Remission and Persistence of Asthma Followed From 7 to 19 Years of Age

WHAT’S KNOWN ON THIS SUBJECT: The natural history of asthma during adolescence is dynamic because both remission and relapse are common. Remission has consistently been associated with mild asthma and the absence of sensitization.

WHAT THIS STUDY ADDS: One in 5 children with asthma remitted from age 7 to 19. Remission was defined as no wheezing and no medication for ≥3 years and was inversely related to female gender, sensitization to furred animals, and asthma severity at baseline.

BACKGROUND AND OBJECTIVE: To date, a limited number of population-based studies have prospectively evaluated the remission of childhood asthma. This work was intended to study the remission and persistence of childhood asthma and related factors.

METHODS: In 1996, a questionnaire was distributed to the parents of all children aged 7 to 8 years in 3 municipalities in northern Sweden, and 3430 (97%) participated. After a validation study, 248 children were identified as having asthma; these children were reassessed annually until age 19 years when 205 (83%) remained. During the follow-up period lung function, bronchial challenge testing, and skin prick tests were performed. Remission was defined as no use of asthma medication and no wheeze during the past 12 months as reported at endpoint and in the 2 annual surveys preceding endpoint (ie, for ≥3 years).

RESULTS: At age 19 years, 21% were in remission, 38% had periodic asthma, and 41% persistent asthma. Remission was more common among boys. Sensitization to furred animals and a more severe asthma (asthma score ≥2) at age 7 to 8 years were both inversely associated with remission, odds ratio 0.14 (95% confidence interval 0.04–0.55) and 0.19 (0.07–0.54), respectively. Among children with these 2 characteristics, 82% had persistent asthma during adolescence. Asthma heredity, damp housing, rural living, and smoking were not associated with remission.

CONCLUSIONS: The probability of remission of childhood asthma from age 7- to 8-years to age 19 years was largely determined by sensitization status, particularly sensitization to animals, asthma severity, and female gender, factors all inversely related to remission. Pediatrics 2013;132:e435–e442

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KEY WORDS: adolescence, asthma, longitudinal, remission, sensitization

ABBREVIATIONS
CI—confidence interval
FEV1—forced expiratory volume in 1 second
ICS—inhaled glucocorticosteroids
IgE—immunoglobulin E
OR—odds ratio
SPT—skin prick test
VC—vital capacity

Dr Andersson carried out the analyses, interpreted the data, and drafted the manuscript; Drs Hedman, Bjerg, Forsberg, and Lundback interpreted the data and reviewed and revised the manuscript; Dr Römmark designed the study, collected and interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Asthma is a major public health challenge. From childhood to young adulthood, remission of asthma is substantial, with rates from 16% to 60% being reported. Remission among adults is considerably lower. The large variation in these reported findings are related to a lack of a uniform definition of remission as well as to differences in follow-up time, age composition, and disease severity in the study populations. Asthma cohorts recruited from hospital clinics are highly selective and may not reflect the general population because mild asthma is likely to be underrepresented. Few population-based studies have recently evaluated remission and factors related to remission of asthma prospectively among children. Although mild disease and absence of allergic sensitization have been associated with an increased probability of remission, the impact of heredity, gender, smoking, and sensitization to specific allergens on asthma remission remains uncertain. The clinical manifestations of diagnosed childhood asthma may change over time due to changes in diagnostic practices, risk factor patterns, and lifestyle, necessitating repeated monitoring of remission rates and predictive factors. Detailed longitudinal studies on asthma are informative because the natural history is highly dynamic, and relapse from remission into clinical disease is also common.

The study design. BHR, bronchial hyperreactivity.

METHODS

Study Population and Design
In 1996 an extended International Study of Asthma and Allergies in Childhood questionnaire was distributed to the parents of all children in the first and second grades (age 7–8 years old) in 3 municipalities in northern Sweden. The participation rate was 97% (n = 3431). The children in 2 of the 3 areas were also invited to skin prick testing (SPT), in which 88% participated (n = 2149). This survey was used as a basis for a longitudinal study of asthma and its associated conditions. In 1997, the reported physician-diagnosed asthma was validated. Structured interviews and clinical assessments were carried out by pediatricians in stratified samples and 248 (7.2%) of the children in the cohort were identified as currently having asthma at baseline. In the current study, these 248 children (58% boys) were reassessed by annual questionnaires until the study endpoint at age 19 years when 205 (83%) participants remained (58% boys Fig 1).

SPT for 10 common allergens was performed at age 7 to 8 years, at age 16 to 17 years, and at age 19 years. At baseline and endpoint, only children living in 2 of the areas were tested. A few children did not allow testing for all specific allergens. The SPT was performed according to European Academy of Allergology and Clinical Immunology standards, and a mean wheal diameter of ≥3 mm was considered positive. SPT results were validated in relation to specific immunoglobulin E (IgE). Total IgE was analyzed in serum by using Immuno CAP (Phadia, Uppsala, Sweden). Lung function was performed according to international guidelines by using a dry volume spirometer (Vicatess Mijnhardt, Odijk, The Netherlands) at the age of 16 to 17 years and at the study endpoint by using a Spirare flow-volume spirometer (Diagnostica, Oslo, Norway). The Swedish Berglund reference equation for lung function values was used. The forced expiratory volume in 1 second (FEV1)/vital capacity (VC) ratio was calculated by using the best of 3 slow and 3 forced vital capacity measurements.
and reversibility in % was calculated as 
(I(FeV1 post-bronchodilator – FeV1 pre-bronchodilator) / FeV1 pre-bronchodilator) \times 100. Methacholine bronchial challenge tests were carried out in the asthma cohort at age 16 to 17 years in a random sample of 54 (76% of invited) subjects (Fig 1). An automatic inhalation-synchronized dosimeter jet nebulizer (Spira Electro 2, Respiratory Care Centre, Hämeenlinna, Finland) was used25 and delivered methacholine chloride in cumulative doses of 35, 176, 529, 1586, 2996, and 5816 \mu g.

Definitions
Remission was defined as no use of asthma medication and no wheeze during the past 12 months as reported at endpoint and in the 2 annual surveys immediately preceding the endpoint (ie, for \( \geq 3 \) years). “Persistent asthma” was defined as having persistence of asthma (wheeze or medication) at endpoint and in at least 8 of the 9 preceding surveys. “Periodic asthma” was defined as neither remission nor persistent asthma.

The asthma status at age 19 was also evaluated by only using the endpoint survey data (results given in the Supplemental Information). “Inactive asthma” was defined as no use of asthma medication and no wheeze during the past 12 months as reported in the endpoint survey. “Active asthma” was defined as either use of asthma medication or wheeze during the past 12 months.

Asthma in the family: father and/or mother have asthma.19

Asthma medication: use of any kind of asthma medicine in the past 12 months.19

Current inhaled corticosteroids (ICS) use: use of ICS in the past 12 months.19

Asthma severity score: Using the baseline questionnaire, an arbitrary asthma severity score ranging from 0 to 5 points was created. The score included current wheeze, daily asthma medication, \( \geq 1 \) nights per week with sleep disturbance from asthma, \( \geq 1 \) episode of speech-limiting wheeze, and \( >12 \) episodes of wheezing, all during the past 12 months. Each item yielded 1 point.15,22

Physician-diagnosed rhinitis (eczema): “Has the child been diagnosed as having rhinitis (eczema) by a physician?”19

Self-reported traffic exposure: A heavily trafficked road or much-used bus stop within 200 m from home.19

Ever dampness at home: Signs of indoor moisture or molds where the child lived at any time during childhood.19

Statistical Analysis
The data were analyzed by using the Statistical Package for Social Science Software version 20 (SPSS Inc, Chicago, IL). The \( \chi^2 \) test and Fisher’s exact test were used for comparison of proportions where appropriate. When comparing distributions of continuous variables across groups, Student’s \( t \) test, analysis of variance, Mann-Whitney \( U \) test, and Kruskal-Wallis 1-way analysis of variance were used for normally and nonnormally distributed data, as appropriate. Risk estimates expressed as odds ratio (OR) for factors related to remission and periodic asthma, respectively, were determined by multinomial logistic regression analysis, using persistent asthma as a reference. The confidence interval (CI) was set to 95%, and \( P < .05 \) was considered statistically significant. Variables with \( P < .10 \) in the bivariate analyses were included in a multivariate model and backward stepwise multinomial regression was used for the second model. Factors related to inactive asthma were calculated by multiple logistic regression analysis.

RESULTS
The participants in the endpoint survey (\( n = 205 \)) had nearly consistent baseline characteristics as the initial asthma cohort (\( n = 248 \)). Of 205 subjects at age 19, 43 (21%) were in remission, 78 (38%) had periodic asthma, and 84 (41%) children had persistent asthma. Among boys, 31 of 118 were in remission versus 12 of 87 girls, \( P = .03 \) (Table 1).

Determinants
Children in remission and children with periodic asthma were similar regarding asthma severity, rhinitis, and eczema. A lower proportion had a severity score \( \geq 2 \), physician-diagnosed rhinitis, and eczema at age 7 to 8 compared with subjects with persistent asthma. The proportion using ICS at age 7 to 8 years was lowest among subjects in remission and highest among subjects with persistent asthma. Remission was not associated with damp housing, rural living, or heredity for asthma. A larger proportion of children in remission and with periodic asthma had a mother who smoked during pregnancy compared with children with persistent asthma (Table 1).

Subjects with persistent asthma at age 19 years had the highest proportions of positive SPT to cat, horse, dog, and birch at age 7 to 8 years. Few children had a positive SPT to molds, but being sensitized to any mold was significantly related to persistent asthma (Table 2).

Clinical parameters measured at age 16 to 17 years and at endpoint are shown in Table 3. At age 16 to 17 years, subjects in remission and with periodic asthma had significantly less airway obstruction, (FeV1/VC 87% and 88%, respectively) compared with subjects with persistent asthma (FeV1/VC 83%), \( P < .001 \). Similarly, subjects in remission and with periodic asthma had significantly higher FeV1 (percent of predicted) and higher PD20 to methacholine compared with subjects with persistent asthma. Among subjects in
remission, 65% had a positive SPT at age 19 compared with 90% among subjects with persistent asthma, \( P = .005 \).

**Multivariate Analysis**

In the multinomial analysis, with persistent asthma as reference, remission was predicted by male gender, OR 2.66 (95% CI 1.00–7.03) and was inversely related to sensitization to animals, OR 0.14 (95% CI 0.04–0.55) and asthma score ≥2, OR 0.19 (95% CI 0.07–0.54). Periodic asthma was inversely related to sensitization to animals, eczema, and asthma score ≥2 (Table 4).

**Prognosis**

The risk of having persistent asthma, versus periodic asthma or remission, at age 19 years differed significantly by sensitization profile and asthma severity at age 7 to 8 years. Among children with a positive SPT to furred animals and an asthma severity score of ≥2, 82% had persistent asthma during the study period (Fig 2).

**Supplemental Material**

At age 19 years, 76 of the 205 participants (37%) neither had wheeze nor had used any asthma medication during the past 12 months (ie, inactive asthma). Whereas male gender significantly predicted inactive asthma, none of the surveyed environmental factors were associated with inactive asthma, although maternal smoking in pregnancy was borderline significant, \( P = .068 \) (Supplemental Information Table 5). In general, the evaluation of possible determinants for inactive asthma yielded similar results as the analysis of remission and periodic asthma (Supplemental Information Tables 6 and 7).

In a multivariate regression model, male gender, OR 2.36 (95% CI 1.11–5.02), predicted inactive asthma at age 19 years, whereas a positive SPT to furred animals and a higher asthma severity score at baseline were negatively associated, OR 0.34 (95% CI 0.16–0.72) and OR 0.28 (95% CI 0.12–0.64), respectively.

**DISCUSSION**

We have studied a population-based cohort of children with asthma from the age of 7- to 8-years to 19 years using annual follow-ups. Remission in the late teen years was common and related to mild disease, male gender, and absence of atopic indices, especially sensitization to furred animals at age 7 to 8 years.
The prognosis of childhood asthma by sensitization to animals and asthma severity at age 7 to 8 years. P for distribution across groups <.001. Severity+, asthma severity score ≥2, SPT+, Positive skin prick testing to any furred animal, Severity−, asthma severity score <2, SPT−, Negative skin prick testing to furred animals.

There is no gold standard for defining asthma remission. However, absence of both symptoms and asthma medication is commonly used, sometimes labeled “clinical remission.”9,26,27 However, indicators of inflammation, airway obstruction, and airway remodeling are often persistent among children reported to be in clinical remission from asthma and may explain the risk of relapse.28,29 In the current study, we used data from all annual surveys to define persistent asthma, periodic asthma, and remission. The objective data collected (lung function, bronchial hyperreactivity, and total IgE) support the validity of this questionnaire-based classification. In the supplemental material, we also present analysis using baseline and endpoint data only, which resulted in a doubling of the proportion of subjects that no longer had active asthma. However, the patterns in predictors of remittent and inactive asthma were analogous.

Childhood asthma frequently remits but may subsequently relapse.5,30,31 By using annual reports, we were able to identify a group of children with periodic asthma, that is, asthma coming and going during the follow-up. This group differed in risk-factor pattern compared with children in remission at endpoint, which further illustrates
the benefit of repeated surveys in longitudinal studies. Moreover, our results clearly point to the importance of clinical follow-ups of children who may temporarily be free from symptoms. Identification of factors associated with the persistence and remission of childhood asthma serves not only as a disease prognostication but also for defining intervention and prevention targets. Previous studies have provided some valuable information on this matter. Sears et al followed an unselected birth cohort in New Zealand until age 26 years. Sensitization and female gender were identified as important predictors of persistent asthma, as reported in our study. Female gender has also been identified as a factor related to childhood asthma persistence in other studies. Togetherv with an increased incidence among girls, the higher remission rate among boys contributes to the switch in boy-to-girl asthma prevalence ratio, from male predominance in early childhood to asthma being more common among girls and women later in life. The underlying mechanisms have yet to be fully elucidated. Allergic sensitization to common inhalant allergens, allergic rhinitis, atopic eczema, and level of total serum IgE have all been linked to persistence of childhood asthma. We found a consistently stronger inverse association between remission and allergic sensitization to furred animals compared with pollen. Furred animal allergens are potent and also present during all seasons; these allergens may also travel to school and other indoor environments on the clothes of pet owners and horseback riders, which might explain the larger impact. Mites are not present in the study area because they are inhibited by the cold and dry climate. Therefore, furred animals and pollen dominate the sensitization profile. Thus our study area is suitable for analyzing the effects of sensitization to allergens other than mites on asthma remission. Today desensitization to a specific animal allergen is a well-established approach for treating severe allergic disease. Whether desensitization is a possible target for preventing mild allergic asthma has yet not been established. The presence of allergic comorbidities such as allergic rhinitis and eczema is associated with persistence of asthma. However, whereas aggressive treatment of allergic rhinitis may also alleviate symptoms of asthma, no studies have targeted whether this may also affect asthma remission probability. We identified a lower asthma severity as a strong predictor of remission from childhood to late adolescence, in accordance with previous studies. We used a cutoff of ≥2 in our asthma scoring to separate mild from more severe asthma. However, it is important to note that our cutoff does not necessarily correspond to the clinical definition of severe asthma. We also revealed a strong association between ICS use and persistent asthma; because use of ICS is related to higher asthma severity, this result was not surprising. Although ICS has been suggested as a causal agent of remission, there is no convincing evidence for this. High BMI has been associated with both prevalent and incident asthma, increased asthma severity, and decreased asthma control. Although in our study, BMI was not an important determinant of remission, those in remission at age 19 years had a lower BMI at age 16 to 17 compared with those with persistent or periodic asthma. Studies analyzing the impact of heredity on asthma prognosis are not consistent, although an increased risk of persistence has been reported. In our study, we found no association between a family history of asthma and remission. The reason for the discrepancy between studies could be attributed to methodologic differences in defining heredity but could also be confounded by environmental factors shared by family members.

We did not find any of the surveyed environmental factors to be of importance for asthma remission within this age range. Living in damp housing has been associated with asthma in childhood, especially in early school age. The relation with asthma remission is less studied, and we did not find any significant association.

The effects of maternal smoking must be interpreted carefully because it may be susceptible to bias. It may be suggestive that parents of children with severe asthma never start smoking, quit, or smoke less, explaining our results in which fewer parents of children with persistent asthma smoked at baseline. Personal smoking has been identified as a predictor of persistence and relapse, but the results are not unequivocal. In our study, the follow-up period was limited to 19 years of age, and few of the participants were long-term smokers, therefore we were not able to study the effect of smoking. However, because both passive and active smoking is related to asthma among children and teenagers, smoking prevention is important.

An increased risk of asthma has been reported for children of mothers who smoked during pregnancy. In our study, persistent asthma was less common among children of mothers who smoked during pregnancy. A possible explanation is that maternal smoking may cause nonallergic asthma which is more likely to remit compared with allergic asthma.

The strengths of the current study include the longitudinal study design with annual follow-ups, which facilitates causal inference and minimizes recall bias for current conditions. Furthermore, the study is based on a validated and
to 17 years predicted asthma status 2 years later and confirmed the classification of our outcome variables. The limitations are mainly related to an incomplete coverage at baseline concerning objective data (i.e., lung function with bronchial challenge, reversibility testing, and lack of data on asthma medication dosage, which was not included in the questionnaire).

CONCLUSIONS
Remission of childhood asthma was common in late adolescence. Special emphasis should be directed toward the clinical management and follow-up of children with sensitization to furred animals, more severe asthma, and asthma among girls because these factors are associated with persistence.

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