

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Remission and Persistence of Asthma Followed From 7 to 19 Years of Age
Martin Andersson, Linnea Hedman, Anders Bjerg, Bertil Forsberg, Bo Lundbäck and
Eva Rönmark

Pediatrics 2013;132:e435; originally published online July 29, 2013;
DOI: 10.1542/peds.2013-0741

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/132/2/e435.full.html>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



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

AUTHORS: Martin Andersson, MD,^{a,b} Linnea Hedman, PhD,^a Anders Bjerg, MD, PhD,^{a,c} Bertil Forsberg, PhD,^b Bo Lundbäck, MD, PhD,^{a,c} and Eva Rönmark, PhD^{a,b}

^aThe OLIN Studies, Norrbotten County Council, Luleå, Sweden; ^bOccupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; and ^cKrefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

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 Lundbäck interpreted the data and reviewed and revised the manuscript; Dr Rönmark designed the study, collected and interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0741

doi:10.1542/peds.2013-0741

Accepted for publication May 23, 2013

Address correspondence to Martin Andersson, MD, The OLIN Studies, Norrbotten County Council, Robertsviksgatan 9, S-971 89, Luleå, Sweden. E-mail: martin.andersson@envmed.umu.se

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Swedish Heart-Lung Foundation, the Swedish Foundation for Health Care Science and Allergy Research (Vårdal), the Swedish Asthma-Allergy Foundation, Visare Norr, Umeå University, Västerbotten County Council, Norrbotten County Council, and the Swedish Research Council. Additional funding was provided by GlaxoSmithKline World Wide Epidemiology, ALK-Abello (Horsholm, Denmark) and ThermoFisher.



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.

abstract



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

Asthma is a major public health challenge.^{1–3} From childhood to young adulthood, remission of asthma is substantial, with rates from 16% to 60% being reported.^{4–8} Remission among adults is considerably lower.^{9,10} The large variation in these reported findings are related to a lack of a uniform definition of remission¹¹ 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.^{5,6,8,12} Although mild disease and absence of allergic sensitization have been associated with an increased probability of remission,^{5,9,12,13} the impact of heredity, gender, smoking, and sensitization to specific allergens on asthma remission remains uncertain.¹⁴ The clinical manifestations of diagnosed childhood asthma may change over time^{1,7,15} 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.^{5,16}

The Obstructive Lung Disease in Northern Sweden studies have reported on the prevalence and incidence of asthma, allergic diseases and sensitization in children, as well as associated factors such as damp housing, environmental tobacco smoke, and traffic-related air pollution since 1996.^{12,17–21} In the current study, a well-defined cohort of asthmatic children derived from the first pediatric Obstructive Lung Disease in Northern Sweden Studies cohort was

followed annually from age 7-to 8-years to age 19 years. The aim was to study the remission and persistence of asthma, as well as to determine any correlated factors.

METHODS

Study Population and Design

In 1996 an extended International Study of Asthma and Allergies in Childhood questionnaire²² 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% ($n = 3431$).¹⁷ The children in 2 of the 3 areas were also invited to skin prick testing (SPT), in which 88% participated ($n = 2149$).¹⁹ 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.¹⁷ 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).

The study was approved by the regional ethical review board at Umeå University.

Measurements

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,²³ and a mean wheal diameter of ≥ 3 mm was considered positive. SPT results were validated in relation to specific immunoglobulin E (IgE).¹⁹ 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 (Vicat 5, 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.²⁴ 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,

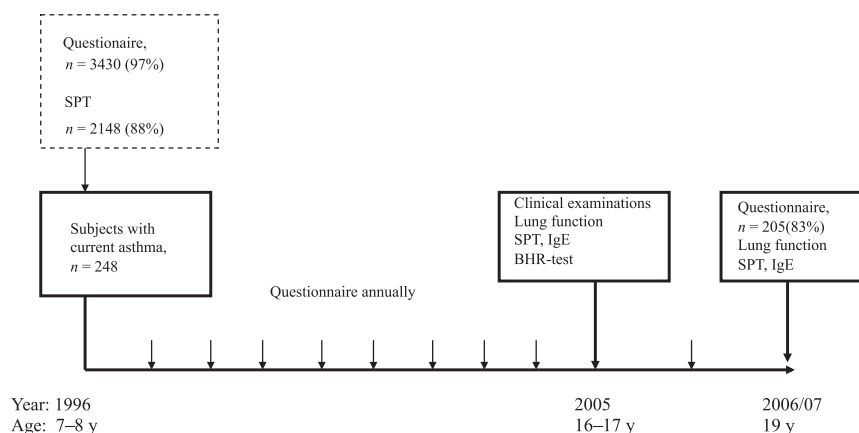


FIGURE 1

The study design. BHR, bronchial hyperreactivity.

and reversibility in % was calculated as $[(FEV_1 \text{ post-bronchodilator} - FEV_1 \text{ pre-bronchodilator}) / FEV_1 \text{ pre-bronchodilator}] \times 100$. 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 μg .

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 ≥ 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, ≥ 1 nights per week with sleep disturbance from asthma, ≥ 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 χ^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 ≥ 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, (FEV_1/VC 87% and 88%, respectively) compared with subjects with persistent asthma (FEV_1/VC 83%), $P < .001$. Similarly, subjects in remission and with periodic asthma had significantly higher FEV_1 (percent of predicted) and higher PD_{20} to methacholine compared with subjects with persistent asthma. Among subjects in

TABLE 1 Prevalence (%) of Baseline Characteristics at Age 7 to 8 Years Among the Entire Cohort, Among All Participants at Endpoint (19 Years), and by Persistent, Periodic, and Remitted Asthma at Age 19 Years

	Entire Cohort (N = 248)	Participants at Endpoint				P ^a
		All (n = 205)	Persistent Asthma (n = 84)	Periodic Asthma (n = 78)	Remission (n = 43)	
Clinical characteristics						
Positive SPT ^b	51% (87/172)	53% (78/146)	77% (44/57)	39% (21/54)	37% (13/35)	<.001
Physician-diagnosed rhinitis	32% (80/248)	35% (71/205)	49% (41/84)	26% (20/78)	23% (10/43)	.002
Physician-diagnosed eczema	37% (91/248)	35% (71/205)	50% (42/84)	24% (19/78)	23% (10/43)	.001
Asthma score ≥2 of 5	35% (87/248)	33% (67/205)	49% (41/84)	22% (17/78)	21% (9/43)	<.001
Current ICS use	49% (122/248)	50% (102/205)	68% (57/84)	44% (34/78)	26% (11/43)	<.001
Demographic and environmental factors						
Male gender	58% (143/248)	58% (118/205)	55% (46/84)	53% (41/78)	72% (31/43)	.091
Asthma in the family	40% (100/248)	40% (82/205)	44% (37/84)	36% (28/78)	40% (17/43)	.570
Rural living	32% (75/233)	29% (57/194)	32% (25/79)	29% (22/75)	25% (10/40)	.754
Mother smokes	39% (94/239)	37% (72/196)	28% (22/79)	45% (34/75)	38% (16/42)	.078
Mother smoked during pregnancy	30% (74/245)	28% (57/203)	18% (15/82)	33% (26/78)	37% (16/43)	.035
Self-reported traffic exposure	32% (77/241)	30% (60/198)	24% (19/80)	36% (27/76)	33% (14/42)	.248
Ever dampness at home	30% (71/240)	26% (52/199)	23% (18/80)	25% (19/76)	35% (15/43)	.316
Living in an apartment	28% (63/229)	23% (45/192)	17% (13/79)	34% (24/71)	19% (8/42)	.033

^a P value for χ^2 test of distribution across groups.

^b Children in only 2 of the study areas were offered SPT.

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.

TABLE 2 Prevalence (%) of Allergic Sensitization at Age 7 to 8 Years by Persistent, Periodic, and Remitted Asthma at Age 19 Years

	Persistent Asthma (n = 57)	Periodic Asthma (n = 54)	Remission (n = 35)	P ^a
Any positive SPT pollen	46% (25/55)	20% (11/54)	29% (10/35)	.017
Positive SPT birch	38% (21/55)	19% (10/54)	20% (7/35)	.041
Positive SPT timothy	23% (12/53)	11% (6/54)	17% (6/35)	.282
Positive SPT mugwort	6% (3/52)	2% (1/53)	3% (1/34)	.550
Any positive SPT animals	75% (41/55)	35% (19/54)	29% (10/35)	<.001
Positive SPT cat	67% (37/55)	32% (17/54)	26% (9/35)	<.001
Positive SPT horse	44% (24/54)	24% (13/54)	14% (5/35)	.005
Positive SPT dog	53% (29/55)	26% (14/54)	18% (6/34)	.001
Any positive SPT molds	19% (10/54)	2% (1/53)	6% (2/33)	.009
Any positive SPT mites	8% (4/53)	0% (0/53)	6% (2/33)	.137

^a P value for χ^2 test of distribution across groups.

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.

TABLE 3 Clinical Characteristics at Age 16 to 17 Years and at the Study Endpoint at 19 Years by Persistent, Periodic, and Remitted Asthma

	Persistent Asthma (n = 84)	Periodic Asthma (n = 78)	Remission (n = 43)	P ^a
Clinical characteristics at 16–17 y				
BMI (mean, kg/m ²)	23.3 (n = 78)	22.7 (n = 66)	21.4 (n = 33)	.052
Total IgE (median, kIU/L)	157 (n = 75)	87 (n = 65)	62 (n = 32)	.005
Positive SPT	87% (67/77)	61% (40/66)	55% (18/33)	<.001
FEV ₁ %pred (mean)	84% (n = 78)	88% (n = 67)	87% (n = 33)	.037
FEV ₁ /VC (mean)	82% (n = 78)	86% (n = 67)	87% (n = 33)	.002
Reversibility (mean)	7% (n = 77)	4% (n = 64)	4% (n = 33)	.030
Methacholine PD ₂₀ (median, mg)	0.2 (n = 24)	1.0 (n = 13)	3.4 (n = 13)	<.001
Clinical characteristics at 19 y				
BMI (mean, kg/m ²)	23.7 (n = 76)	23.7 (n = 73)	22.9 (n = 38)	.734
Positive SPT ^b	90% (51/57)	66% (33/50)	65% (22/34)	.005
FEV ₁ %pred (mean)	88% (n = 55)	91% (n = 49)	90% (n = 35)	.279
FEV ₁ /VC (mean)	81% (n = 55)	85% (n = 49)	85% (n = 35)	.007

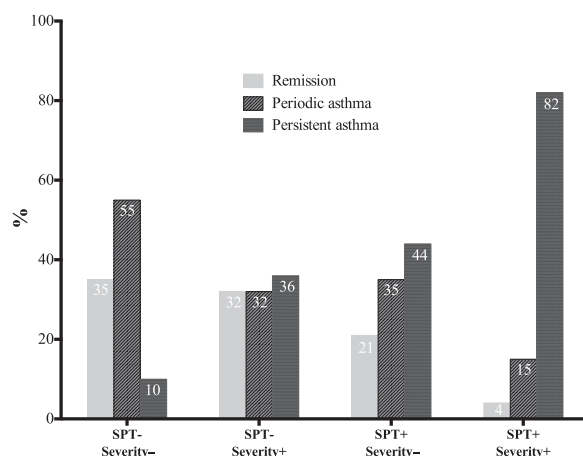
^a P value for χ^2 test, analysis of variance or Kruskal-Wallis 1-way analysis of variance test, as appropriate, of distribution across groups.

^b Children in only 2 of the study areas were offered SPT.

TABLE 4 Factors Related to Remission and Periodic Asthma, Respectively, Analyzed by Multinomial Logistic Regression With Persistent Asthma as Reference

Independent Baseline Variables	Remission		Periodic Asthma	
	OR (95%CI)	OR (95%CI) ^a	OR (95%CI)	OR (95%CI) ^a
Male gender	2.66 (1.00–7.03)	2.53 (1.04–6.15)	1.01 (0.46–2.25)	
Positive SPT to any animal	0.14 (0.04–0.55)	0.17 (0.06–0.48)	0.21 (0.07–0.66)	0.22 (0.09–0.58)
Positive SPT to any pollen	1.84 (0.41–8.37)		1.29 (0.35–4.80)	
Positive SPT to any mold	1.44 (0.16–12.9)		0.64 (0.06–7.40)	
Physician-diagnosed rhinitis	0.41 (0.14–1.20)		0.71 (0.29–1.72)	
Physician-diagnosed eczema	0.51 (0.19–1.42)		0.30 (0.12–0.73)	0.28 (0.12–0.64)
Asthma score $\geq 2/5$	0.19 (0.07–0.54)	0.22 (0.08–0.57)	0.24 (0.10–0.57)	0.23 (0.10–0.52)
Living in an apartment	1.05 (0.32–3.50)		3.12 (1.15–8.44)	3.86 (1.51–9.86)
Mother smokes	0.75 (0.22–2.54)		1.84 (0.68–4.97)	
Mother smoked during pregnancy	1.87 (0.52–6.80)		1.08 (0.36–3.26)	

^a Results from the stepwise backward multinomial regression model.

**FIGURE 2**

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.

The remission proportion in the current study was 21%, which is similar to that reported in other studies.^{4–8} However, remission frequency is determined by several study factors including its definition, time of follow-up, and age of the subjects. Naturally, differences in follow-up spans affect the remission frequency as a longer follow-up time provides a larger window for both remission and relapse. Another important factor is the age of the participants. However, the proportion of sensitized children increases over time, which may confound an association of age and asthma remission.¹²

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.⁵ 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.^{4,32} Together with an increased incidence among girls,³³ 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.³²

Allergic sensitization to common inhalant allergens,^{5,12,13} allergic rhinitis, atopic eczema,⁸ and level of total serum IgE³⁴ 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,³⁵ 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.¹⁸ 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.⁸ However, whereas aggressive treatment of allergic rhinitis may also alleviate symptoms of asthma,³⁶ 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.^{26,34} 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.¹⁵ 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.²⁷

High BMI has been associated with both prevalent and incident asthma,³⁷ increased asthma severity, and decreased asthma control.³⁸ 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.^{8,39} 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.^{12,40} 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 persistence⁵ and relapse,¹⁶ but the results are not unequivocal.^{8,26,30} 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,⁴¹ smoking prevention is important.

An increased risk of asthma has been reported for children of mothers who smoked during pregnancy.⁴² 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 asthma¹⁷ 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

internationally used questionnaire, and the asthma cohort was identified and validated through structured interviews as well as clinical examinations by experienced pediatricians.¹⁷ Atopy was registered by objective SPT, which has been validated against specific IgE with a high level of agreement.¹⁹ The participation rate was high each year, and those responding at the study endpoint had baseline characteristics that corresponded with the whole group at the study starting point, eliminating selection bias and ensuring representativeness. Bronchial hyperreactivity at age 16

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 (ie, 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.

ACKNOWLEDGMENTS

We thank the study participants and their parents and the Obstructive Lung Disease in Northern Sweden Studies research staff in Luleå for their efforts in collecting the data.

REFERENCES

1. Asher MI, Montefort S, Björkstén B, et al; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733–743.
2. Bjerg A, Sandström T, Lundbäck B, Rönmark E. Time trends in asthma and wheeze in Swedish children 1996–2006: prevalence and risk factors by sex. *Allergy*. 2010;65(1):48–55.
3. de Marco R, Cappa V, Accordini S, et al; GEIRD Study Group. Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. *Eur Respir J*. 2012;39(4):883–892.
4. Roorda RJ, Gerritsen J, van Aalderen WM, et al. Follow-up of asthma from childhood to adulthood: influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J Allergy Clin Immunol*. 1994;93(3):575–584.
5. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med*. 2003;349(15):1414–1422.
6. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. *J Allergy Clin Immunol*. 2002;109(2):189–194.
7. Sekerel BE, Civelek E, Karabulut E, Yildirim S, Tuncer A, Adalioglu G. Are risk factors of childhood asthma predicting disease persistence in early adulthood different in the developing world? *Allergy*. 2006;61(7):869–877.
8. Burgess JA, Matheson MC, Gurrin LC, et al. Factors influencing asthma remission: a longitudinal study from childhood to middle age. *Thorax*. 2011;66(6):508–513.
9. Rönmark E, Lindberg A, Watson L, Lundbäck B. Outcome and severity of adult onset asthma—report from the obstructive lung disease in northern Sweden studies (OLIN). *Respir Med*. 2007;101(11):2370–2377.
10. De Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G; Italian Study on Asthma in Young Adults study group. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol*. 2002;110(2):228–235.
11. Panhuysen CI, Vonk JM, Koeter GH, et al. Adult patients may outgrow their asthma: a 25-year follow-up study. *Am J Respir Crit Care Med*. 1997;155(4):1267–1272.
12. Bjerg-Bäcklund A, Perzanowski MS, Platts-Mills T, Sandström T, Lundbäck B, Rönmark E. Asthma during the primary school ages—prevalence, remission and the impact of allergic sensitization [published correction appears in *Allergy*. 2007;62(8):968]. *Allergy*. 2006;61(5):549–555.
13. Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. *Eur Respir J*. 2004;23(1):66–70.
14. Vonk JM, Boezen HM. Predicting adult asthma in childhood. *Curr Opin Pulm Med*. 2006;12(1):42–47.
15. Andersson M, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. The clinical expression of asthma in schoolchildren has changed between 1996 and 2006. *Pediatr Allergy Immunol*. 2010;21(5):859–866.
16. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*. 1996;312(7040):1195–1199.
17. Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Different pattern of risk factors for atopic and nonatopic asthma among children—report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy*. 1999;54(9):926–935.
18. Rönmark E, Perzanowski M, Platts-Mills T, Lundbäck B; Obstructive Lung Disease in Northern Sweden Study Group. Four-year incidence of allergic sensitization among schoolchildren in a community where allergy to cat and dog dominates sensitization: report from the Obstructive Lung Disease in Northern Sweden Study Group. *J Allergy Clin Immunol*. 2003;112(4):747–754.
19. Rönmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundbäck B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol*. 2009;124(2):357–363. 63.e1–15.
20. Andersson M, Modig L, Hedman L, Forsberg B, Rönmark E. Heavy vehicle traffic is related to wheeze among schoolchildren: a population-based study in an area with low traffic flows. *Environ Health*. 2011;10:91.
21. Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Incidence and remission of asthma in schoolchildren: report from the obstructive lung disease in northern Sweden studies. *Pediatrics*. 2001;107(3). Available at:

www.pediatrics.org/cgi/content/full/107/3/e37

22. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483–491
23. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Skin tests used in type I allergy testing position paper. *Allergy*. 1989;44(suppl 10):1–59
24. Berglund E, Birath G, Bjure J, et al. Spirometric studies in normal subjects. I. Forced expirograms in subjects between 7 and 70 years of age. *Acta Med Scand*. 1963;173:185–192
25. Nieminen MM. Unimodal distribution of bronchial hyperresponsiveness to methacholine in asthmatic patients. *Chest*. 1992;102(5):1537–1543
26. Vonk JM, Postma DS, Boezen HM, et al. Childhood factors associated with asthma remission after 30 year follow up. *Thorax*. 2004;59(11):925–929
27. Spahn JD, Covar R. Clinical assessment of asthma progression in children and adults. *J Allergy Clin Immunol*. 2008;121(3):548–557, quiz 558–559
28. Warke TJ, Fitch PS, Brown V, et al. Outgrown asthma does not mean no airways inflammation. *Eur Respir J*. 2002;19(2):284–287
29. van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. *Am J Respir Crit Care Med*. 2001;164(11):2107–2113
30. Taylor DR, Cowan JO, Greene JM, Willan AR, Sears MR. Asthma in remission: can relapse in early adulthood be predicted at 18 years of age? *Chest*. 2005;127(3):845–850
31. Covar RA, Strunk R, Zeiger RS, Wilson LA, Liu AH, Weiss S, et al. Predictors of remitting, periodic, and persistent childhood asthma. *J Allergy Clin Immunol*. 2010;125(2):359–66 e3
32. Vink NM, Postma DS, Schouten JP, Rosmalen JG, Boezen HM. Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. *J Allergy Clin Immunol*. 2010;126(3):498–504.e1–6
33. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax*. 1992;47(7):537–542
34. Limb SL, Brown KC, Wood RA, et al. Adult asthma severity in individuals with a history of childhood asthma. *J Allergy Clin Immunol*. 2005;115(1):61–66
35. Karlsson AS, Andersson B, Renström A, Svedmyr J, Larsson K, Borres MP. Airborne cat allergen reduction in classrooms that use special school clothing or ban pet ownership. *J Allergy Clin Immunol*. 2004;113(6):1172–1177
36. Bousquet J, Khaltaev N, Cruz AA, et al; World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8–160
37. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: The hunt study. *Eur Respir J*. 2013;41(2):323–329
38. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest*. 2008;134(2):317–323
39. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *Eur Respir J*. 2003;22(5):767–771
40. Pekkanen J, Hyvärinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A. Moisture damage and childhood asthma: a population-based incident case-control study. *Eur Respir J*. 2007;29(3):509–515
41. Hedman L, Bjerg A, Sundberg S, Forsberg B, Rönmark E. Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. *Thorax*. 2011;66(1):20–25
42. Bjerg A, Hedman L, Perzanowski M, Lundbäck B, Rönmark E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics*. 2011;127(4). Available at: www.pediatrics.org/cgi/content/full/127/4/e905

Remission and Persistence of Asthma Followed From 7 to 19 Years of Age
Martin Andersson, Linnea Hedman, Anders Bjerg, Bertil Forsberg, Bo Lundbäck and
Eva Rönmark

Pediatrics 2013;132:e435; originally published online July 29, 2013;

DOI: 10.1542/peds.2013-0741

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/132/2/e435.full.html
Supplementary Material	Supplementary material can be found at: http://pediatrics.aappublications.org/content/suppl/2013/07/23/peds.2013-0741.DCSupplemental.html
References	This article cites 38 articles, 14 of which can be accessed free at: http://pediatrics.aappublications.org/content/132/2/e435.full.html#ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

