
<td>29.6</td>
<td>89.7</td>
<td>Wheeze + early AD (≤2yrs)</td>
<td>95.5</td>
<td>20.3</td>
<td>41.4</td>
<td>88.6</td>
</tr>
<tr>
<td>Repeated LRIs (≤3yrs)</td>
<td>66.7</td>
<td>33.9</td>
<td>13.6</td>
<td>86.7</td>
<td>Wheeze + repeated LRIs (≤3yrs)</td>
<td>88.0</td>
<td>16.9</td>
<td>17.9</td>
<td>87.3</td>
</tr>
<tr>
<td>High allergen exposure (≤3yrs)</td>
<td>39.8</td>
<td>58.6</td>
<td>13.3</td>
<td>86.0</td>
<td>Wheeze + high allergen exposure (≤3yrs)</td>
<td>86.4</td>
<td>34.5</td>
<td>28.6</td>
<td>89.4</td>
</tr>
<tr>
<td>High allergen exposure + sensitisation (≤3yrs)</td>
<td>98.2</td>
<td>13.0</td>
<td>53.8</td>
<td>87.8</td>
<td>Wheeze + high allergen exposure + sensitisation (≤3yrs)</td>
<td>99.7</td>
<td>9.3</td>
<td>83.3</td>
<td>87.5</td>
</tr>
</tbody>
</table>

§ Exposure to cat or mite allergen ≤3yrs in the upper quartile of the respective distribution in the total MAS population

‡ Sensitisation to cat or mite ≤3yrs and concurrent exposure to the respective allergen in the upper quartile of the distribution in the total MAS population