

# Allergic rhinitis as a predictor for wheezing onset in school-aged children

Mascha K. Rochat, MD,<sup>a,\*</sup> Sabina Illi, PhD,<sup>a</sup> Markus J. Ege, MD,<sup>a</sup> Susanne Lau, MD,<sup>b</sup> Thomas Keil, MD, MSc,<sup>c</sup> Ulrich Wahn, MD,<sup>b</sup> Erika von Mutius, MD,<sup>a</sup> and the Multicentre Allergy Study (MAS) group\* Munich and Berlin, Germany

**Background:** Rhinitis in older children and adults has been shown to be a predictor for adolescent- and adult-onset asthma. These findings suggest an interaction between the upper and lower airways. Whether rhinitis is a predictor for childhood-onset asthma is unknown.

**Objective:** We sought to investigate whether rhinitis in early childhood is an independent predictor for wheezing between the ages of 5 and 13 years in the German Multicentre Allergy Study birth cohort.

**Methods:** The German Multicentre Allergy Study cohort initially included 1314 healthy children. They were followed from birth to the age of 13 years with regular questionnaires and interviews. Specific IgE levels were measured at yearly intervals. Airway hyperresponsiveness was assessed at 7 years.

**Results:** Allergic rhinitis until the age of 5 years was found to be a predictor for developing wheezing between the ages of 5 and 13 years, with an adjusted relative risk of 3.82 ( $P < .001$ ). This association was not attributable to the type of sensitization, the severity of sensitization, or atopic dermatitis during the first 2 years of life. In this group of children, 41.5% of all new cases of wheezing occurred among children with preceding allergic rhinitis.

**Conclusions:** The first manifestation of allergic rhinitis occurs in preschool children in whom it is a predictor for subsequent wheezing onset. Preschool children with rhinitis might thus benefit from early assessment of allergic sensitization to identify the children at high risk of wheezing. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

**Key words:** Allergic rhinitis, birth cohort study, wheezing, allergic sensitization, risk factors

## Abbreviations used

AHR: Airway hyperresponsiveness  
MAS: German Multicentre Allergy Study  
PARF: Population-attributable risk fraction  
RR: Relative risk

Rhinitis, even in the absence of atopy, has been shown to be a strong predictor for adult-onset asthma,<sup>1,2</sup> suggesting an interaction between the upper and lower airways. This link has been explored in a number of studies,<sup>3</sup> leading to the “united airways concept,”<sup>4</sup> which suggests that the respiratory system functions as an integrated unit. Support for this concept can be found in studies showing that pathophysiological processes involving the upper airways generally occur in conjunction with lower airway diseases and that diffuse inflammation often affects the respiratory mucosa at different sites simultaneously.<sup>5</sup>

Rhinitis until the age of 7 years has also been shown to be a strong predictor for adolescent- and adult-onset asthma.<sup>6</sup> It is, however, unknown whether rhinitis is associated with childhood-onset asthma. Childhood asthma is not one disease but rather a syndrome characterized by several distinct wheezing phenotypes.<sup>7-9</sup> The new onset of most wheezing phenotypes occurs in the first and second years of life,<sup>10</sup> too early for other symptoms to precede them. Yet other wheezing phenotypes begin after the age of 2 years or even later.<sup>10</sup>

These phenotypes are strongly associated with atopy and airway hyperresponsiveness (AHR) later in life.<sup>10,11</sup> Furthermore, pulmonary function abnormalities associated with persistent wheezing become established during early childhood and track to adult life.<sup>12,13</sup> The identification of a potential predictor for wheezing onset in early childhood, an age at which wheezing phenotypes might still be altered or progression to asthma halted,<sup>10,12</sup> might thus lead to new therapeutic strategies and possibly influence asthma morbidity.<sup>12</sup>

Therefore we investigated whether rhinitis in early childhood was an independent risk factor for childhood-onset wheezing in the German Multicentre Allergy Study (MAS) population-based birth cohort.

## METHODS

### Study population

The MAS, a birth cohort, recruited 1314 healthy mature infants born in 1990 in 5 German cities. A detailed description of the sampling method and the study participants has been published elsewhere.<sup>14</sup> Briefly, 499 newborns with risk factors for atopy (increased cord blood IgE levels  $\geq 0.9$  kU/L,  $\geq 2$  atopic family members, or both) and 815 newborns without these risk factors

From <sup>a</sup>Children's Hospital, University of Munich, and <sup>b</sup>the Department of Pediatric Pneumology and Immunology and <sup>c</sup>the Institute for Social Medicine and Epidemiology, Charité-Universitätsmedizin Berlin.

\*The MAS study group: Volker Wahn, Marketa Groeger, Antje Schuster (Dusseldorf, Germany); Fred Zepp, Imke Bieber, Wolfgang Kamin (Mainz, Germany); Johannes Forster, Uta Tacke (Freiburg, Germany); Carl-Peter Bauer (Gaisach, Germany); Renate Bergmann, Young-Ae Lee, Renate Nickel (Berlin, Germany); Ute Hoffmann (Munich, Germany).

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Reprint requests: Mascha K. Rochat, MD, Dr. von Haunersche Kinderklinik, Lindwurmstrasse 4, 80337 Munich, Germany. E-mail: [wehntaler@gmail.com](mailto:wehntaler@gmail.com). 0091-6749/\$36.00

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were included in the cohort and the presented analyses (see the Methods section in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Blood sampling

Serum samples were obtained from the children at 1, 2, 3, 5, 6, 7, and 10 years of age. Specific IgE antibodies to food allergens (cow's milk, egg white, soy bean, and wheat) and inhalant allergens (house dust mites *Dermatophagoides pteronyssinus*, cat dander, mixed grass, birch pollen, and dog dander from age 3 years on) were determined with ImmunoCAP (Phadia, Freiburg, Germany).

### Definition of rhinitis, sensitization, and wheezing

Current rhinitis was defined as parents answering yes to the question "Has your child had a congested or runny nose since our last follow up?" and no to the question "Were these symptoms during a cold?" until the age of 2 years. After this time, it was defined as answering yes to the following question: "Did your child have sneezing attacks (at least 5 consecutively) or a congested or runny nose without a cold or an infection during the last 12 months?" To avoid underreporting of rhinitis and to increase the probability of not only assessing children with severe rhinitis,<sup>15</sup> we included parent-reported rhinitis and not a physician's diagnosis of rhinitis. Sensitization was defined as specific IgE levels of 0.35 kU/L or greater to at least 1 allergen.

In accordance with international guidelines,<sup>16</sup> children were stratified into 4 rhinitis phenotypes at each follow-up depending on the presence of rhinitis or sensitization until the age at the respective follow-up. First, children were stratified into the group of allergic rhinitis if they had rhinitis and were sensitized. Second, children with rhinitis but without sensitization were stratified into the group of nonallergic rhinitis. Third, children sensitized but without rhinitis were stratified into the group of atopy without rhinitis. Finally, the children with neither rhinitis nor sensitization formed the control group.

Current wheeze was defined as answering yes to the following question: "Has your child wheezed during the last 12 months or since our last visit?"

### AHR

At the age of 7 years, an airway challenge was performed in 647 of the 800 children whose lung function had been measured. According to a standard procedure, the airway challenge was performed with a body plethysmograph (Master-Lab; E Jaeger, Würzburg, Germany), with doses of histamine ranging from 0.5 to 8.0 mg/mL.<sup>17</sup> A histamine concentration of 0.85 mg/mL or less caused a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub> FEV<sub>1</sub>) in 10% of the population. Therefore AHR was defined as a PC<sub>20</sub> FEV<sub>1</sub> value of less than this. A dichotomous variable was used for the analysis. A sensitivity analysis has been performed and described elsewhere.<sup>17</sup>

### Statistical analyses

Cumulative incidence was defined as the number of new cases within the age range divided by all children at risk (without the symptom) at the beginning of the age range. Period prevalence refers to the time period from birth to the respective age. It was defined as the sum of cases in the respective time period divided by the number of children at the end of the time period (ie, the respective age). The occurrence of rhinitis, wheezing, or sensitization was assessed when the children were 2 and 5 years old. We distinguished 2 time periods.

First, rhinitis, wheezing, or sensitization until a given age (ie, 2 or 5 years) was defined as having rhinitis, wheezing, or being sensitized at least once until the given age. For example, a child beginning to wheeze at the age of 3 years was coded as negative for wheezing until the age of 2 years but positive for wheezing until the age of 5 years.

Second, for the purpose of the study, we defined incidence of rhinitis or wheezing as having rhinitis or wheezing at least once after the given age but not before. For example, a child beginning to wheeze at the age of 3 years was coded as positive for incidence of wheezing after the age of 2 years but negative for incidence of wheezing after the age of 5 years. Each reference group was composed of children present at more than 50% of all follow-up visits until the given age.

Cox proportional-hazard regression models were used to study the relation between rhinitis, wheezing, or sensitization and the new onset of wheezing or

**TABLE I.** Temporal relation between rhinitis, wheeze, and atopic sensitization

| Relation                            | Age              | Adjusted RR                | 95% CI                                   | P value                            |
|-------------------------------------|------------------|----------------------------|------------------------------------------|------------------------------------|
| Rhinitis before wheezing onset      | At 2 y<br>At 5 y | 0.95<br><b>1.83</b>        | 0.56-1.63<br><b>1.06-3.17</b>            | .862<br><b>.030</b>                |
| Wheezing before rhinitis onset      | At 2 y<br>At 5 y | 1.22<br>1.12               | 0.96-1.56<br>0.78-1.60                   | .104<br>.550                       |
| Sensitization before wheezing onset | At 2 y<br>At 5 y | <b>1.62</b><br><b>2.24</b> | <b>1.12-2.33</b><br><b>1.26-4.01</b>     | <b>.009</b><br><b>.006</b>         |
| Sensitization before rhinitis onset | At 2 y<br>At 5 y | <b>1.89</b><br><b>1.92</b> | <b>1.49-2.39</b><br><b>1.36-&gt;2.71</b> | <b>&lt;.001</b><br><b>&lt;.001</b> |

Cox regression models are mutually adjusted within the model, as well as adjusted for at least 2 first-degree family members with atopic diseases, parental education, maternal smoking during pregnancy, at least 1 older sibling, sex, and center. Significant *P* values (<.05) are shown in boldface.

rhinitis. The association between rhinitis and sensitization with AHR at the age of 7 years was performed by using multivariate logistic regression analysis. For both approaches, study center, parental atopy, sex, parental education, maternal smoking during pregnancy, and 1 or more older siblings were forced into the model as potential confounders.

The population-attributable risk fraction (PARF) was calculated by using the population prevalence of the different rhinitis phenotypes (*p*) and the adjusted relative risk (RR) associated with the exposure as follows:  $p(RR - 1) / (1 + p(RR - 1))$ . The 95% CI for the PARF was estimated by using a substitution method described by Daly.<sup>18</sup>

## RESULTS

### Study population

Of the 1314 children recruited at birth, 1,092 (83.1%) were followed to the age of 2 years, 1,004 (76.4%) to the age of 5 years, 939 (71.5%) to the age of 7 years, and 766 (58.3%) to the age of 13 years.

### Prevalence and incidence of rhinitis, wheezing, sensitization, and AHR

Rhinitis point prevalence was highest at 3 years at 9.2% and ranged between 2.5% and 7.7% throughout the other years. By the age of 13 years, the cumulative incidence of rhinitis was 47.8%. Wheezing point prevalence was highest at the end of the second year, with a value of 19.8% decreasing to less than 7% throughout the following years. The cumulative incidence of wheezing was 40.5% by the age of 13 years. Proportions of 89.1% and 93.7% of all children with wheezing beginning after the ages of 2 and 5 years, respectively, were sensitized to at least 1 allergen during the whole follow-up period. The cumulative incidence of sensitization was 41.2% by the age of 10 years. In the high-risk stratum it was 46.3%, and in the low-risk stratum it was 38.0%. At the age of 7 years, the prevalence of AHR was 16.1%.

### Predictors for wheezing and rhinitis onset

To explore the temporal sequence of wheezing and rhinitis onset, we analyzed whether these 2 symptoms predicted each other at the ages of 2 and 5 years (Table I). Rhinitis significantly predicted the incidence of wheezing only at the age of 5 years, whereas wheezing was not a predictor for the incidence of rhinitis at either age considered. Independent of the age considered, sensitization was a predictor for the incidence of wheezing and rhinitis onset (Table I).

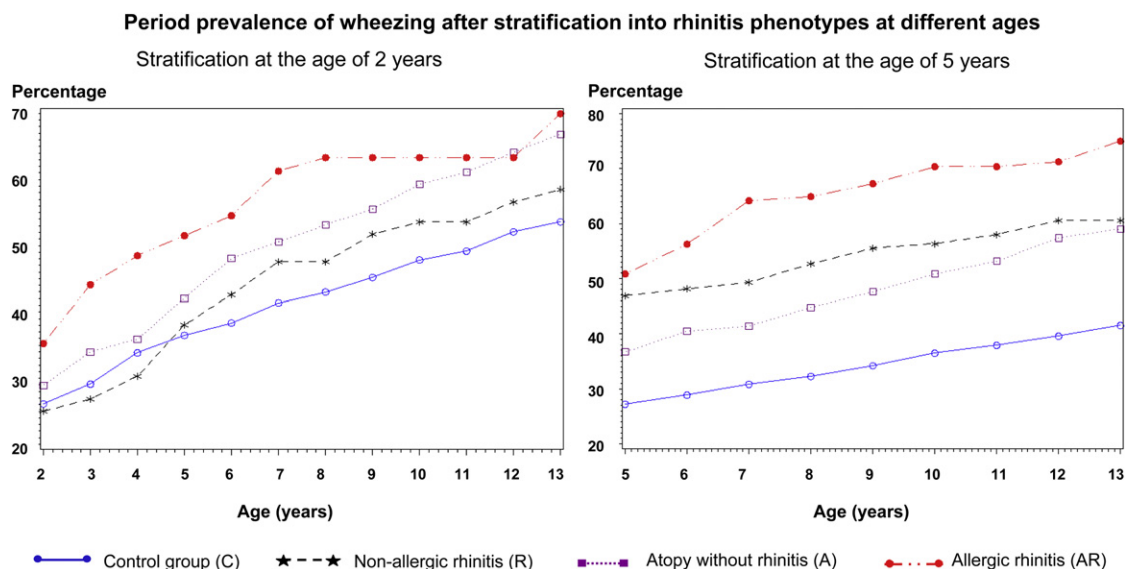


**FIG 1.** The period prevalence of wheezing (sum of the incidences until each age divided by the number of children in the follow-up at that age) after stratification in the 4 rhinitis phenotypes at different ages is shown. The 4 rhinitis phenotypes are allergic rhinitis, nonallergic rhinitis, atopy without rhinitis, and the control group.

To better characterize the association between sensitization and rhinitis on the incidence of wheezing, we defined the following 4 rhinitis phenotypes: allergic rhinitis, nonallergic rhinitis, atopy without rhinitis, and control groups.

### Period prevalence of wheezing stratified by rhinitis phenotypes at different ages

The period prevalence of wheezing varied depending on the rhinitis phenotypes and the age of stratification (Fig 1). When defining the stratum at the age of 2 years, the period prevalence of wheezing was lower both in the control group and in the group with nonallergic rhinitis compared with that seen in the other 2 groups, suggesting a difference between children sensitized and nonsensitized to any allergen. This difference reached statistical significance at the age of 6 years (Fig 1).

When defining the stratum at the age of 5 years, the 4 rhinitis phenotypes tracked proportionally along the initial values, with significant differences throughout the follow-up period. Contrary to the definition at 2 years, nonallergic rhinitis showed significantly higher period prevalences than atopy without rhinitis (Fig 1).

### Baseline characteristics and selected outcomes according to rhinitis phenotype

At the age of 2 years, there were 604 children in the control group, 197 with atopy without rhinitis, 68 with nonallergic rhinitis, and 34 with allergic rhinitis. A comparison of baseline characteristics and selected outcomes did not differ among the rhinitis phenotype strata when these were defined at 2 years of age (data not shown). At the age of 5 years, there were significantly more boys, more children with a family history of atopy, and more children with asthma or AHR at the age of 7 years in the group with allergic rhinitis compared with the control group. Additionally, the children with allergic rhinitis were sensitized to more outdoor and indoor inhalant allergens compared with the group with atopy without rhinitis (Table II).

### Stratified analysis of new-onset wheeze

Fig 2 shows the probability of remaining free of wheezing for each rhinitis phenotype at the ages of 2 and 5 years, respectively. The probability of remaining free of wheezing is the inverse of the probability of wheezing onset. When assessing the probability of wheezing onset after the ages of 2 and 5 years, respectively, distinct patterns emerged. At the age of 2 years and relative to the control group, a significant increase in the incidence of wheeze was seen for children with atopy without rhinitis (adjusted RR, 1.70;  $P = .007$ ) but not for the other strata. Even though an increased risk was seen for allergic rhinitis (adjusted RR, 1.37;  $P = .496$ ), the association was not significant, possibly because of small numbers in this group.

When analyzing the probability of wheezing onset after the age of 5 years, however, only the children with allergic rhinitis had a significantly increased probability (adjusted RR, 3.82;  $P < .001$ ). This association was not attributable to specific allergens because the risk of subsequent wheeze was increased consistently for all allergens tested (see Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Additionally, the association was not attributable to the severity of sensitization (additionally adjusting for total IgE: RR, 3.23;  $P = .002$ ) or atopic dermatitis during the first 2 years of life (additionally adjusting for atopic dermatitis during the first 2 years of life: RR, 3.44;  $P < .001$ ; additionally adjusting for both total IgE and atopic dermatitis: RR, 2.86;  $P = .008$ ). As can be seen in Fig 2, at the age of 5 years, the group with allergic rhinitis varied substantially from the other 3 groups. Therefore we analyzed the effect of allergic rhinitis compared with a pooled group of the 3 other phenotypes on the risk for subsequent wheezing onset and found a significant increase (adjusted RR, 3.37;  $P < .001$ ).

### PARF

The PARF of rhinitis phenotypes on the incidence of wheezing was highest for allergic rhinitis until the age of 5 years (41.5%; 95% CI, 20.0% to 61.3%), followed by sensitization to any allergen until the age of 5 years (39.0%; 95% CI, 10.2% to

**TABLE II.** Characteristics of children at the age of 5 years according to rhinitis phenotype

|                                           | Total (n= 699)  | Control group (n= 235) | Nonallergic rhinitis (n = 79) | Atopy without rhinitis (n = 207) | Allergic rhinitis (n = 178) |
|-------------------------------------------|-----------------|------------------------|-------------------------------|----------------------------------|-----------------------------|
| Girls                                     | 331/699 (47.4%) | 121/235 (51.5%)        | 42/79 (53.2%)                 | 95/207 (45.9%)                   | 73/178 (41.0%)*             |
| High parental education                   | 367/662 (55.4%) | 126/222 (56.8%)        | 34/76 (44.7%)                 | 110/195 (56.4%)                  | 97/169 (57.4%)              |
| Maternal smoking during pregnancy         | 166/697 (23.8%) | 51/235 (21.7%)         | 15/79 (19.0%)                 | 52/205 (25.4%)                   | 48/178 (27.0%)              |
| One or more older siblings                | 326/699 (46.6%) | 113/235 (48.1%)        | 36/79 (45.6%)                 | 102/207 (49.3%)                  | 75/178 (42.1%)              |
| Early-life exposure to cats ( $\leq 3$ y) | 74/683 (11.6%)  | 32/219 (14.6%)         | 5/72 (6.9%)                   | 20/188 (10.6%)                   | 17/159 (10.7%)              |
| Early-life exposure to dogs ( $\leq 3$ y) | 43/639 (6.7%)   | 15/221 (6.8%)          | 7/71 (9.9%)                   | 17/189 (9.0%)                    | 4/158 (2.5%)                |
| Family history of atopy                   | 150/697 (21.5%) | 40/234 (17.1%)         | 22/79 (27.8%)*                | 38/207 (18.4%)                   | 50/177 (28.2%)†             |
| Outdoor sensitization until 5 y           | 204/326 (62.6%) |                        |                               | 94/172 (54.7%)                   | 110/154 (71.4%)§            |
| Food sensitization until 5 y              | 271/353 (76.8%) |                        |                               | 149/196 (76.0%)                  | 122/157 (77.7%)             |
| Indoor sensitization until 5 y            | 140/319 (43.9%) |                        |                               | 66/173 (38.2%)                   | 74/146 (50.7%)‡             |
| Inhalant sensitization until 5 y          | 267/349 (76.5%) |                        |                               | 131/186 (70.4%)                  | 136/163 (83.4%)§            |
| Asthma at 7 y                             | 50/649 (7.7%)   | 7/222 (3.2%)           | 1/74 (1.4%)                   | 9/191 (4.7%)                     | 33/162 (20.4%)†             |
| AHR at 7 y                                | 83/496 (16.7%)  | 17/169 (10.1%)         | 7/60 (11.7%)                  | 23/146 (15.8%)                   | 36/121 (29.8%)†             |

The frequency between the 4 rhinitis phenotypes is compared by using the Pearson  $\chi^2$  test.

\* $P < .05$  compared with the control group.

† $P < .01$  compared with the control group.

‡ $P < .05$  compared with the atopy without rhinitis group.

§ $P < .01$  compared with the atopy without rhinitis group.

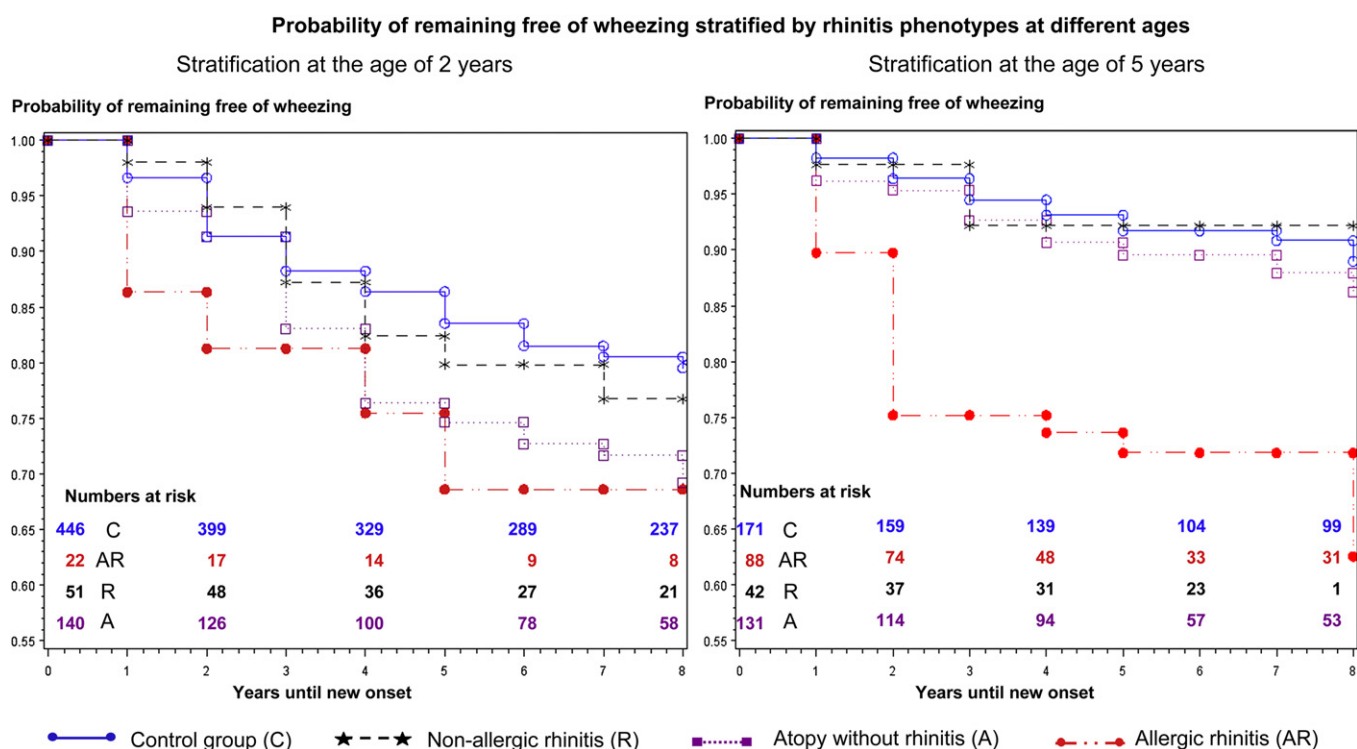


**FIG 2.** Kaplan-Meier plots of the probability of remaining free of wheezing stratified by the 4 rhinitis phenotypes at the ages of 2 and 5 years. The 4 rhinitis phenotypes were allergic rhinitis, nonallergic rhinitis, atopy without rhinitis, and the control group. The probability of remaining free of wheezing decreases over time. In the figure the probability ranges from 0.55 to 1. One represents a 100% probability of remaining free of wheezing in the corresponding year. A probability of 0.75, for example, represents a 75% probability of remaining free of wheezing, meaning a 25% probability of wheezing onset.

61.1%). The PARF for the other rhinitis phenotypes ranged between 0.7% and 24.1% depending on age and the phenotype analyzed.

## AHR

When analyzing the prevalence of AHR at the age of 7 years, a similar pattern as for wheezing emerged. Children with allergic

rhinitis until the age of 5 years had the highest risk for AHR at the age of 7 years (Table III).

## DISCUSSION

The findings of this study suggest that the first manifestation of allergic rhinitis occurs in preschool children. In this age group allergic rhinitis is a risk factor for subsequent wheezing onset. In

**TABLE III.** Multivariate analysis of the effect of rhinitis and sensitization on AHR at the age of 7 years

|                                      | OR          | 95% CI           | P value         |
|--------------------------------------|-------------|------------------|-----------------|
| Any sensitization until age 2 y      | <b>2.61</b> | <b>1.58-4.33</b> | <b>&lt;.001</b> |
| Ever rhinitis until age 2 y          | 0.85        | 0.39-1.88        | .69             |
| Stratified analysis                  |             |                  |                 |
| Control until age 2 y                | 1           |                  |                 |
| Atopy without rhinitis until age 2 y | <b>2.32</b> | <b>1.35-3.97</b> | <b>.002</b>     |
| Nonallergic rhinitis until age 2 y   | 0.50        | 0.15-1.73        | .276            |
| Allergic rhinitis until age 2 y      | <b>3.37</b> | <b>1.17-9.73</b> | <b>.025</b>     |
| Any sensitization until age 5 y      | <b>2.09</b> | <b>1.22-3.60</b> | <b>.008</b>     |
| Ever rhinitis until age 5 y          | <b>1.68</b> | <b>1.01-2.79</b> | <b>.047</b>     |
| Stratified analysis                  |             |                  |                 |
| Control until age 5 y                | 1           |                  |                 |
| Atopy without rhinitis until age 5 y | 1.53        | 0.77-3.10        | .221            |
| Nonallergic rhinitis until age 5 y   | 0.99        | 0.38-2.56        | .977            |
| Allergic rhinitis until age 5 y      | <b>3.30</b> | <b>1.71-6.38</b> | <b>&lt;.001</b> |

Multivariate logistic regressions are mutually adjusted for at least 2 first-degree family members with atopic diseases, parental education, maternal smoking during pregnancy, at least 1 older sibling, sex, and center.

Significant *P* values (<.05) are shown in boldface.

OR, Odds ratio.

contrast, neither the rare manifestation of allergic rhinitis in the first 2 years of life nor nonallergic rhinitis up to the age of 5 years was associated with the onset of wheezing in childhood. These findings suggest that some childhood wheezing phenotypes are associated with rhinitis in children.

Rhinitis in the first 2 years of life was not associated with wheezing thereafter. As reported in a previous analysis of the MAS cohort,<sup>19</sup> as well as in other studies,<sup>7,20,21</sup> sensitization is a driving risk factor for the development of wheezing in this age group. This finding contrasts with the concept of united airways,<sup>4</sup> which implicates an association between rhinitis and wheezing. Additionally, the discrepancy between the cumulative incidence of rhinitis (47.8%) and its peak period prevalence (9.2%) suggests that rhinitis is a transient phenomenon in early childhood and manifests years before wheezing begins. However, the effect of rhinitis on the incidence of wheezing might require a certain amount of time to become clinically apparent and might therefore not be detectable before school age. This notion is supported by the fact that although allergic rhinitis until the age of 2 years was not associated with subsequent wheeze, it was associated with AHR at the age of 7 years, which might precede the clinical manifestation of wheeze. Indeed, AHR has been suggested as an intermediate factor between allergic rhinitis and asthma in adults.<sup>1</sup> In children allergic rhinitis has also been shown to increase the prevalence of AHR,<sup>22</sup> and the presence of AHR with concomitant atopic manifestation increases the risk of asthma.<sup>23,24</sup>

Rhinitis in preschool children is a risk factor for wheezing onset after the age of 5 years, but only when associated with atopic sensitization. Although this finding goes in line with the concept of united airways,<sup>4</sup> nonallergic rhinitis would also be expected to be associated with wheezing onset in this concept. As reported previously in the MAS cohort, only the atopic children wheeze beyond the ages of 5 to 7 years. The nonatopic children stop wheezing around that age.<sup>19</sup> Therefore this cohort might not have the power to detect the effect of nonallergic rhinitis on the incidence of nonallergic wheezing.

Together, these findings suggest that in young children, as in adults, a progression from rhinitis to wheezing can be found. This

progression could possibly be mediated by common features or by an interaction between the upper and lower airways. Several potential mechanisms might explain the observed association.

One potential mechanism implies impaired mucosal function. An impaired mucosal barrier leads to an increased allergen uptake and a mounting of IgE responses, which eventually results in allergic airway inflammation, AHR, and asthma.<sup>25</sup> Conversely, impaired mucosa of the upper and lower airways might be more susceptible to viral infections, which could interact with the process of allergic sensitization and thereby increase the risk of asthma.<sup>26</sup> This hypothesis is supported by studies showing that mutations in the gene encoding filaggrin, a protein known to have an important role in the integrity of the epithelial barrier,<sup>27</sup> were also associated with the prevalence of allergic rhinitis.<sup>28</sup>

Additionally, recent studies have shown that asthma is also associated with polymorphisms in genes expressed in the airway mucosa, indicating that events at epithelial cell surfaces might be driving disease processes.<sup>29</sup>

Another hypothesis linking the upper and lower airways implies a shared airway inflammation throughout the respiratory system. The mucosa of the different parts of the respiratory system being structurally and physiologically uniform, disorders of the entire respiratory system present with similar inflammatory responses.<sup>30</sup> Additionally, stimulation of one part of the respiratory mucosa with antigens has been shown to result in system-wide inflammatory changes within hours.<sup>31</sup> These results suggest that inflammatory crosstalk or immune communication throughout the respiratory tract is responsible for system-wide changes, resulting in an upregulation of airway inflammation.<sup>31,32</sup> Therefore continuous antigenic stimulation of the respiratory tract could lead to a cumulative increase of airway inflammation, resulting in the observed progression of airway inflammation from allergic rhinitis to asthma.<sup>5</sup> Our results support this hypothesis by showing a clear progression from rhinitis to wheezing but not from wheezing to rhinitis.

Independent of the underlying mechanism, the PARF of wheezing incidence from allergic rhinitis in preschool children in our study was substantial. Similar PARFs can be found in adult populations.<sup>1</sup> In adults, however, the second-highest PARF is seen for nonallergic rhinitis, whereas in children it is seen for atopy without rhinitis. This, once more, illustrates the difference in wheezing phenotypes between school-aged children and adults.

A considerable proportion of children with persistent asthma are not identified until their disease has already consolidated, and thus any potential benefits of early intervention are not achieved.<sup>8</sup> If the association we found is truly causal, the question arises whether the natural history of wheezing illnesses could be altered or the progression to asthma could be halted by reducing childhood allergic rhinitis. Efforts at primary prevention of asthma through rhinitis have concentrated on immunomodulation in children already sensitized or immunoprophylaxis in children not yet sensitized.<sup>33</sup> Allergen immunotherapy has been well established as an effective treatment of allergic rhinitis,<sup>34,35</sup> yet few of these studies have included children younger than 5 years.<sup>36</sup> Results from studies with subcutaneous and sublingual immunotherapy for secondary prevention of asthma have had mixed results.<sup>36,37</sup>

Data are either lacking<sup>33</sup> or inconclusive<sup>38</sup> on other therapeutic approaches, such as antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, or anti-IL-5.

Therefore more studies are required to further assess whether early intervention can result in disease modification, especially in preschool children.

The main strengths of the MAS are a well-defined prospective birth cohort study population, the use of standardized questionnaires, and objective sensitization measurements. As in all epidemiologic studies, misclassification because of the outcome relying on parental recall might have biased the results. However, similar results were seen when analyzing the association between rhinitis and AHR, which is an objective measure of lower airway disorders.

The diagnosis of rhinitis in early childhood presents several diagnostic challenges because the symptoms might not be distinguishable from those of the common cold. Although we used a stepwise assessment of allergic rhinitis in 1- and 2-year-olds, we cannot exclude that a considerable part of the symptoms in the first years of life might be related to viral infections. However, viral infections interacting with atopy in infancy have been reported to promote asthma onset.<sup>26</sup> Because we did not find any association between rhinitis in infancy and the subsequent incidence of wheezing, misclassification of rhinitis is improbable.

In conclusion, the present analysis suggests that the first manifestation of allergic rhinitis occurs in preschool children, in whom it is a risk factor for subsequent wheezing onset. Preschool children with rhinitis might thus benefit from early assessment of allergic sensitization to identify children at high risk of wheezing. Identification of these children might help targeted selection for clinical trials on secondary prevention of asthma at school age and provide individual benefit by ensuring they are actively monitored. However, because the outcome cannot be predicted with certainty for an individual patient, parents should be counseled cautiously.

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**Clinical implications: Allergic rhinitis in preschool children is a risk factor for subsequent wheezing onset. Preschool children with rhinitis might benefit from early assessment of allergic sensitization.**

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## METHODS

### Study population

The MAS, a birth cohort, recruited 1314 healthy mature infants born in 1990 in 5 German cities. A detailed description of the sampling method and the study participants has been published elsewhere.<sup>E1</sup> Briefly, 499 newborns with risk factors for atopy (increased cord blood IgE level [ $\geq 0.9$  kU/L],  $\geq 2$  atopic family members, or both) and 815 newborns without these risk factors were included in the cohort and the presented analyses. All children were followed up at ages 1, 3, 6, 12, 18, and 24 months and from then on yearly until the age of 13 years. The study was approved by local ethics committees. The parents of each child provided written informed consent at the time of enrollment. At each follow-up visit, parents either gave structured interviews to a study physician or completed postal questionnaires (at ages 8, 9, 11, and 12 years). The main topics of these interviews were asthmatic and atopic symptoms and disease. From the age of 5 years onward, questions relating to wheeze corresponded to the International Study of Asthma and Allergies in Childhood core questions.<sup>E2</sup>

To assess potential participation bias, we analyzed the number of attended follow-up visits per child, testing whether some children participated in more follow-up visits than other children based on data collected at birth. Of the 1314 children included in the study at birth, 52 attended only 1 follow-up visit, and 454 attended the maximum number of 17 follow-up visits. Children who have an atopic parent ( $P < .001$  for trend), whose parents have a high level of education ( $P < .001$  for trend), or whose mothers did not smoke during pregnancy ( $P < .001$  for trend) were significantly more likely to attend regular follow-up visits than children without these characteristics. All multivariate models were therefore adjusted for these variables, as stated in the statistics section.

### Statistical analyses

Statistical analysis was performed with SAS 9.2 software (SAS Institute, Inc, Cary, NC).

Reported  $P$  values are 2-sided.  $P$  values of less than .05 were considered significant.  $\chi^2$  Tests were used to compare the prevalence between groups.

Cumulative incidence was defined as the number of new cases within the age range divided by all children at risk (without the symptom) at the beginning of the age range. Period prevalence refers to the time period from birth to the respective age. It was defined as the sum of cases in the respective time period divided by the number of children at the end of the time period

(ie, the respective age). The occurrence of rhinitis, wheezing, or sensitization was assessed when the children were 2 and 5 years old. We distinguished 2 time periods.

First, rhinitis, wheezing, or sensitization until a given age (ie, 2 or 5 years) was defined as having rhinitis, wheezing, or being sensitized at least once until the given age. For example, a child beginning to wheeze at the age of 3 years was coded as negative for wheezing until the age of 2 years but positive for wheezing until the age of 5 years.

Second, for the purpose of the study, we defined incidence of rhinitis or wheezing as having rhinitis or wheezing at least once after the given age but not before. For example, the child beginning to wheeze at the age of 3 years was coded as positive for the incidence of wheezing after the age of 2 years but negative for the incidence of wheezing after the age of 5 years. Each reference group was composed of children present at more than 50% of all follow-up visits until the given age.

Cox proportional-hazard regression models were used to study the relation between rhinitis, wheezing, or sensitization and the new onset of wheezing or rhinitis. The timescale was the number of years from the given age until the end of the follow-up period (age 13 years). All possible interactions between potential confounders and rhinitis, sensitization, and the different rhinitis phenotypes were tested and found to be nonsignificant. The proportional-hazard assumption was checked by testing the time dependence of all variables in the regression model. In the stratified analysis we only considered results with a cell frequency of 10 or more children.

The association between rhinitis and sensitization with AHR at the age of 7 years was performed by using multivariate logistic regression analysis. For both approaches, study center, parental atopy, sex, parental education, maternal smoking during pregnancy, and 1 or more older siblings were forced into the model as potential confounders.

The maximum number of subjects with available data was used for all analyses, resulting in varying sample sizes.

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**TABLE E1.** Specific sensitization pattern until the ages of 2 and 5 years

| <b>Risk for new onset of wheezing after age 2 y</b> |                               |                   |                 |             |                          |                 |
|-----------------------------------------------------|-------------------------------|-------------------|-----------------|-------------|--------------------------|-----------------|
|                                                     | <b>Atopy without rhinitis</b> |                   |                 |             | <b>Allergic rhinitis</b> |                 |
|                                                     | <b>RR</b>                     | <b>95% CI</b>     | <b>P value</b>  |             | <b>RR</b>                | <b>95% CI</b>   |
| Birch                                               | 2.02                          | 0.87-4.67         | .102            | *           |                          |                 |
| Cat                                                 | <b>2.28</b>                   | <b>1.09-4.77</b>  | <b>.028</b>     | *           |                          |                 |
| Egg                                                 | <b>1.67</b>                   | <b>1.03-2.70</b>  | <b>.038</b>     | 1.49        | 0.54-4.09                | .441            |
| Grass                                               | 1.47                          | 0.76-2.83         | .252            | *           |                          |                 |
| Milk                                                | <b>1.93</b>                   | <b>1.18-3.17</b>  | <b>.009</b>     | 0.49        | 0.07-3.54                | .477            |
| Mite                                                | 2.08                          | 0.90-4.81         | 0.089           | *           |                          |                 |
| Soy                                                 | <b>5.14</b>                   | <b>2.39-11.03</b> | <b>&lt;.001</b> | *           |                          |                 |
| Wheat                                               | 1.71                          | 0.79-3.72         | .173            | *           |                          |                 |
| <b>Risk for new onset of wheezing after age 5 y</b> |                               |                   |                 |             |                          |                 |
|                                                     | <b>Atopy without rhinitis</b> |                   |                 |             | <b>Allergic rhinitis</b> |                 |
|                                                     | <b>RR</b>                     | <b>95% CI</b>     | <b>P value</b>  |             | <b>RR</b>                | <b>95% CI</b>   |
| Birch                                               | 2.57                          | 0.95-6.99         | .064            | <b>5.51</b> | <b>2.50-12.11</b>        | <b>&lt;.001</b> |
| Cat                                                 | 1.88                          | 0.42-8.36         | .405            | <b>3.04</b> | <b>1.11-8.36</b>         | <b>.031</b>     |
| Egg                                                 | 0.96                          | 0.32-2.86         | .944            | <b>3.68</b> | <b>1.74-7.80</b>         | <b>.001</b>     |
| Grass                                               | <b>3.26</b>                   | <b>1.42-7.48</b>  | <b>.005</b>     | <b>6.57</b> | <b>3.29-13.10</b>        | <b>&lt;.001</b> |
| Milk                                                | 1.22                          | 0.49-3.06         | .665            | <b>3.70</b> | <b>1.73-7.89</b>         | <b>.001</b>     |
| Mite                                                | 2.38                          | 0.89-6.36         | .084            | <b>3.52</b> | <b>1.30-9.55</b>         | <b>.013</b>     |
| Soy                                                 | 1.27                          | 0.17-9.80         | .816            | <b>9.15</b> | <b>4.00-20.92</b>        | <b>&lt;.001</b> |
| Wheat                                               | <b>2.95</b>                   | <b>1.08-8.06</b>  | <b>.035</b>     | <b>7.26</b> | <b>3.13-16.84</b>        | <b>&lt;.001</b> |

Cox regression models are mutually adjusted within the model, as well as adjusted for at least 2 first-degree family members with atopic diseases, parental education, maternal smoking during pregnancy, at least 1 older sibling, sex, and center. Significant *P* values (<.05) are shown in boldface.

\*Estimation was not possible because of low cell numbers ( $n \leq 10$ ).