

Persistence of Asthma Symptoms during Adolescence

Role of Obesity and Age at the Onset of Puberty

Stefano Guerra, Anne L. Wright, Wayne J. Morgan, Duane L. Sherrill, Catharine J. Holberg, and Fernando D. Martinez

Arizona Respiratory Center, University of Arizona, College of Medicine, Tucson, Arizona

Little is known about rates and predictors of remission of childhood asthma after the onset of puberty. We used data collected at ages 6, 8, 11, 13, and 16 years from the Tucson Children's Respiratory Study, a population-based birth cohort. The onset of puberty was defined as the age of appearance of the first pubertal signs as reported by parents. Information on wheezing both before and after onset of puberty (mean $\pm$ SD follow-up from onset of puberty, 4.2 ± 1 year) was available for 781 children. Of these, 166 had asthma (either frequent wheezing or a physician-confirmed diagnosis plus any wheezing) in at least one survey before puberty. In this group, 58% of the children (97 of 166) reported the presence of wheezing after the onset of puberty (unremitting asthma). In contrast, only 30% (39 of 131) of the children with infrequent wheezing before puberty experienced wheezing episodes after the onset of puberty (unremitting wheezing). In addition to frequent wheezing before puberty, obesity, early onset of puberty, active sinusitis, and skin test sensitization were significant and independent predictors of unremitting asthma after the onset of puberty. Our findings from a population-based longitudinal cohort challenge the commonly held view that asthma usually remits during adolescence.

Keywords: asthma; wheezing; obesity; puberty

Children with asthma are at an increased risk of experiencing asthma-related respiratory symptoms in adult life (1–4) and possibly of developing long-term nonreversible airway obstruction (5). It has been also known for some time that adults with chronic obstructive pulmonary disease are more likely to recall respiratory troubles during childhood than those without such illnesses (6).

Cohort studies of children followed longitudinally as they enter adulthood can provide important information on the natural history of asthma and on the risk factors affecting the persistence of the disease into adult life. This is a matter of particular interest, as it is plausible that the persistence of asthma symptoms may be more frequently associated with long-term sequelae on lung function than remitting or intermittent asthma.

Adolescence is characterized by rapid hormonal, physical, and behavioral changes, all of which may affect the natural course of asthma. It has been long accepted that many children with asthma outgrow the disease after the onset of puberty. However, this impression is based on anecdotal clinical experience rather than unbiased epidemiologic data, and to date, the proportion of children with asthma experiencing a remission of the disease after the onset of puberty and the factors affecting the

outcome remain unknown (7, 8). Only longitudinal population-based cohort studies may provide unbiased answers to these questions.

To date, only a few population-based cohort studies have investigated the factors associated with the outcome of childhood asthma in adolescence (9–12); however, limited data have been presented relating asthma remission specifically to puberty. To study such an outcome, longitudinal cohorts of children need to be followed at least at two to three yearly intervals to identify reliably the onset of puberty, which can occur within a relatively wide range of ages. The longitudinal birth cohort of the Tucson Children's Respiratory Study has been followed consistently with frequent follow-up surveys, and it is now approaching its third decade. We used data from this cohort up to age 16 to study the factors influencing persistence and remission of childhood asthma after the onset of puberty. Some of the results of this study have been previously reported in the form of an abstract (13).

METHODS

Study Population and Design

The children included in this study are a subset from the birth cohort enrolled in the Tucson Children's Respiratory Study between May 1980 and October 1984. Detailed information on the design and enrollment process of this longitudinal study has been published previously (14). The parents of the 1,246 enrolled children completed an initial questionnaire on parental history of respiratory diseases and smoking habits and, subsequently, a series of questionnaires regarding their child's health status at different ages: YR2 survey (mean age $\pm$ SD, 1.62 ± 0.3 years), YR3 (2.92 ± 0.5 years), YR6 (6.27 ± 0.9 years), YR8 (8.62 ± 0.7 years), YR11 (10.90 ± 0.7 years), YR13 (13.47 ± 0.6 years), and YR16 (16.61 ± 0.6 years).

Questions on whether and when puberty started were included in the YR13 and YR16 questionnaires. Parents completing these questionnaires were provided with specific examples of signs identifying the onset of puberty: "pubic and/or underarm hair, breast development or menstruation in girls, voice changes in boys." The prepubertal period was defined as that between the YR6 survey and the reported onset of puberty. Outcomes during adolescence were studied in the follow-up period after the onset of puberty and up to the YR16 survey.

Questions on the presence and frequency of wheezing episodes during the previous year were asked in each of the surveys. Children reporting no wheezing either in the prepubertal period or after the onset of puberty were included in the "no wheezing" group. Children reporting wheezing after the onset of puberty but not in the prepubertal period were included in the "incident wheezing" group. Children reporting episodes of wheezing in the prepubertal period were divided in two groups: "infrequent wheezing" and "asthma." The infrequent wheezing group included subjects experiencing three or less wheezing episodes during the previous year in at least one survey and never reporting a physician-confirmed diagnosis of asthma. The asthma group included children reporting the presence of frequent wheezing (> 3 episodes during the previous year) in at least one survey or a physician-confirmed diagnosis of asthma. Based on the symptom experience in adolescence, the infrequent wheezing and asthma groups were then further classified as "unremitting" if any wheezing episodes were reported in at least one survey after the onset of puberty and "remitting" if they were not reported.

(Received in original form September 3, 2003; accepted in final form March 12, 2004)

Supported in part by National Heart, Lung, and Blood Institute grants HL 56177 and HL 14136.

Correspondence and requests for reprints should be addressed to Fernando D. Martinez, M.D., Arizona Respiratory Center, University of Arizona, 1501 North Campbell Avenue, P.O. Box 245030, Tucson, AZ 85724–5030. E-mail: fernando@resp-sci.arizona.edu

Am J Respir Crit Care Med Vol 170, pp 78–85, 2004

Originally Published in Press as DOI: 10.1164/rccm.200309-1224OC on March 17, 2004
Internet address: www.atsjournals.org

Based on the proportion of surveys in the prepubertal period in which the subjects reported wheezing episodes during the previous year, three mutually exclusive categories were created: “episodic” (less than 50% of the surveys), “recurrent” (50% or more and less than 100%), and “continuous” (100%) wheezing. These categories were created to describe prepubertal wheezing severity as a predictor of outcome after puberty.

Table 1 gives information on the definition and time of assessment of some of the risk factors included in our analyses and provides references (15–17) for a more detailed description of them.

Statistical Analyses

Statistical comparisons were performed across the five groups of no wheezing, remitting wheezing, unremitting wheezing, remitting asthma, and unremitting asthma (one-way analysis of variance plus Duncan multiple range test for continuous variables, and χ^2 tests for proportions) to detect overall differences between subjects with no wheezing, infrequent wheezing, and asthma in the prepubertal period. In these statistical comparisons, no trend across the groups was tested. In addition, statistical comparisons were specifically performed between remitting and unremitting wheezing and between remitting and unremitting asthma groups to identify risk factors associated with the persistence of asthma symptoms after the onset of puberty. Student's *t* test was used for continuous variables and the χ^2 test for proportions. The effects of categorical variables on the persistence of asthma symptoms after the onset of puberty were also expressed as relative risks (RRs). In those analyses, risk factors measured at YR11 were considered only if the child had not yet started puberty by that age. Risk factors were tested for potential confounding in logistic regression models, and adjusted odds ratios were converted to corrected RR, as described by Zhang and Yu (18), to provide a better estimate of the risk for persistence of asthma after puberty associated with each prepubertal risk factor.

Proportions of positive skin prick tests and means of body mass index (BMI) were compared across the five groups at YR6, YR11, and YR16 surveys. To take into account the serial correlation between observations on the same subject, these statistical comparisons were performed using linear mixed models (19) (generalized estimating equations for skin tests and random effects models, including sex and age for BMI).

RESULTS

In our study, information on wheezing in the prepubertal period and after the onset of puberty was available for 781 subjects. The mean age $\pm$ SD at the onset of puberty was 12.2 ± 1 years, with a mean follow-up period of 4.2 ± 1 years after the onset of puberty. The onset of puberty was reported by 543 (70%) subjects at the YR13 survey and by the remaining 238 (30%) subjects at the YR16 survey.

As shown in Table 2, 401 (51%) children never experienced wheezing attacks, either in the prepubertal period or after onset of puberty (no wheezing group), and 83 (11%) reported wheezing attacks only after the onset of puberty (incident wheezing). Among the remaining 297 subjects who experienced wheezing episodes during the prepubertal period, 131 (17%) had only infrequent wheezing, whereas 166 (21%) met the criteria for asthma definition. The majority of the children with infrequent wheezing experienced remission of wheezing episodes after the onset of puberty and were classified in the remitting wheezing group (92 of 131 [70%]) as contrasted with the unremitting wheezing group (39 of 131 [30%]). The 95% confidence interval for the proportion of children with unremitting wheezing was included between 22% and 38%. In contrast, among the children with asthma in the prepubertal period, 58% (97 of 166) had wheezing episodes after the onset of puberty and were included in the unremitting asthma group, whereas 42% (69 of 166) had remitting asthma. The 95% confidence interval for the proportion of children with unremitting asthma was included between 51% and 66%. Table 2 summarizes inclusion criteria and sample sizes for the six groups. Subjects (*n* = 83) in the incident wheezing group were excluded from most analyses because the specific aims of this study were to identify rates and predictors of persistence of asthma symptoms after the onset of puberty, rather than to assess risk factors for incidence of new wheeze.

Demographics, Smoking, and BMI

As shown in Table 3, the distribution by sex significantly differed across the six groups. The proportion of boys was higher in the remitting and unremitting wheezing and asthma groups than in the no wheezing and incident wheezing groups. The proportion of girls was higher in the unremitting groups as compared with the corresponding remitting groups, but the association did not reach statistical significance. An early onset of puberty was associated with the persistence of asthma symptoms in adolescence, with children in the unremitting wheezing and asthma groups having onset of puberty significantly earlier than children in the corresponding remitting groups. Neither maternal smoking during pregnancy nor active smoking during adolescence was significantly related to the six groups. As compared with parents of children in the no wheezing group, parents of children in the wheezing and asthma groups were more likely to smoke in any of the YR6, YR8, or YR11 surveys. However, parental smoking was not associated with persistence of wheezing or asthma after the onset of puberty.

TABLE 1. MEASUREMENT METHODS, TIME OF ASSESSMENT, AND CRITERIA FOR DEFINING A POSITIVE EXPOSURE FOR SOME OF THE VARIABLES USED IN THIS STUDY

	Measurement Method	Time of Assessment	Criteria for Positive Exposure
Passive smoking	Questionnaire by parents	YR6, YR8, and YR11	Mother or father are current smoker in at least one survey
Active smoking	Questionnaire by children	YR16	Child smokes cigarettes at least weekly
Overweight/obesity	Direct measurement of height and weight by study nurses	YR6, YR11, and YR16	BMI (weight [kg]/square of height [m ²]) $\geq$ 85th percentile of U.S. age- and sex-standardized values (15, 42)
RSV lower respiratory illness	Nasopharyngeal swabs and throat specimens	Up to YR3 (if lower respiratory tract illness)	Viral culture positive for RSV (16)
Active recurrent cough	Questionnaire	Last completed survey before the onset of puberty	Two or more episodes of cough without a cold in the past year
Skin tests	Skin prick tests for allergens common in the Tucson area*	YR6, YR11, and YR16	Wheal at least three mm larger than the control wheal for at least one tested allergen
Bronchial hyperresponsiveness	Methacholine challenge test	YR11	Methacholine-DRS $\leq$ -0.403 ml/log dose unit (17)

Definition of abbreviations: DRS = dose-response slope; RSV = respiratory syncytial virus.

* For reasons of consistency, only the six common allergens (i.e., *Alternaria alternata*, Bermuda grass, olive, careless weed, mesquite, and mulberry) tested in each of the skin prick tests (YR6, YR11, and YR16) were considered.

TABLE 2. CRITERIA USED FOR CLASSIFYING THE 781 SUBJECTS INTO THE SIX GROUPS

Prepubertal Period	After Onset of Puberty	
	No Wheezing	Any Wheezing
No wheezing, no asthma	No wheezing (n = 401)	Incident wheezing (n = 83)
Infrequent wheezing, no asthma*	Remitting wheezing (n = 92)	Unremitting wheezing (n = 39)
Asthma†	Remitting asthma (n = 69)	Unremitting asthma (n = 97)

* During the prepubertal period, these subjects experienced only infrequent wheezing and did not receive a physician-confirmed diagnosis of asthma.

† During the prepubertal period, these subjects experienced frequent wheezing or had infrequent wheezing plus a physician-confirmed diagnosis of asthma.

Figure 1 shows the mean BMI at YR6, YR11, and YR16 for the groups of no wheezing, remitting wheezing, unremitting wheezing, remitting asthma, and unremitting asthma. The mean BMI significantly differed across the five groups at YR11 and YR16. When comparisons between corresponding pairs were performed, the mean BMI was found to be significantly higher in the unremitting wheezing group than in the remitting wheezing group at each point in time and in the unremitting asthma group than in the remitting asthma group at YR11 and YR16. The average slopes of increase of BMI between YR6 and YR11 also differed significantly across the five groups (analysis of variance, $p = 0.003$). Duncan multiple range test indicated that the slopes of BMI increase for the groups of unremitting wheezing and unremitting asthma (0.891 ± 0.16 [SEM] and 0.696 ± 0.07 kg/m² per year, respectively) were homogeneous and higher than those of the remitting wheezing, remitting asthma, and no wheezing groups (0.602 ± 0.08 , 0.443 ± 0.05 , and 0.538 ± 0.03 kg/m² per year).

Respiratory Symptoms, Diagnoses, and Bronchial Hyperresponsiveness

As shown in Table 4, the amount of wheezing during the prepubertal period was strongly associated with persistence of asthma symptoms after the onset of puberty and showed a dose-response relationship. When compared with the reference category of episodic wheezing, children with continuous wheezing were 2.29 times more likely (95% confidence ratio, 1.23–4.27) to experience unremitting wheezing after the onset of puberty. Chil-

dren with recurrent wheezing before puberty showed a marginal and nonsignificantly increased risk of persistent wheezing after puberty (RR, 1.24, 0.63–2.46). This trend was also present among children with asthma. Children with asthma with continuous wheezing in the prepubertal period were 2.34 times (95% confidence interval, 1.35–4.07) more likely to experience unremitting asthma than children with episodic wheezing; recurrent wheezing was associated with a slight but nonsignificant increase in risk (RR 1.41, 0.76–2.60).

The proportions of subjects with other respiratory symptoms and diagnoses listed in Table 4 differed significantly across the five groups. However, only recurrent cough, active rhinitis, and physician-confirmed sinusitis were significantly associated with persistence of asthma symptoms after the onset of puberty. Approximately 71% of children with asthma with active recurrent cough at the last completed survey before the onset of puberty experienced unremitting asthma, as compared with less than 50% of children with asthma with no recurrent cough (RR 1.44, 1.12–1.86). The corresponding RRs for unremitting asthma were 1.51 (1.12–2.04) for children with active rhinitis and 1.41 (1.11–1.79) for children with active sinusitis.

Methacholine challenge test at YR11 was considered only for subjects who completed it before the onset of puberty ($n = 275$). Between 17% and 27% of the children in the no wheezing, remitting wheezing, and unremitting wheezing groups showed bronchial hyperresponsiveness, as compared with 37% and 68% in the remitting asthma and unremitting asthma groups, respectively ($p < 0.0001$). When we compared the last two groups,

TABLE 3. DEMOGRAPHICS AND SMOKING EXPOSURE ACROSS THE GROUPS

	No Wheezing	Incident Wheezing	Remitting Wheezing	Unremitting Wheezing	Remitting Asthma	Unremitting Asthma	Overall p Value (df = 5)
n	401	83	92	39	69	97	
Sex, female, %	56.6	66.3	46.7	56.4	33.3	44.3	0.0003
Ethnic background: at least one white parent, %	87.0	88.0	79.1	82.1	84.1	77.3	0.120
Age at onset of puberty in years, mean $\pm$ SEM	12.17 $\pm$ 0.05	11.79 $\pm$ 0.13	12.34 $\pm$ 0.11	11.74 $\pm$ 0.23*	12.70 $\pm$ 0.14	11.95 $\pm$ 0.12†	< 0.0001
Maternal smoking during pregnancy, %	13.4	19.0	14.6	18.4	20.9	11.7	0.434
Mother or father smoked at YR6, YR8, or YR11, %	28.6	49.4	34.1	46.2	42.0	28.9	0.002
Active smoking at YR16, %	14.5	26.3	11.3	11.1	8.3	15.9	0.129

Definition of abbreviation: df = degrees of freedom.

* Unremitting wheezing significantly differed from remitting wheezing ($p = 0.01$).

† Unremitting asthma significantly differed from remitting asthma ($p = 0.0001$).

Percentages refer to the proportion of subjects in each group positive for the specific factor. Statistical comparisons were conducted across the six groups treated as a categorical variable (the χ^2 test overall p value is provided in the last column). No trend across the groups was tested. Statistical comparisons were also performed between remitting and unremitting wheezing groups (p values provided in footnotes if ≤ 0.05) and between remitting and unremitting asthma groups (p values provided in footnotes if ≤ 0.05).

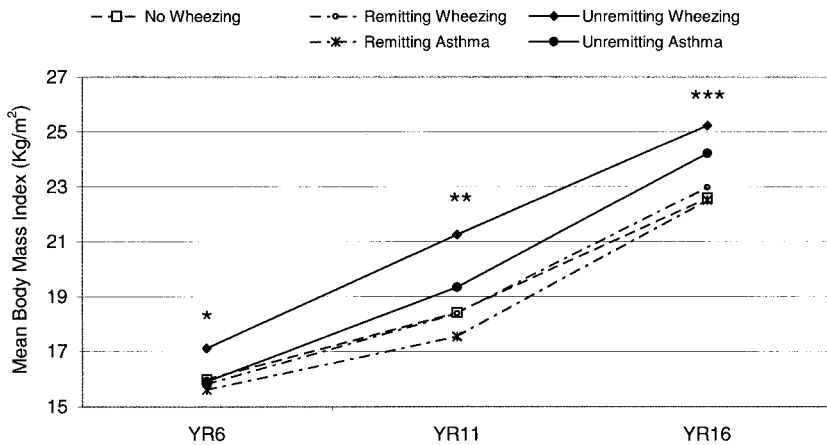


Figure 1. Mean body mass index (BMI) among the groups at surveys YR6, YR11, and YR16. Statistical comparisons of BMI values (after adjusting for sex and age): *YR6: across the groups, $p = 0.334$; remitting versus unremitting wheezing, $p = 0.054$; remitting versus unremitting asthma, $p = 0.496$. **YR11: across the groups, $p = 0.0002$; remitting versus unremitting wheezing, $p = 0.0007$; remitting versus unremitting asthma, $p = 0.009$. ***YR16: across the groups, $p < 0.0001$; remitting versus unremitting wheezing, $p = 0.0009$; remitting versus unremitting asthma, $p = 0.009$.

bronchial hyperresponsiveness was significantly associated with an increased risk of persistence of asthma after the onset of puberty (RR 1.88, 1.01–3.51).

Atopy

As shown in Table 5, the proportion of children with skin tests positive to any of the tested allergens differed significantly across the five groups at YR6, YR11 and YR16, with the no wheezing and remitting wheezing groups showing the lowest percentages of sensitization. Similarly, in each survey, we found the proportion of atopic children higher in the unremitting wheezing group than in the remitting wheezing group and in the unremitting asthma group than in the remitting asthma group.

When we analyzed the effect of the sensitization to specific allergens on the persistence of asthma symptoms after the onset of puberty, *Alternaria* was the only allergen at YR6 and YR11

associated with an increased risk for persistence of wheezing and asthma after the onset of puberty. Children sensitized to *Alternaria* at YR11 were twice as likely to experience unremitting wheezing after the onset of puberty than children not sensitized to *Alternaria* (RR 1.99, 1.00–3.98). Similarly, the RRs for unremitting asthma were 1.61 (1.22–2.11) for children sensitized to *Alternaria* at YR6 and 1.48 (1.07–2.05) for children sensitized to *Alternaria* at YR11. For all of the other allergens, the percentage of skin-sensitized subjects did not differ significantly between the remitting and unremitting groups at YR6 and YR11. In contrast, at YR16, sensitizations to *Alternaria*, Bermuda, and other pollen species were all significantly more common among unremitting than remitting asthma cases.

Multivariate Analysis

In Table 6, the results of the multivariate analysis for predicting the persistence of wheezing after the onset of puberty are shown

TABLE 4. RESPIRATORY SYMPTOMS, DIAGNOSES, AND BRONCHIAL HYPERRESPONSIVENESS IN THE PREPUBERTAL PERIOD ACROSS THE GROUPS

	No Wheezing (<i>n</i> = 401) (%)	Remitting Wheezing (<i>n</i> = 92) (%)	Unremitting Wheezing (<i>n</i> = 39) (%)	Remitting Asthma (<i>n</i> = 69) (%)	Unremitting Asthma (<i>n</i> = 97) (%)	Overall p Value
Wheezing in the prepubertal period						
Episodic		46.7	30.8*	27.5	9.3 [†]	< 0.0001 [‡]
Recurrent	N/A	38.0	33.3*	42.0	24.7 [†]	< 0.0001 [‡]
Continuous		15.2	35.9*	30.4	66.0 [†]	< 0.0001 [‡]
Wheezing without cold before the age of 5 years	8.3	12.2	18.4	30.9	34.4	< 0.0001
RSV lower respiratory illness in the first 3 years	18.0	29.1	36.4	29.0	30.4	0.013
At the last completed survey before the onset of puberty						
Active recurrent cough	6.5	16.3	23.1	29.4	51.5 [‡]	< 0.0001
Active rhinitis	21.2	31.5	30.8	46.4	69.1 [‡]	< 0.0001
Active physician-confirmed sinusitis	8.7	14.1	23.1	17.4	35.1 [§]	< 0.0001
BHR at YR11 (<i>n</i> = 275) (if test completed before the onset of puberty)	17.2	23.8	26.7	37.5	68.0 [§]	< 0.0001

Definition of abbreviations: BHR = bronchial hyperresponsiveness; N/A = not applicable.

* Unremitting wheezing significantly differed from remitting wheezing ($p < 0.05$).

[†] Unremitting asthma significantly differed from remitting asthma ($p < 0.0001$).

[‡] Unremitting asthma significantly differed from remitting asthma ($p < 0.005$).

[§] Significantly differed from remitting asthma ($p < 0.05$).

[‡] The p value refers to the comparison between remitting wheezing, unremitting wheezing, remitting asthma, and unremitting asthma.

Percentages refer to the proportion of subjects in each group positive for the specific factor. Statistical comparisons were conducted across the five groups treated as a categorical variable (the χ^2 test overall p value is provided in the last column). No trend across the groups was tested. Statistical comparisons were also performed between remitting and unremitting wheezing groups (p values provided are in footnotes if ≤ 0.05) and between remitting and unremitting asthma groups (p values are provided in footnotes if ≤ 0.05).

TABLE 5. SKIN TESTS RESULTS AT YR6, YR11, AND YR16 ACROSS THE GROUPS

	No Wheezing	Remitting Wheezing	Unremitting Wheezing	Remitting Asthma	Unremitting Asthma	Overall p Value (df = 4)
YR6 (n = 545), %						
Any positive	26.4	29.5	53.8*	54.0	73.2 [‡]	< 0.0001
<i>Alternaria</i> -positive	9.2	10.3	19.2	22.2	48.8 [§]	< 0.0001
Bermuda-positive	18.3	28.2	23.1	41.3	50.0	< 0.0001
Other pollen-positive	14.9	19.2	26.9	38.1	46.3	< 0.0001
YR11 (n = 530), %						
Any positive	42.8	50.0	75.8 [†]	62.7	84.8 [§]	< 0.0001
<i>Alternaria</i> -positive	12.7	17.6	36.4*	28.8	46.8 [‡]	< 0.0001
Bermuda-positive	28.2	31.1	48.5	44.1	57.0	< 0.0001
Other pollen-positive	32.0	45.9	51.5	55.9	68.4	< 0.0001
YR16 (n = 451), %						
Any positive	63.5	61.9	85.2*	80.0	95.5 [§]	< 0.0001
<i>Alternaria</i> -positive	16.4	25.4	40.7	34.0	59.7 [†]	< 0.0001
Bermuda-positive	44.3	41.3	63.0	62.0	78.8 [‡]	< 0.0001
Other pollen-positive	57.4	55.6	77.8	76.0	88.1 [‡]	< 0.0001

Definition of abbreviation: df = degrees of freedom.

Statistical comparisons are performed across the five groups (p value is reported in the last column) between remitting and unremitting wheezing and between remitting and unremitting asthma.

* Unremitting wheezing significantly differed from remitting wheezing ($p < 0.05$).

[†] Unremitting wheezing significantly differed from remitting wheezing ($p < 0.01$).

[‡] Unremitting asthma significantly differed from remitting asthma ($p < 0.05$).

[§] Unremitting asthma significantly differed from remitting asthma ($p < 0.005$).

[†] Unremitting asthma significantly differed from remitting asthma ($p < 0.0005$).

Percentages refer to the proportion of subjects in each group that are positive for the specific allergen. Statistical comparisons were conducted across the five groups treated as a categorical variable (the χ^2 test overall p value is provided in the last column). No trend across the groups was tested. Statistical comparisons were also performed between remitting and unremitting wheezing groups (p values are provided in footnotes if ≤ 0.05) and between remitting and unremitting asthma groups (p values are provided in footnotes if ≤ 0.05).

separately for subjects who experienced only infrequent wheezing (model 1) and for subjects who had asthma (model 2) in the prepubertal period. Bronchial hyperresponsiveness was the only independent variable significant in the bivariate analysis that was not tested in the multivariate analysis because of the limited number of subjects who completed the test (57 children with infrequent wheezing and 49 children with asthma). Despite the nonsignificant odds ratios, sex was included in the models to control for its potential confounding effect. An early onset of puberty and being overweight or obese at YR11 were the only risk factors independently associated with persistence of asthma-like symptoms in both models. In addition, the presence of continuous wheezing during the prepubertal period, active sinusitis at the last completed survey before puberty, and skin test sensitization at YR11 were independently associated with persistence of asthma (model 2). In both models, the corrected RRs provide an estimate of the risk for persistence of wheezing/asthma after the onset of puberty associated with each of the prepubertal risk factors. The results of the Hosmer and Lemeshow tests showed satisfactory goodness of fit for both the models.

Analysis Based Solely on Outcome at YR16 Survey

To reduce the risk that the association between early onset of puberty and persistence of wheezing and asthma could be due to observational bias (children with an early onset of puberty had longer follow-up and thus more opportunities to report active wheezing), we performed a second analysis in which persistence or remission of wheezing and asthma were based solely on the symptoms reported at the YR16 survey. In this analysis, children with unremitting asthma still had a younger mean age at the onset of puberty than children with remitting asthma (11.98 ± 0.14 [SEM] vs. 12.64 ± 0.15 years, respectively; $p = 0.001$). A similar trend, although with borderline significance,

was present for children with unremitting versus remitting wheezing (11.84 ± 0.28 vs. 12.32 ± 0.12 , $p = 0.069$).

DISCUSSION

In this longitudinal population-based cohort study, we estimated remission rates of asthma symptoms after the onset of puberty and defined patterns of risk factors for persistence of asthma in adolescence. We found that approximately 30% of children with infrequent wheezing but almost 60% of children with asthma in the prepubertal period keep experiencing wheezing episodes in the first 4 years after the onset of puberty. These findings challenge the commonly held view that asthma usually remits during adolescence, although they might reflect persistence rates that are specific to the Tucson area. They might also reflect specific temporal trends, as the prevalence of some of the strongest predictors for persistent asthma, such as atopy and overweight, has increased dramatically during the last decades.

Despite the commonly held view that asthma may frequently remit in adolescence, very few studies have reported estimates of remission rates of asthma symptoms during adolescence from samples of the general population. Nicolai and coworkers (10) found that almost 70% of children with asthma at age 10 reported no asthma symptoms during the last 12 months in a follow-up survey completed at the age of 14 years, if they had already had signs of puberty (change of voice in boys and menarche in girls). These children were identified from a large cohort representative of the general population of schoolchildren in Munich. However, these remission rates of asthma during adolescence should be interpreted cautiously because they are based on a single follow-up survey and reflect the experience of a single year (last 12 months before the survey completed in adolescence). Indeed, in a similar cohort from the United Kingdom (11), only 45% of children

TABLE 6. LOGISTIC REGRESSION MODELS FOR PREDICTING PERSISTENCE OF WHEEZING AFTER ONSET OF PUBERTY

	Model 1 Subjects with Infrequent Wheezing in the Prepubertal Period (n = 131) [‡]			Model 2 Subjects with Asthma in the Prepubertal Period (n = 166) [§]		
	OR (95% CI)	Corrected RR	p Value	OR (95% CI)	Corrected RR	p Value
Sex, female	1.09 (0.48–2.48)	1.07	0.827	1.03 (0.46–2.30)	1.01	0.946
Age at onset of puberty, yr	0.65 (0.45–0.94)	N/A	0.022	0.64 (0.44–0.93)	N/A	0.019
Wheezing in the prepubertal period*						
Recurrent	—	—	—	1.77 (0.60–5.22)	1.42	0.304
Continuous	—	—	—	5.33 (1.88–15.1)	2.23	0.002
Overweight or obese at YR11	5.19 (1.58–17.1)	2.80	0.007	8.93 (1.70–46.8)	1.87	0.010
Active sinusitis at the last completed survey before the onset of puberty	—	—	—	2.88 (1.16–7.17)	1.45	0.022
Skin tests at YR11 [†]						
<i>Alternaria</i> -positive	—	—	—	4.17 (1.34–13.0)	2.14	0.014
Other allergen-positive	—	—	—	2.95 (0.95–9.16)	1.86	0.061
Hosmer and Lemeshow Test			0.578			0.150

Definition of abbreviations: CI = confidence interval; N/A = not applicable; OR = odds ratio; RR = relative risk.

* Episodic wheezing is the reference group.

[†] Negative skin tests is the reference group.

[‡] Thirty-nine cases with unremitting wheezing.

[§] Ninety-seven cases with unremitting asthma.

Subjects from the remitting wheezing and unremitting wheezing groups were included in the first model and subjects from the remitting asthma and unremitting asthma groups were included in the second model. Skin tests results and body mass index at YR11 were considered only if the subject had completed the YR11 survey before the onset of puberty. In addition to sex, variables were retained in the models at the $\alpha = 0.05$ level. Both odds ratios (95% confidence interval) and corrected RRs are presented. Results of the Hosmer and Lemeshow tests are shown as a measure of the models' goodness of fit.

with wheeze at the age of 6–8 years reported no current wheeze at the age of 14–16 years. These two cohort studies also shed some light on the effect of sex on persistence of asthma in adolescence. It is well known that the male/female ratio among asthma cases is high during childhood, but it tends to decrease or even reverse after puberty (20). This can be related to higher rates of incidence or higher rates of persistence of asthma, or both, among females after puberty. Consistent with these previous reports (10, 11), we did not find sex to be a significant predictor of persistence of asthma after the onset of puberty, although a trend toward a higher proportion of persistent wheezing among girls than boys was present. Interestingly, this trend disappeared completely when adjusting for the age at onset of puberty, as girls also showed a significantly younger age at onset of puberty than boys.

Several other longitudinal studies with longer follow-up periods have investigated factors influencing the outcome of childhood asthma in adult life, but none of them has identified rates and predictors of asthma persistence in adolescence. Using a random stratified sample from the 1968 Tasmanian Asthma Survey, Jenkins and colleagues (3) found that only 26% of the subjects with asthma or wheezy breathing by the age of 7 years reported current asthma as an adult (age 29–32 years). Interestingly, the severity of childhood asthma, as assessed by the presence of more than 10 asthma attacks, was among the strongest predictors of persistent asthma in adulthood. Similarly, in another Australian cohort, the Melbourne Asthma Study (21), a clear trend for persistent asthma at age 35 years (4) and at age 42 years (22) was found across increasing levels of wheezing severity at age 7 years. However, it is difficult to generalize the overall rates of persistence of asthma from this study to the population of children with asthma because this cohort was enriched with a further sampling of children with severe asthma at age 10 years. Prognosis of wheezing illness by ages 11 and 16 years was found to be related to severity at age 7 years also in a large national British cohort (9). Consistent with these reports, we found that, as compared with children with frequent wheezing

or asthma, those experiencing only infrequent wheezing in the prepubertal period were much more likely to report no wheezing episodes after the onset of puberty. Furthermore, we observed that the proportion of surveys in the prepubertal period in which the subjects reported wheezing was a strong predictor of persistence of asthma after the onset of puberty. The effect of frequency and severity of wheezing in childhood on persistence of asthma after puberty illustrates the importance of using population-based cohorts, rather than “at-risk” cohorts or outpatient populations, to study the outcome of childhood asthma in adult life.

One of the major findings of this study is the strong and independent effect of elevated BMI and the early onset of puberty on the persistence of wheezing in adolescence. After adjusting for other risk factors, being overweight or obese at age 11 was associated with a threefold increased risk for persistence of infrequent wheezing after the onset of puberty and with a twofold increased risk for persistence of asthma. Consistently, both the unremitting wheezing and unremitting asthma groups had a mean BMI that was significantly higher than those of the corresponding remitting groups. These findings expand our understanding of the relationship between obesity and asthma. In recent years, several studies have shown that obesity is associated cross-sectionally (23, 24) and longitudinally (15, 25, 26) with the prevalence and incidence of asthma symptoms, particularly among females. In this same cohort, we have already found females who were overweight or obese at age 11 years to be at increased risk for incident wheezing and the strongest association between overweight status and asthma risk was observed among girls whose puberty started before the age of 11 years (15). Here, we show that both the presence of obesity during the prepubertal period and an early onset of puberty are significant and independent risk factors for persistent asthma after puberty. We did not observe an interaction between obesity and sex or between obesity and age at onset of puberty in predicting persistence of asthma (data not shown), but this finding should be interpreted with caution because of the limited statistical power related to the small sample size.

It could be argued that subjects with asthma might be less likely to exercise and, in turn, more likely to gain weight and that obesity might be an effect rather than a cause of asthma. It should be acknowledged that in a study design like ours it is impossible to exclude this possibility, and indeed, we found the unremitting wheezing and unremitting asthma groups to show the steeper slope of BMI increase between YR6 and YR11. However, children with infrequent, rather than frequent, wheezing were the group gaining weight most rapidly between YR6 and YR11. The hypothesis that obesity plays a direct role in the persistence of asthma symptoms is also supported by the fact that weight reduction in obese patients with asthma improves lung function and symptoms, at least among adults (27, 28). However, we cannot dismiss the possible role of physical activity because the level of physical exercise is difficult to estimate in epidemiologic studies (29) and because physical activity is often included in weight loss regimens (30).

It is known that obesity is a risk factor for the early onset of puberty and menarche (31). Nevertheless, in our study an early onset of puberty remained a significant risk factor for persistent asthma, after adjusting for obesity in the multivariate model. This finding can be interpreted in several ways. First, the association between early onset of puberty and persistent asthma might be an artifact, as children with an early onset of puberty had on average a longer follow-up and, therefore, an increased opportunity to report wheezing in adolescence. This possibility cannot be completely excluded. The age at the onset of puberty, the length of follow-up, and the number of surveys completed after the onset of puberty are variables so strongly intercorrelated that the information they carry can hardly be dissected, even in a multivariate analysis. However, it is noteworthy that the association between early onset of puberty and persistent asthma was confirmed when analyses were performed based solely on symptom experience as reported at the YR16 survey. This analysis should be insensitive to potential observation bias related to a differential length of follow-up between children with early or later onset of puberty. A second explanation for this association could be that early onset of puberty and asthma persistence are affected by common risk factors, such as exposure to some endocrine disruption or dietary and psychological influences (32).

Finally, the relationship between the early onset of puberty and persistent asthma may be a real biological phenomenon. It is well known that the course of asthma can drastically change during pregnancy (33) or in relationship to the menstrual cycle (34), most likely because of hormonal fluctuations. Sex hormones can alter β_2 -adrenergic responsiveness (35), and female hormones have been shown to increase the production of Th2-like cytokines from peripheral blood mononuclear cells (36). In addition, leptin represents another potential candidate molecule to explain the link between the early onset of puberty and persistent asthma. Leptin has been proposed as one of the signals controlling sexual maturation (37), and at the same time, leptin receptors have been shown to be present in airway and lung cells and possibly to be involved in the peripheral regulation of respiratory function (38). Further research is required to dissect the complex interactions between the developmental processes of body growth and sexual maturation and their impact on the natural history of childhood asthma.

In this study, we found that a physician-confirmed diagnosis of sinusitis in the prepubertal period was a significant predictor of persistence of asthma after puberty. Sinusitis has been associated with asthma severity (39), and consistently, asthma symptoms frequently improve after sinusitis treatment. However, it should be acknowledged that in epidemiologic studies it may be very

difficult to distinguish between sinusitis, even when confirmed by a physician and symptoms of perennial or severe rhinitis.

We also found that sensitization to *Alternaria* at YR6 or YR11 among children with asthma strongly predicts the persistence of wheezing after the onset of puberty. No other single allergen showed this association. Although it is unclear why *Alternaria* is the only allergen independently associated with asthma in this environment (40), these findings emphasize the importance of evaluating not only the presence of skin test sensitization but also the specific pattern of sensitization among children with asthma to predict their likelihood of outgrowing the disease. The patterns of sensitization associated with asthma persistence are likely to differ in different environments. For example, in a recent report from Dunedin, New Zealand, where mites and cat dander are the strongest asthma-related allergens, skin test response at age 13 years to house-dust-mite and cat allergens, but not *Alternaria*, predicted persistent wheezing from childhood up to year 26 (1).

This study has several limitations. First, the onset of puberty was estimated based on parental report. Although specific examples of signs identifying the onset of puberty were provided in the questionnaires, it is likely that some misclassification has occurred. However, because there is no reason to believe that the degree of misclassification was differential for the groups with remitting and unremitting wheezing/asthma, this should not jeopardize the validity of our findings. Second, in each questionnaire, participants were asked about the presence of wheezing episodes in the previous 12 months. This approach increases the reliability of self-reports and minimizes any recall bias. However, because the questionnaires were administered every 2–3 years, this approach disregards information on the presence of wheezing during several “time windows.” This could have provoked an underestimation of the rates of period prevalence for wheezing in adolescence. Finally, the small sample size of some of our study groups did not provide sufficient statistical power to test the interaction between sex and other risk factors in predicting persistence of asthma after puberty, although it is biologically plausible that the patterns of risk factors may differ between the two sexes.

In conclusion, in a population-based birth cohort, we identified the following independent prepubertal risk factors for persistence of asthma after the onset of puberty: presence of frequent or continuous wheezing, obesity, early onset of puberty, active sinusitis, and skin test sensitization. Our findings challenge the commonly held view that asthma usually remits during adolescence: only 42% of children with asthma reported no wheezing in the first 4 years after the onset of puberty. Furthermore, it remains to be determined in what proportion of remitting cases subclinical airway inflammation persists (41) and to what extent this may increase the risk for relapses of the disease later in life (2).

Conflict of Interest Statement: S.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.L.W. has given lectures in sessions at national and regional meetings which were funded in part by Merck and Company, Inc.; W.J.M. received \$7,500 in 2001, 2002, and 2003 from Genentech for serving as Chair of the Epidemiologic Study of Cystic Fibrosis and has participated as a speaker in scientific meetings sponsored by Glaxo Smith Kline (Canada) and his institution has received an unrestricted educational grant from Glaxo Smith Kline; D.L.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.J.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.D.M. received \$12,000 in 2000, \$16,000 in 2001, and \$13,000 in 2002 for serving on an advisory board for Merck.

Acknowledgment: The authors thank the members of the Group Health Medical Associates; the study nurses, Marilyn Lindell, RN, and Lydia De La Ossa, RN; and Bruce Saul, MS, for technical assistance.

References

1. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414–1422.
2. 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;312:1195–1199.
3. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. *BMJ* 1994;309:90–93.
4. Oswald H, Phelan PD, Lanigan A, Hibbert M, Bowes G, Olinsky A. Outcome of childhood asthma in mid-adult life. *BMJ* 1994;309:95–96.
5. Vonk JM, Jongepier H, Panhuysen CI, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003;58:322–327.
6. Burrows B, Knudson RJ, Lebowitz MD. The relationship of childhood respiratory illness to adult obstructive airway disease. *Am Rev Respir Dis* 1977;115:751–760.
7. von Mutius E. Paediatric origins of adult lung disease. *Thorax* 2001;56:153–157.
8. Roorda RJ. Prognostic factors for the outcome of childhood asthma in adolescence. *Thorax* 1996;51:S7–12.
9. Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. *J Epidemiol Community Health* 1986;40:121–129.
10. Nicolai T, Illi S, Tenborg J, Kiess W, v Mutius E. Puberty and prognosis of asthma and bronchial hyper-reactivity. *Pediatr Allergy Immunol* 2001;12:142–148.
11. Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *Am J Respir Crit Care Med* 1998;158:352–357.
12. Peat JK, Salome CM, Sedgwick CS, Kerrebijn J, Woolcock AJ. A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian schoolchildren. *Clin Exp Allergy* 1989;19:299–306.
13. Guerra S, Wright AL, Morgan WJ, Holberg CJ, Martinez FD. Factors affecting the outcome of asthma after the onset of puberty. *Am J Respir Crit Care Med* 2002;165:A435.
14. Taussig LM, Wright AL, Morgan WJ, Harrison HR, Ray CG. The Tucson Children's Respiratory Study: I: design and implementation of a prospective study of acute and chronic respiratory illness in children. *Am J Epidemiol* 1989;129:1219–1231.
15. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001;163:1344–1349.
16. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–545.
17. Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig L, Martinez FD. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52:946–952.
18. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690–1691.
19. Brown H, Prescott R. Applied mixed models in medicine, statistics in practice. Chichester, UK: John Wiley & Sons; 1999.
20. Sears MR. Evolution of asthma through childhood. *Clin Exp Allergy* 1998;28(Suppl 5):82–89; discussion 90–91.
21. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. *J Allergy Clin Immunol* 2002;109:189–194.
22. Horak E, Lanigan A, Roberts M, Welsh L, Wilson J, Carlin JB, Olinsky A, Robertson CF. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. *BMJ* 2003;326:422–423.
23. Figueroa-Munoz JI, Chinn S, Rona RJ. Association between obesity and asthma in 4–11 year old children in the UK. *Thorax* 2001;56:133–137.
24. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;54:396–402.
25. Guerra S, Sherrill DL, Bobadilla A, Martinez FD, Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest* 2002;122:1256–1263.
26. Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159:2582–2588.
27. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;320:827–832. (published erratum appears in *BMJ* 2000;320:984).
28. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118:1315–1321.
29. Platts-Mills TA, Carter MC, Heymann PW. Specific and nonspecific obstructive lung disease in childhood: causes of changes in the prevalence of asthma. *Environ Health Perspect* 2000;108:725–731.
30. Ford ES, Mannino DM, Redd SC, Mokdad AH, Galuska DA, Serdula MK. Weight-loss practices and asthma: findings from the behavioral risk factor surveillance system. *Obes Res* 2003;11:81–86.
31. Cooper C, Kuh D, Egger P, Wadsworth M, Barker D. Childhood growth and age at menarche. *Br J Obstet Gynaecol* 1996;103:814–817.
32. Teilmann G, Juul A, Skakkebaek NE, Toppa J. Putative effects of endocrine disruptors on pubertal development in the human. *Best Pract Res Clin Endocrinol Metab* 2002;16:105–121.
33. Schatz M. Interrelationships between asthma and pregnancy: a literature review. *J Allergy Clin Immunol* 1999;103:S330–S336.
34. Haggerty CL, Ness RB, Kelsey S, Waterer GW. The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol* 2003;90:284–291; quiz 291–293, 347.
35. Mills PJ, Ziegler MG, Nelesen RA, Kennedy BP. The effects of the menstrual cycle, race, and gender on adrenergic receptors and agonists. *Clin Pharmacol Ther* 1996;60:99–104.
36. Hamano N, Terada N, Maesako K, Hohki G, Ito T, Yamashita T, Konno A. Effect of female hormones on the production of IL-4 and IL-13 from peripheral blood mononuclear cells. *Acta Otolaryngol Suppl* 1998;537:27–31.
37. Reitman ML, Bi S, Marcus-Samuels B, Gavrilova O. Leptin and its role in pregnancy and fetal development: an overview. *Biochem Soc Trans* 2001;29:68–72.
38. Tsuchiya T, Shimizu H, Horie T, Mori M. Expression of leptin receptor in lung: leptin as a growth factor. *Eur J Pharmacol* 1999;365:273–279.
39. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, Bousquet J, Chanez P. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;107:73–80.
40. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155:1356–1361.
41. van Den Toorn LM, Prins JB, Overbeek SE, Hoogsteden HC, de Jongste JC. Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000;162:953–957.
42. Rosner B, Prineas R, Loggie J, Daniels SR. Percentiles for body mass index in US children 5 to 17 years of age. *J Pediatr* 1998;132:211–222.