Teenage Asthma After Severe Early Childhood Wheezing: An 11-Year Prospective Follow-Up

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Summary. The role of factors related to early wheezing and their associations with subsequent development of asthma are controversial. We reevaluated 81 children who had been prospectively followed up since hospitalization for wheezing at less than 2 years of age. The baseline data on characteristics of the children, family-related factors, and viral causes of wheezing were collected on entry into the study. At the median age of 12.3 years, current symptoms suggestive of asthma and allergy were recorded. As part of the clinical examination, an outdoor exercise challenge test and skin prick tests to common inhalant allergens were performed. Asthma, as indicated by current inhaled anti-inflammatory medication or repeated wheezing and positive result in the challenge test, was present in 32 (40%) children, and 90% of them were sensitized to at least one allergen. Early asthma-predictive factors were atopic dermatitis (odds ratio (OR), 3.5; 95% confidence interval (CI), 1.2–10.1) and the presence of specific IgE to inhalant allergens (OR, 11.3; 95% CI, 1.9–67.6). Respiratory syncytial virus (RSV) identification during wheezing in infancy was relatively rare (20%) among later asthmatics compared with other or no viral identification (52%) or rhinovirus identification (58%). Since the prevalence of childhood asthma in our area is 4.0–5.0%, we conclude that the increased risk of asthma persists until the teenage years after hospitalization for wheezing in infancy. The risk was about 5-fold after respiratory syncytial virus-induced wheezing, and more than 10-fold after rhinovirus-induced wheezing in the present study. Pediatr Pulmonol. 2005; 40:316–323. © 2005 Wiley-Liss, Inc.

Key words: atopic hypersensitivity; atopic dermatitis; child; respiratory syncytial virus; rhinovirus; inhalant allergen.

INTRODUCTION

Children who wheeze during respiratory viral infection in infancy are at risk of wheezing disorders in later childhood, with the risk continuing even into adulthood.1–5 Wheezing is common in infancy; approximately a third of all children suffer from wheezing before 3 years of age.6 However, wheezy children seem to form a heterogeneous group, and both host- and virus-specific factors modify the severity of wheezing and the risk of subsequent respiratory symptoms.7 Therefore, the identification of those wheezing infants who are at risk of asthma in later childhood is difficult.

The Tucson Children’s Respiratory Study showed that early childhood wheezing can be classified into transient wheezing, nonatopic permanent wheezing, and atopic permanent wheezing or asthma.6 Children with transient wheezing probably have low levels of lung function before any lower respiratory tract illness develops, and in most of them, wheezing symptoms disappear before school age.6 In children with nonatopic permanent wheezing, the risk of wheezing decreases with age and is not any more significant at ages 11–13 years.6,8 The asthmatic subgroup of early wheezing consists of children with allergy, and the risk of wheezing persists at least until early adolescence.6

Thus, the years before puberty seem to be critical for the persistence of asthma. The risk of asthma after hospitalization for severe wheezing in infancy has varied from 28–39% at ages 10–13 years.4,9,10 The aim of the present prospective follow-up study was to evaluate the occurrence of asthma and atopy at ages 11–13 years, 10–12 years after early childhood wheezing treated in

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hospital. Special attention was paid to the early host- and virus-specific factors, which at this critical age may predict the development of asthma or persistence of the disease.

MATERIALS AND METHODS

Patient and Baseline Data Collection

As described earlier in detail,1,2 100 children, aged 1–23 months, were recruited into the present prospective follow-up study in 1992–1993. The enrollment criterion was the presence of wheezing and respiratory distress leading to hospital care during an acute respiratory tract infection.

The baseline data were collected by interviewing the parents during the hospitalization by using a structured questionnaire, including questions on the history of wheezing and atopic dermatitis, as well as the family history of asthma and atopic diseases. Only diagnoses made by a physician were accepted. Additional information on maternal smoking during pregnancy, and passive smoking and pet contacts at home or at daycare, was also recorded.3

Viral infections were studied by antigen detection in the nasopharyngeal aspirates (NPA) taken at entry and by antibody measurements in paired sera. The adeno group, influenza A and B, parainfluenza types 1, 2, and 3, and respiratory syncytial viruses (RSV) were assayed.1 In 2000, 81 frozen good-quality NPA samples, taken on admission in 1992–1993, were available for reverse transcription-polymerase chain reaction (RT-PCR) for detection of rhinoviruses, enteroviruses, and coronaviruses.11 In 2002, an adequate NPA sample was available for RSV PCR in 61 cases.12

During the primary hospitalization, a venous blood sample was obtained to determine blood eosinophils, serum eosinophil cationic protein (ECP), and total immunoglobulin E (IgE). The cutoff level was 0.44 cells × 10⁹/l for blood eosinophils,13 a value of 16 µg/l for serum ECP,14 and a value of 60 kU/l (144 µg/l) for total serum IgE.15 In 2000, allergen-specific IgE antibodies (Phadiatop CombiRI) were determined in frozen serum samples, which had been obtained at enrollment in 1992–1993, by the fluoroenzyme-immunometric assay (FEIA) UniCAPTM (Pharmacia, Uppsala, Sweden).16 The presence of IgE antibodies in the mixtures of inhalant and food allergens was screened by the detection limit (>0.35 kU/l), and if positive, allergen-specific IgE antibodies were measured by the same limit. The Phadiatop CombiRI panel for food allergens includes egg white, cow’s milk, fish, wheat, peanut, and soy bean, and for inhalant allergens, timothy grass, birch and mugwort pollens, cat, dog, and horse danders, house dust mite Dermatophagoides pteronyssinus, and spores of the mold Cladosporium herbarum.

Follow-Up Data

During the follow-up time from the index episode of wheezing to the latest visit in 2004, six study visits were organized in order to follow up respiratory status and allergic manifestations in the children.1–3 Eighty-one children, 60 boys and 21 girls, attended the follow-up in 2004, and they constitute the subjects of this paper. The ages of the children varied from 10.9–13.7 years (median, 12.3), and the follow-up time from the index episode of wheezing ranged from 10.3–12.3 years (median, 11.4).

In the follow-up study from January–March 2004, a structured questionnaire was used to record the symptoms suggestive of asthma associated with exercise, infections, and allergens. One of the authors (M.K.H.) checked the answers by interviewing the children and their parents during the clinical study. In addition to asthma symptoms, symptoms suggestive of allergic rhinitis, conjunctivitis, and atopic dermatitis occurring after the previous follow-up visit in 1999 were recorded.3 Allergic diseases were classified as current if there had been clinical manifestations during the preceding 12 months. The ongoing medication was registered at the earlier1–3 and current follow-up visits. The need for and types of medication were assessed by the doctors responsible for the treatment, independent of the authors.

At the follow-up visit in 2004, skin prick tests (SPT) were performed. The allergens (ALK SPT extracts, ALK Laboratories, Copenhagen, Denmark) were tested were the outdoor allergens birch, common alder, and mugwort pollens, pollens of meadow fescue and timothy grass, and spores of C. herbarum, and the indoor allergens cat, dog, horse, and cow epithelial danders, house dust mites D. pteronyssinus and D. farinae, and spores of the mold Alternaria alternata. The concentrations of standardized allergen extracts were 10 histamine equivalent points except for cow (1/100 w/v), C. herbarum (1/20 w/v), and A. alternata (100 BU/ml) extracts. Histamine hydrochloride (10 mg/ml) was used as a positive control, and 50% glycerol as a negative control. Wheals with a mean diameter of at least 3 mm were regarded as positive.17 No reactions were allowed to negative controls.

Baseline pulmonary function was examined by a flow-volume spirometer (FVS) (Medikro, Kuopio, Finland). Forced expiratory volume in 1 sec (FEV₁) was the parameter applied in challenge tests. First, the children were carefully instructed on how to perform the test. Thereafter, the measurements were repeated three times, and accepted if the FEV₁ value was less than 5% and the graphic curves were appropriate and equal in shape. The highest FEV₁ value was used in later comparisons. The baseline pulmonary testing was followed by an exercise that consisted of free running outdoors for 8 min at a heart rate of 80% or more of the predicted maximum. Heart rate was monitored by telemetry (Polar Sport Tester,
Polar Elektro Ltd., Kempele, Finland) at 1-min intervals. The FVS was measured, and lungs were auscultated 5, 10, and 15 min after exercise. FEV\(_1\) changes were calculated as follows: \(((\text{pre-exercise } \text{FEV}_1 - \text{postexercise } \text{FEV}_1)/\text{pre-exercise } \text{FEV}_1) \times 100\%\). The exercise challenge test was regarded as positive if there was a 10% or greater fall in \(\text{FEV}_1\) values 5, 10, or 15 min after the test.\(^{18}\) One of the authors (M.K.H.) was responsible for both the performance of lung function and exercise challenge tests and the interpretation of results.

**Asthma Definition**

At the follow-up visit in 2004, asthma was considered present if 1) the child was on a continuous maintenance medication for asthma, or 2) she/he had suffered from repeated (≥2) episodes of wheezing or prolonged (≥4 weeks) cough apart from infections during the preceding 12 months as reported by parents, and the exercise challenge test was regarded as positive.\(^{19}\)

**Statistics**

The data were analyzed using SPSS 11.5 software (SPSS, Inc., Chicago, IL). The statistical significance of differences between groups was assessed with the chi-square test for proportions, supplemented by odds ratios (OR) with 95% confidence intervals (CI). Fisher’s exact test was used when the expected frequency for any cell was <5. The logistic regression was used to analyze parental asthma and atopy, atopy in children, and markers of atopy in children, adjusted for sex and age (in months) on admission, and viral etiology during primary hospitalization, adjusted for sex, age, passive smoking, and atopic dermatitis on admission, as risk factors for asthma.

**Ethics**

This study was approved by the Research Ethics Committee of Kuopio University and Kuopio University Hospital. Informed written consent was obtained from the parents and the children.

**RESULTS**

Eighty-one children, hospitalized for wheezing under the age of 24 months, attended the follow-up study at a median age of 12.3 years (range, 10.9–13.7 years). Asthma was considered present in 32 (40%) children, and 29 of them were on inhaled anti-inflammatory asthma medication; 17 used inhaled steroids, and one used Cromones as continuous medication; and 11 used inhaled steroids intermittently during pollen seasons and/or infections. The other 3 children with asthma had suffered from parent-reported repeated wheezing, and as an objective asthma criterion, had a diagnostic fall in \(\text{FEV}_1\) (range, 12–31%) after exercise. Despite the maintenance medication, 20 (69%) children had suffered from repeated wheezing episodes (n = 19) or prolonged cough apart from infection (n = 5) during the preceding 12 months. The exercise challenge test was positive in 13 (45%) children with maintenance medication, with falls in \(\text{FEV}_1\) varying from 11–34%.

Forty-nine children were considered nonasthmatics; 5 (10%) of them had suffered from parent-reported repeated wheezing during the preceding 12 months, but none of them had a positive exercise challenge test. Five nonsymptomatic children had a diagnostic fall in \(\text{FEV}_1\) (range, 11–25%) after the test. Since no wheezing or prolonged cough symptoms were reported, the children were considered not to have asthma. In all, the exercise challenge was appropriately performed in 78/81 children, and the test was positive in 21 (27%) children; 16 (76%) of them were symptomatic.

Asthma was present in 40% (24/60) of males and in 38% (8/21) of females, and in 31% (16/52) of those hospitalized when under age 12 months and in 55% (16/29) of those hospitalized when over age 12 months (\(P = 0.031\)).

The baseline characteristics and laboratory data of the children, in relation to the presence of asthma, are given in Table 1. The significant asthma predictive factors, present in infancy, were atopic dermatitis and specific IgE to the mixture of inhalant allergens, but not to the mixture of food allergens. In addition, there was a tendency that the risk of asthma increased in children with elevated serum total IgE, and as seen in Table 2, in children with a parental (specifically, maternal) history of asthma.

Asthma was relatively rare after RSV infection on study entry compared with other or no viral findings (20% vs. 52%; OR, 0.269; \(P = 0.016\)) (Table 3). After adjustment for sex and age on admission, the OR remained low (0.341), and after further adjustment for atopic dermatitis on admission and passive smoking in infancy, the OR was 0.407. After adjustments, the statistical significance was lost. The respective figures were 58% and 34% for rhinovirus infection at admission, but the differences were not statistically significant (Table 3).

In SPTs, 90% of the 32 asthmatics had at least one positive reaction to either outdoor or indoor allergens (data not shown). The corresponding figure was 77%, calculated separately for outdoor and indoor allergens. Thirty-two children (40%) had positive reactions to both indoor and outdoor allergens, 20 of them having and 12 of them not having asthma (\(P < 0.001\)). Allergic rhinitis and/or conjunctivitis was present in 21 (66%) children with asthma, compared to 9 (18%) in those with no asthma (\(P < 0.001\)). In contrast, no such association was found between asthma and atopic dermatitis (data not shown).

Seventy-four of the participants in 2004 had also taken part in the clinical study in 1999 (Fig. 1). Asthma was present in 22/74 (30%) children at both studies performed 5 years apart; asthma had remitted in 7/29 (24%) children.
with earlier asthma, and relapsed in 7/29 (24%) children with current asthma.

There were 19 dropouts among the original study group of 100 children. Basic data on infantile characteristics, as expressed for the 81 participants in Tables 1 and 2, were available also for them. Maternal smoking, at time of index infection, was less common among participants than among dropouts (28% vs. 56%; P = 0.027). There were no other statistically significant differences between these two groups.

In addition to those 81 children who attended the follow-up visit in 2004, parents of the 8 dropout children answered the structured questionnaire. Two of the children were on ongoing anti-inflammatory medication for asthma, and the other 6 reported no respiratory symptoms during the preceding 12 months. We performed supplementary analyses by including the 2 children with maintenance medication into the asthma group and the 6 other children into the nonasthma group. Parental (OR, 4.3; 95% CI, 1.2–15.2) and maternal (OR, 6.6; 95% CI, 1.8–37.3) asthma appeared to be significant risk factors for asthma; all other results remained similar, as in the primary analyses. On admission, 4 children had RSV etiology of bronchiolitis (all belonged to the nonasthma group), and none of the 8 children had rhinovirus etiology. Therefore, the inverse relationship between early RSV infection and asthma at ages 11–13 years became stronger in the supplementary analysis. In crude models, the effect

### TABLE 1—Baseline Data in Children, Related to Index Episode of Wheezing Before 2 Years of Age, With Regard to Asthma at Ages 11–13 Years

| Baseline characteristics | All children (n = 81) | Asthmatic children (n = 32) | P | OR (95% CI) |
|--------------------------|-----------------------|-----------------------------|---|-------------|
| Earlier episode of wheezing (physician-diagnosed) | 10 | 7 | 0.077 | 3.726 (0.866–16.037) |
| Blood eosinophil count of ≥0.44 × 10⁹/l | 25 | 12 | 0.883 | 1.086 (0.364–3.239) |
| Serum ECP of ≥16 μg/l | 12 | 7 | 0.447 | 1.687 (0.439–6.487) |
| Serum total IgE of ≥60 kU/l | 22 | 14 | 0.022 | 3.476 (1.197–10.091) |
| Serum specific IgE of ≥0.35 kU/l² | 16 | 11 | 0.059 | 3.513 (0.953–12.951) |
| Inhalant allergens ³ | 13 | 11 | 0.008 | 11.296 (1.888–67.596) |
| Food allergens ⁴ | 34 | 18 | 0.132 | 2.280 (0.781–6.660) |
| Inhalant or food allergens | 36 | 20 | 0.050 | 3.173 (1.002–10.054) |
| Inhalant and food allergens | 11 | 9 | 0.026 | 6.969 (1.256–38.661) |

¹P-values, ORs, and 95% CIs between asthmatics and nonasthmatics were determined by logistic regression adjusted for sex and age on entry into study. Analyses were done separately for each factor.

²Specific IgE was obtained from 73 children; asthma was present in 28.

³Specific IgE was detectable to birch in 15, timothy grass in 14, mugwort in 3, cat in 21, dog in 20, horse in 13, dust mites in 6, and C. herbarum in 3 children.

⁴Specific IgE was detectable to egg white in 38, fish in 9, cow’s milk protein in 33, wheat in 17, nuts in 27, and soy bean in 6 children.

### TABLE 2—Baseline Family Data, Related to Index Episode of Wheezing Before 2 Years of Age, With Regard to Asthma at Ages 11–13 Years

| Baseline characteristics | All children (n = 81) | Asthmatic children (n = 32) | P | OR (95% CI) |
|--------------------------|-----------------------|-----------------------------|---|-------------|
| Parental history of asthma ² | 13 | 8 | 0.067 | 3.355 (0.920–12.235) |
| Maternal history of asthma ² | 7 | 5 | 0.071 | 5.083 (0.871–29.653) |
| Parental history of atopy ³ | 36 | 15 | 0.734 | 1.173 (0.467–2.948) |
| Maternal history of atopy ³ | 25 | 13 | 0.236 | 1.820 (0.676–4.898) |
| Passive smoking during infancy | 37 | 15 | 0.532 | 1.354 (0.523–3.509) |
| Maternal smoking during pregnancy | 17 | 9 | 0.207 | 2.024 (0.677–6.051) |
| Furry pet at home or at daycare during infancy | 24 | 8 | 0.660 | 0.794 (0.284–2.219) |

¹P-values, ORs, and 95% CIs between asthmatics and nonasthmatics were determined by logistic regression adjusted for sex and age on entry into study. Analyses were done separately for each factor.

²Diagnosed by physician.

³Atopic dermatitis or allergic rhinitis diagnosed by physician.
of rhinovirus became significant (OR, 3.0; 95% CI, 1.0–8.8), but like the primary analyses, the significance was lost in adjusted models.

DISCUSSION

Recent observations confirmed that the years before puberty are critical for the persistence of asthma. In previous studies, children with mild bronchiolitis in infancy, not requiring hospitalization, were at risk for asthma until ages 6–8 years, but not any more at ages 11–13 years, whereas severe bronchiolitis, requiring hospitalization, predicted asthma at least until ages 10–13 years. We prospectively followed up a group of children with wheezing requiring hospitalization in infancy, and over half of them had outgrown the symptoms related to wheezing before school age.

In the present study, we reexamined the children at ages 11–13 years, which seems to be a critical age for the persistence of asthma, and there were three main results. First, at a median age of 12.3 years, asthma was still common among children hospitalized for wheezing in infancy, now present in 40%. This figure is in line with the previously reported 28–39% asthma prevalences at the same age in children hospitalized for wheezing in infancy. Second, rhinovirus as a causative agent of the index episode of wheezing in infancy was common (58%), but RSV was rare (20%), in those children considered asthmatics in this study. The results confirm that the outcome after bronchiolitis is dependent on its viral etiology, as observed in this same cohort at early school age. Third, atopic dermatitis and sensitization to inhalant allergens on study entry predicted asthma 10 years later. This is in accordance with the commonly accepted view that atopy has a very central role in the development of asthma.

During the follow-up, we evaluated, by comparable criteria, the occurrence of asthma on average 6 years and in the present study 11 years after wheezing in infancy. The occurrence of asthma was similar (40%) in both studies. Asthma was stable in two thirds of the cases, and in one third, both remissions and relapses were seen. Thus, the risk of asthma after early childhood wheezing persists through childhood until the teenage years, though some children are nonsymptomatic for long periods. This is in accordance with previous follow-up studies on severe bronchiolitis in infancy and asthma in the teen years. According to Sigurs et al., the asthma rate after early RSV bronchiolitis increased from 23% to 28% at the corresponding ages 7 and 13 years. In Noble et al., in contrast, the prevalence of wheezing fell from 43% at age 5 years, to 34% at age 10 years, in children with bronchiolitis in infancy. A similar decreasing trend was also seen in studies by Wennergren et al.: the asthma
figures after hospitalization for wheezing in infancy were 47% at ages 3–6 years, and 30% at age 10 years.\textsuperscript{10,23} Thus, the natural course of asthma is fluctuating, as was also seen in a recent follow-up until adulthood; the risk of asthma after bronchiolitis was even higher in adults than in schoolchildren or adolescents.\textsuperscript{24}

In the present study, the asthma risk was increased if there was atopic dermatitis or detectable specific IgE to inhalant allergens at time of study entry in infancy. In the previous follow-ups until age 10 years or more, only a few or no infantile risk factors were evaluated in regard to asthma after bronchiolitis.\textsuperscript{4,9,10} Wennergren et al.\textsuperscript{23} reported that 18% of wheezing infants had atopic dermatitis and 14% had elevated serum IgE by using a population-based limit of mean + 2 SD, as in our present study, but neither finding was predictive for asthma at age 10 years.\textsuperscript{10} Heymann et al. reported similar figures, i.e., 18% for atopic dermatitis and 15% for serum IgE >64 kU/l, in wheezing children under 3 years old.\textsuperscript{7} The figures were slightly higher in the present study: 20% for atopic dermatitis, and 28% for serum IgE >60 kU/l. The differences in total IgE results raise the question that in our study, compared with other hospital-based studies, atopic children may have been overrepresented. Unfortunately, none of the earlier studies evaluated allergen-specific IgE in children younger than 2 years. The high figures in our study, 16% for inhalation allergens and 43% for food allergens, were comparable with those of 25% and 23% in the study of Sigurs et al. at ages 2.5–3.5 years.\textsuperscript{25} In that study, children were tested 2.5 years after RSV bronchiolitis, and a positive family history of atopy further increased the risk of sensitization.\textsuperscript{25} In both studies, the detection limit of the test (0.35 kU/l) was used, due to a lack of population-based references or clinically established diagnostic limits. In our study, sensitization to inhalation allergens, measured at admission, was seen only in children over 12 months old. These children, compared to children under 12 months old, reacted more beneficially to early anti-inflammatory treatment,\textsuperscript{1} and were at greater risk for later asthma.\textsuperscript{13} In this subgroup, early wheezing was evidently the first sign of asthma.

Several studies reported that maternal history of asthma has a larger influence on children’s asthma risk than history of asthma in other family members.\textsuperscript{26} It was speculated that events during pregnancy, like maternal immune responses, may directly affect the immune system of the fetus.\textsuperscript{27} Likewise, maternal smoking, due to intrauterine exposure, seems to be more harmful than the smoking of fathers or other family members.\textsuperscript{28} In our study, there was a tendency that maternal asthma may associate with asthma in children after wheezing in infancy. In contrast, no association or tendency was seen for paternal asthma or maternal or paternal atopy. The statistically negative result for maternal asthma was probably due to insufficient power of the study, since the association was significant in the analyses of questionnaire data. Atopy, in contrast, was common in both mothers and fathers, allowing reliable statistical conclusions. Childhood exposure to tobacco smoke is relatively low in Finland; the reported figures vary between 6–13%.\textsuperscript{29} Thus, passive smoking was surprisingly common in this study group. Over 40% of the children were exposed to tobacco smoke during infancy, and over 20% during pregnancy. The risk of asthma was increased, compared with nonexposed children, 1.4–2.0-fold, but the difference was not statistically significant. This negative result carries a potential risk of being biased, since smoking was rare in high-risk families; only 3 parents with asthma smoked at the time of study entry.

Earlier studies on the outcome after bronchiolitis stressed the role of RSV in the pathogenesis of asthma.\textsuperscript{4,22} In a recent case-control study, RSV was the predominant virus during winter, and rhinovirus during spring and summer, in children under 3 years old hospitalized for wheezing.\textsuperscript{7} Rhinoviruses were found in children at all ages, including even infants under 6 months old. The authors correlated viral and serum IgE data and concluded that allergic sensitization seems to be a predisposing risk factor for an augmented response to acute infections, with rhinovirus leading to wheezing.\textsuperscript{7} However, no follow-up data were available. According to the birth cohort data from Tucson, the risk of wheezing after RSV lower respiratory tract infection decreases gradually with age and growth of the child, and finally becomes insignificant by age 13 years.\textsuperscript{8} In that study, no data on rhinoviruses were available. In the present study, rhinoviruses were associated with the development of asthma at early school age, but RSVs, in contrast, were associated with a more favorable outcome.\textsuperscript{11} Now, at ages 11–13 years, early RSV-induced wheezing was still associated with a relatively favorable outcome. The effect of early rhinovirus infection was the opposite, but the risk, probably due to many confounding factors the children faced at school age, was not significant anymore. Therefore, rather than being an independent risk factor for asthma, rhinovirus-induced wheezing could serve as a marker in infants, revealing those who are prone to wheeze due to either ongoing airway inflammation or even early structural changes in the airway wall.\textsuperscript{30}

The lack of a simple, widely accepted definition of asthma has hampered the study of childhood asthma. In the present study, the applied asthma criteria were strict; children had to be on maintenance medication for asthma, or had to have repeated subjective symptoms and a positive result in the exercise challenge test as an objective criterion. The exercise challenge test has been specific but not very sensitive for the diagnosis of asthma,\textsuperscript{18} and 10–15% falls in FEV\textsubscript{1} were used as cutoff points.\textsuperscript{18} We chose, in order to improve the sensitivity of the test, the 10% limit
for the present study. Our decision that all 29 children with inhaled anti-inflammatory medication for asthma be registered current asthmatics may have biased the results. However, 75% of them had either repeated episodes of wheezing, prolonged cough, or a positive result in the exercise challenge test. The exclusion of 7 children with no symptoms from the analyses did not change the main results. Likewise, sensitivity analyses, by moving them into the nonasthma group, gave similar main results as with the primary analyses.

The proportion of dropouts was 19% in the clinical study and only 11% in the questionnaire study. The baseline characteristics of the dropouts did not differ from the participants, except for maternal smoking in infancy, which was less common among participants than among dropouts. When the 8 children whose parents answered the structured questionnaire were included in the analyses, the main results did not change, except for the more evident effect of parental and maternal asthma. Therefore, we find our results representative for all 100 subjects hospitalized for wheezing in infancy.

The strengths of the present study were the long, prospective follow-up time from infancy until the median age of 12.3 years, careful data collection of infantile characteristics, viral diagnosis in over 80% of cases, and good attendance. The main shortcoming of the study was the absence of a control group. However, the prevalence of childhood asthma at ages 7–13 years has been carefully studied in our area, and in this population study, the criteria for asthma were comparable to the criteria applied in the present study. The prevalence of asthma at school age is 4.0–5.0% in our area. In the present study, the risk was about 5-fold after RSV-induced wheezing. The respective risk was rather similar, 6–8-fold after RSV bronchiolitis, compared with controls in the study of Sigurs et al. However, the asthma risk was more than 10-fold after rhinovirus-induced wheezing in the present study. Since the study group was highly selected, i.e., children hospitalized for wheezing in infancy, our results reflect only the outcome after the severe clinical form of bronchiolitis or early wheezing.

In conclusion, our study shows that asthma is common after early childhood wheezing in the teen years, which is a critical age for the persistence of asthma. Infants with early atopy and wheezing induced by viruses other than RSV carry the highest risk for chronic asthma. At this young age, atopy is often silent, with a later onset of clinical symptoms. Our result, that the presence of specific IgE antibodies to inhaled allergens in infancy predicted asthma in teenage years, confirms the validity of the algorithms applied in recent studies, including early sensitization to aeroallergens as a major risk factor for asthma. Thus, laboratory tests are indicated to reveal silent atopy in wheezing infants, at least in severe cases requiring hospitalization, and if clinical or laboratory findings of atopy are present, a follow-up, lasting until school age or even longer, should be considered.

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