

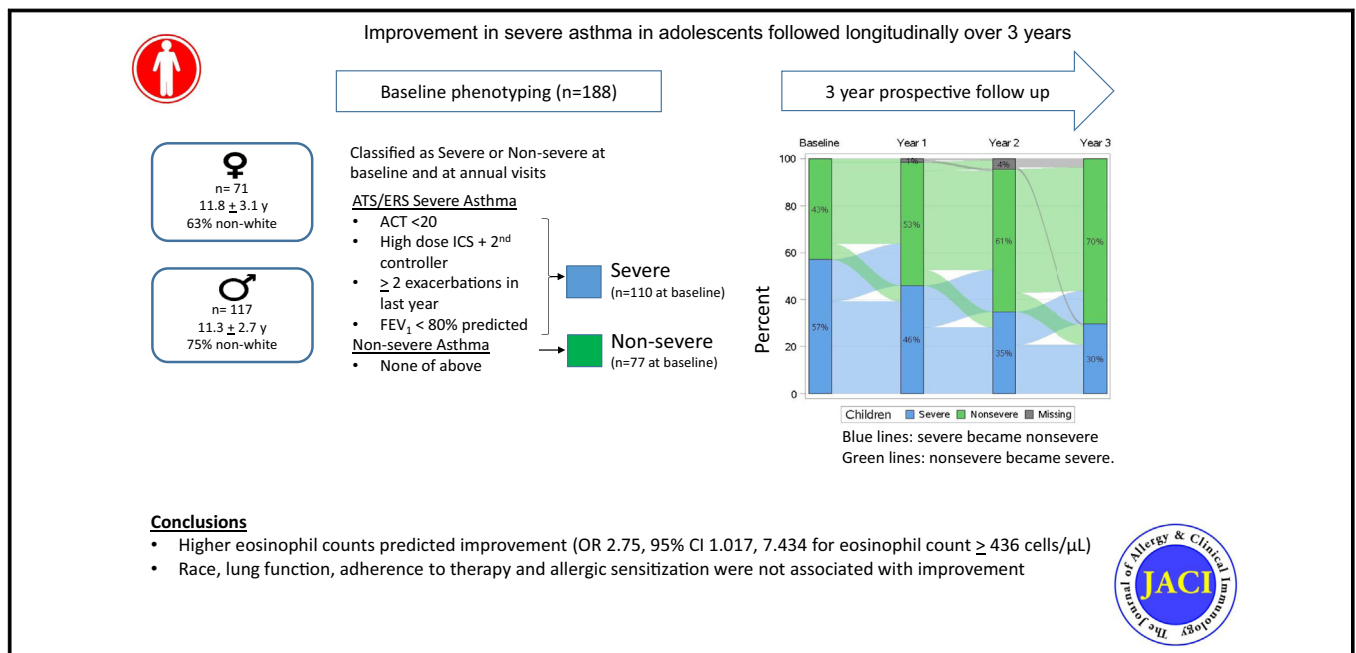
Severe asthma during childhood and adolescence: A longitudinal study



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GRAPHICAL ABSTRACT



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Background: Morbidity and mortality associated with childhood asthma are driven disproportionately by children with severe asthma. However, it is not known from longitudinal studies whether children outgrow severe asthma.

Objective: We sought to study prospectively whether well-characterized children with severe asthma outgrow their asthma during adolescence.

Methods: Children with asthma were assessed at baseline with detailed questionnaires, allergy tests, and lung function tests and were reassessed annually for 3 years. The population was enriched for children with severe asthma, as assessed by the American Thoracic Society/European Respiratory Society guidelines, and subject classification was reassessed annually.

Results: At baseline, 111 (59%) children had severe asthma. Year to year, there was a decrease in the proportion meeting the criteria for severe asthma. After 3 years, only 30% of subjects met the criteria for severe asthma ($P < .001$ compared with enrollment). Subjects experienced improvements in most indices of severity, including symptom scores, exacerbations, and controller medication requirements, but not lung function. Surprisingly, boys and girls were equally likely to have resolved asthma (33% vs 29%). The odds ratio in favor of resolution of severe asthma was 2.75 (95% CI, 1.02-7.43) for those with a peripheral eosinophil count of greater than 436 cells/ μ L.

Conclusions: In longitudinal analysis of this well-characterized cohort, half of the children with severe asthma no longer had severe asthma after 3 years; there was a stepwise decrease in the proportion meeting severe asthma criteria. Surprisingly, asthma severity decreased equally in male and female subjects.

Peripheral eosinophilia predicted resolution. These data will be important for planning clinical trials in this population. (J Allergy Clin Immunol 2020;145:140-6.)

Key words: Severe asthma, lung function, eosinophilia, adolescence

Severe asthma is defined by American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria as asthma symptoms that remain uncontrolled despite having an asthma specialist oversee treatment with high-dose inhaled corticosteroids (ICSs) plus a second controller and/or systemic corticosteroids (see Table E1 in this article's Online Repository at www.jacionline.org).¹ Although severe asthma affects approximately 4% to 5% of children with asthma, it accounts for a disproportionate fraction of the morbidity, mortality, and cost of asthma.¹⁻³ The first and second cycles of the National Heart, Lung, and Blood Institute-funded Severe Asthma Research Program (SARP I and II) enrolled children and adults with asthma in cross-sectional studies to identify biologic processes differentiating severe from nonsevere asthma.^{4,5} The third cohort study (SARP III) has examined how severe asthma changes over time. Here we present longitudinal analyses of well-characterized adolescents with severe asthma during 3 years of study.

Recent data suggest that asthma-related hospitalizations might be lower in late adolescence (13-18 years old) and early adulthood (19-30 years old) than in earlier childhood and middle age.^{6,7} However, longitudinal studies of children with severe asthma have not been performed. Because cross-sectional data show that boys are more likely than girls to have asthma and that women are more likely than men to have asthma,^{3,8,9} we

Abbreviations used

ATS: American Thoracic Society
BMI: Body mass index
ERS: European Respiratory Society
ICS: Inhaled corticosteroid
SARP: Severe Asthma Research Program

hypothesized that longitudinal analysis would reveal that asthma severity decreases in boys and increases in girls during adolescence. Furthermore, we hypothesized that lower lung function⁹⁻¹² and obesity^{13,14} would be associated with a decreased likelihood that severe asthma would resolve during adolescence. We tested these hypotheses using our uniquely well-characterized longitudinal SARP III pediatric cohort.^{5,15,16}

METHODS

Participants and baseline characterization

Children aged 6 to 17 years with asthma were recruited between 2012 and 2015 from the 11 clinical centers participating in SARP III. Details of the screening and enrollment criteria have been published previously,¹⁴⁻¹⁶ and the study was approved by the institutional review boards at each clinical center. All participants provided written informed consent. Enrollment was prespecified to include at least 700 participants, including 25% children and adolescents, 30% from racial and ethnic minorities, and 60% with severe asthma. Asthma severity at the time of enrollment was classified based on ATS/ERS criteria (see Table E1).¹ Participants underwent baseline characterization using questionnaires, genetics, allergy testing, lung function testing with reversibility measures, and evaluation before and after an intramuscular dose of triamcinolone, as previously described¹⁵; study procedures are listed in the full protocol, which was approved by the Data and Safety Monitoring Board (see this article's Online Repository at www.jacionline.org). To the best of our knowledge, this is the most thoroughly characterized cohort of children enriched for severe asthma. At enrollment, male and female participants had mean ages of 11.3 ± 2.7 and 11.8 ± 3.1 years, respectively, with the majority of male and female participants in the early stages of puberty (Tanner stages I and II).¹¹

Longitudinal assessment

Research visits were conducted annually after enrollment. Here we present the completed data for the first 3 years. SARP III was not a treatment trial, and the participants' primary providers or asthma specialists prescribed all treatments. Questionnaires regarding asthma control, exacerbations, and health care use were performed at annual visits and by telephone midway between annual visits. At each visit, asthma was classified as severe or nonsevere by using ATS/ERS criteria.¹

Questionnaires

Questionnaires were administered to assess the severity of symptoms and interval asthma exacerbations, health care use, and changes in medications. Validated questionnaires used asthma quality of life (Asthma Quality of Life Questionnaire [standardized]/Pediatric Asthma Quality of Life Questionnaire [standardized]) and asthma control (Asthma Control Questionnaire and Asthma Control Test/Childhood Asthma Control Test). Adherence was measured by using the Medication Adherence Rating Scale and by measuring change with dosing or intramuscular triamcinolone (little improvement suggested good adherence, as we reported recently in this population¹⁵). Asthma exacerbations were defined and assessed as recently reported.¹⁷

TABLE I. Baseline demographics of the pediatric SARP III cohort

	Male subjects (n = 116)	Female subjects (n = 71)
Age (y), mean $\pm$ SD	11.3 $\pm$ 2.7	11.8 $\pm$ 3.1
Race and ethnicity, no. (%)		
White, non-Hispanic	29 (25)	26 (37)
African American, non-Hispanic	51 (44)	26 (37)
Other	20 (17)	8 (11)
Hispanic	17 (15)	11 (15)
Asthma severity classification, no. (%)		
Severe	66 (57)	44 (62)
Nonsevere	50 (43)	27 (38)
Controller therapy		
High-dose ICS	81 (70)	49 (69)
Low- to medium-dose ICS	24 (21)	13 (18)

There were no significant differences between male and female participants.

TABLE II. Asthma severity classification at annual assessments, years 1-3

Sex	Asthma severity classification, no. (%)	
	Severe	Nonsevere
Year 1		
Male	51 (48)	55 (52)
Female	30 (43)	40 (57)
Year 2		
Male	37 (39)	59 (61)
Female	23 (37)	40 (63)
Year 3		
Male	22 (28)	58 (73)
Female	18 (33)	37 (67)

The proportion of male and female subjects with severe asthma decreased year to year ($P < .0001$).

Physical examination, airflow, airway reactivity, fraction of exhaled nitric oxide, and atopy assessments

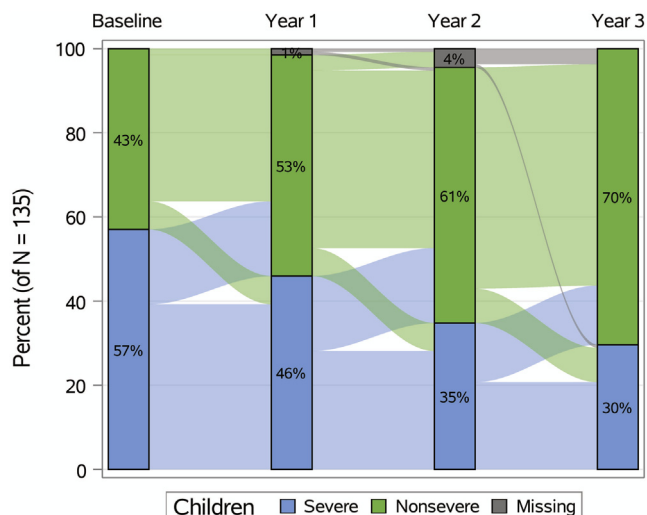
Physical examination included vital signs; height; weight; evaluation of the lungs, cardiovascular system, and nasopharynx; and assessment of pubertal status. Trained and certified coordinators used standardized equipment to assess airflow by using spirometry, with reversibility determined by using maximum bronchodilation, as previously prescribed.³ The 2012 Global Lung Initiative standard reference equations were used to determine predicted values.¹⁸ Fraction of exhaled nitric oxide was measured by using a standardized approach.¹⁹ Quality standards were followed at each site, with auditing by the data coordinating center. Total IgE and allergen-specific IgE levels to *Alternaria tenuis*, *Aspergillus fumigatus*, cat dander, *Cladosporium herbarum*, cockroach, common ragweed, *Dermatophagoides farinae* and *pteronissinus*, dog, grass mix, mouse, rat, 2 tree mixes (to account for local differences), and ragweed using ImmunoCAP were measured. Blood eosinophil and neutrophil counts were quantified.

Asthma severity classification and definition of resolution

At each yearly assessment, asthma severity was classified as either severe or nonsevere by using ATS/ERS criteria (Table I).⁴ Severe asthma was considered to be resolved if asthma was severe at baseline and nonsevere at year 3.

Statistical analysis

The primary outcome variable was the proportion of patients with severe asthma at each year of follow-up stratified by sex. Categorical measures were

**FIG 1.** Year-to-year change in asthma severity in the SARP III pediatric cohort. Sankey plot showing year-to-year change in asthma severity in the SARP III Pediatric cohort. Stacked bars show percentages of participants with severe and nonsevere asthma at each yearly visit, whereas connecting regions show the proportion that changed categories from one year to the next.

summarized by percentages, with a Pearson χ^2 test for associations with severity status and study completion status. Continuous measures were summarized by either medians and first and third quartiles or by mean and SDs, with Kruskal-Wallis and t tests for differences, respectively, between categories. Logistic regression with repeated measures was used to assess trends in distributions of severity components over time. The McNemar test compared severity status at enrollment versus year 3.

Summary statistics, analyses, and graphs were performed with SAS/STAT and SAS/GRAPH software (version 9.4) using the SAS System for Windows (SAS Institute, Cary, NC). Sankey bar plots were created by using the % SANKEY macro.²⁰

RESULTS

Characterization study participants at each annual visit/study sample

Characteristics of the study population at baseline and at each annual assessment are shown in Table II. Of the 188 children for whom baseline data were collected, annual research visits were completed in 176 (93.6%), 159 (84.6%), and 135 (71.8%) of participants at 12, 24, and 36 months, respectively. Children who met the enrollment criteria were classified as lost to follow-up if they were terminated before the visit or if the visit was missed. Children with severe and nonsevere asthma were lost to follow-up in similar proportions at each of the annual visits (see Table E2 in this article's Online Repository at www.jacionline.org). With the exception of the body mass index (BMI) percentile, characteristics of the participants lost to follow-up were not different than those of participants who completed the year 3 annual visit (see Table E3 in this article's Online Repository at www.jacionline.org).

Change in asthma severity as measured longitudinally during adolescence

The proportion of children meeting the criteria for severe asthma decreased steadily year to year on longitudinal analysis (Fig 1). This decrease in asthma severity was not driven by improvement in any 1 parameter (Fig 2). Children improved

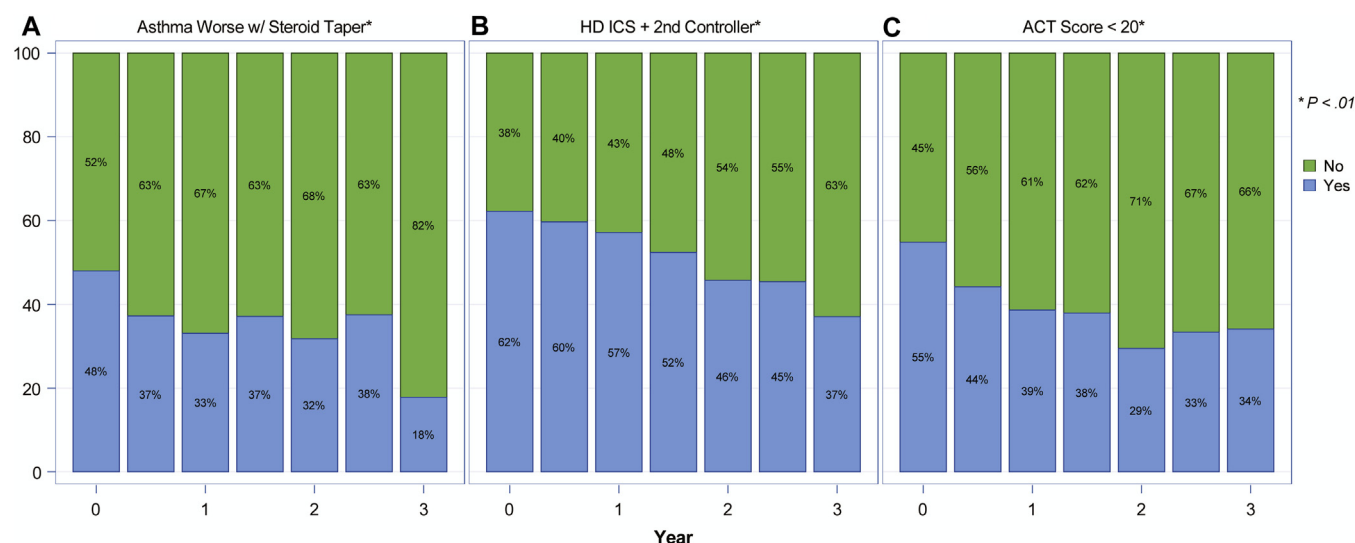


FIG 2. Components contributing to the asthma severity score. Select asthma severity components at each participant's in-person yearly and intermediate telephone visit. Percentage of the subset of pediatric participants with severe asthma at baseline who reported their asthma worsening with steroid taper (A), high-dose (HD) ICS with a second controller (B), and Asthma Control Test (ACT) score of less than 20 (C). A linear trend test accounting for repeated measures is significant at a P value of less than .01. Hospitalization rate, annual exacerbation number and ACT also tended to improve, but not significantly. See Fig E2 in this article's Online Repository at www.jacionline.org.

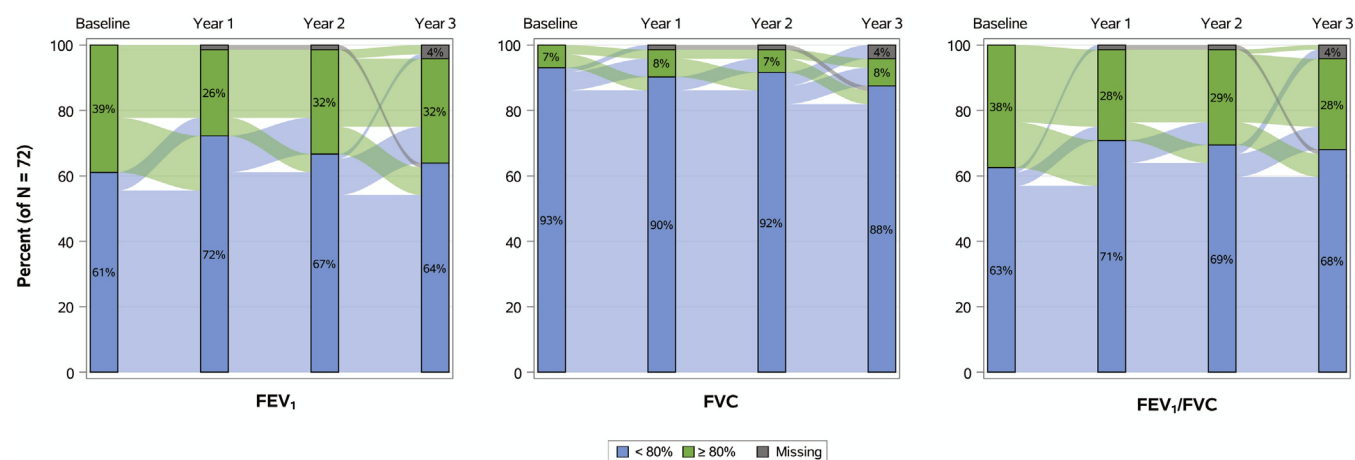


FIG 3. Longitudinal lung function did not improve in adolescents who had severe asthma initially and who completed 3 years of follow-up. Sankey plots of lung function data for yearly visits are shown. Percentages of subset of pediatric participants with severe asthma at baseline who had FEV₁, forced vital capacity (FVC), or FEV₁/FVC of less than 80% of predicted value. Proportions did not change significantly over time.

with regard to (1) symptoms (both Asthma Control Test and Childhood Asthma Control Test scores), (2) response to tapering of the ICS dose, (3) treatment with high-dose ICS and a second medication in 6 of the last 12 months, (4) asthma exacerbations, and (5) asthma-related hospitalizations in the last 12 months. In the case of 8 children, resolution of severe asthma classification was associated with continuing to take a childhood high-dose combination therapy after the 12th birthday without requiring an increase to an adult dose. The exception to this pattern of improvement was lung function, which did not improve over time (Fig 3). In contrast, the proportion of adults with severe

asthma followed longitudinally over the same 3 years in SARP III did not change (see Fig E1 in this article's Online Repository at www.jacionline.org). Treatment with biological therapies was 4% at baseline ($n = 8$, all receiving omalizumab) and 10% at 3 years ($n = 7$ receiving omalizumab and 3 receiving mepolizumab) and did not differ between those with severe asthma whose symptoms did and did not resolve ($P =$ not significant). Only 1 child participated in a therapeutic trial (mepolizumab vs placebo) and that was in year 2. Few children entering the study with nonsevere asthma were later reclassified with severe asthma during the 3 years ($n = 10$, Fig 1).

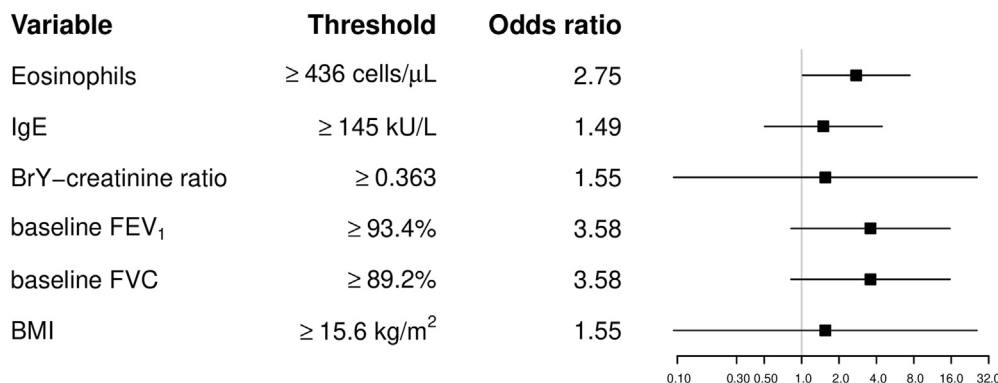


FIG 4. Forest plot of odds ratios for baseline characteristics of the children that predicted loss of the severe asthma designation over the next 3 years. For every variable, the threshold was identified so that it has the greatest informedness (ie, Specificity + Sensitivity – 1) on the receiver operating characteristic (ROC) curve. Odds ratio and 95% CIs were computed accordingly; these were significant for eosinophil counts of greater than 436 cells/ μ L (95% CI, 1.017-7.434).

Change in proportion of male and female participants with severe asthma

Because asthma incidence is greater in boys than in girls and greater in women than in men, our initial hypothesis was that female participants would be less likely to have resolution of their severe asthma than male participants. This hypothesis proved incorrect. There was no difference in the probability of severe asthma resolution between male and female participants (see Fig E1). The remaining results were analyzed without stratifying by sex.

Predictors of severe asthma resolution

Among participants with severe asthma at baseline, univariate analysis did not reveal any significant predictors of resolution (see Table E2). Although we hypothesized that low baseline lung function and obesity would predict the persistence of severe asthma, there were no significant differences in any parameter that predicted persistence of severe asthma (Fig 3 and see Table E4 in this article's Online Repository at www.jacionline.org), nor did allergen-specific IgE asthma (see Table E5 in this article's Online Repository at www.jacionline.org), adherence (Medication Adherence Rating Scale) score at outset, or history of immunotherapy at outset (see Table E4). Analysis using the receiver operating characteristic showed that an eosinophil count of 436 cells/ μ L had an optimal sensitivity and specificity for predicting resolution, and children with an eosinophil count of greater than this threshold had an odds ratio of 2.75 in favor of resolution (Fig 4; 95% CI, 1.017-7.434; $P = .043$).

DISCUSSION

Severe asthma accounts for a high proportion of the morbidity, mortality, and cost of childhood asthma,^{1,3,21} and new treatments are needed for children affected by severe asthma. However, the natural history of severe asthma in children is incompletely understood. Here, in longitudinal analysis of our well-characterized pediatric SARP III cohort, we show for the first time that approximately half of childhood severe asthma resolves during adolescence. These data will be important for planning therapeutic trials in this population.

Resolution of severe asthma during adolescence was as likely in girls as it was in boys (Table II and see Fig E1). This finding was contrary to the initial hypothesis. Cross-sectional studies have shown that severe asthma is more common in boys than in girls and more common in women than in men.^{8,22,23} Furthermore, androgens have beneficial effects on the asthmatic airway. For example, dehydroepiandrosterone-sulfate inhibits human airway smooth muscle and fibroblast proliferation and might reduce airway epithelial-to-mesenchymal transition.²³⁻²⁸ Testosterone also promotes airway smooth muscle relaxation.²⁶ Androgens are associated with decreased inflammation in asthma models.^{27,28} *In vivo* androgens are associated with better lung function in healthy cohorts.^{29,30} Thus it was surprising that, during the transition between childhood and adulthood, severe asthma resolved at an equal rate in both sexes. Note that both male and female subjects have increased androgen levels during adolescence¹⁶; both sexes could have benefitted equally from increased androgen levels, airway caliber,³¹ and chest wall strength.

The odds that childhood severe asthma would resolve were greater in children who were eosinophilic at enrollment (Fig 4). Thus children who outgrow severe asthma are more likely to be those with eosinophilic inflammation. Obesity has been suggested as an allergy-independent determinant of asthma severity, affecting chest wall function, particularly through visceral fat.^{14,32-35} However, obesity at enrollment was not a determinant of failure to improve. Furthermore, visceral fat increases in adolescence,³⁶ making it unlikely to be related to decreasing asthma severity. Thus determinants of severe asthma persistence from childhood to adulthood remain hypothetical and warrant further study.

There is clearly a subset of children with asthma who have persistently low lung function throughout childhood.^{3,12,37} However, persistently low lung function did not predict resolution of severe asthma. Specifically, half of children with severe asthma did not experience improvement in symptoms, exacerbation frequency, and medication requirements over the 3 years, but these children were not characterized by low lung function at study enrollment. Thus although persistently low lung function can predict low adult lung function and an early chronic obstructive pulmonary disease-like phenotype,¹⁰ it did not predict that severe asthma would not resolve.

Although ours was the first longitudinal assessment of childhood asthma severity status *per se*, our results are consistent with studies of asthma in general. Based on cross-sectional data, we and others have recently suggested that adolescence and young adulthood is an “eye of the hurricane” period during which asthma admission rates decrease.² Indeed, longitudinal analyses of population-based studies and of cohorts of children at increased risk for asthma in general but not enriched for severe asthma have shown remission of asthma during adolescence.³⁵⁻³⁷ In the Tucson Children’s Respiratory Study birth cohort, among those with at least 1 episode of wheezing, more than half experienced remission of wheezing and asthma at 16 years of age.³⁷ In the unselected birth cohort in New Zealand, only 30% of those with at least 2 wheezing episodes in childhood had persistent symptoms through age 26 years.³⁵ Of those with remission during adolescence, 60% subsequently relapsed before the age of 26 years. Bronchodilator reversible airways obstruction, airway reactivity to methacholine, allergic sensitization to dust mites, earlier age at symptom onset, and female sex were predictors of persistence or relapse by age 26 years in multivariate modeling.³⁵ Further longitudinal follow-up of the adolescents in our cohort will be needed to determine whether there are similar risk factors for relapse among those with severe childhood asthma.

Several cohort studies have demonstrated that asthma in general is more common in boys than girls and that it is more common in women than men.^{3,8,9,16,38,39} Therefore we were surprised that boys and girls with severe asthma were equally likely to improve. One explanation is that adolescence is a crossover period in which both girls and boys with severe asthma improve,³⁹ and older women with asthma were not typically girls with severe asthma who never improved. Additional longitudinal studies of severe asthma will be required to investigate this phenomenon.

The ATS/ERS criteria for severe asthma diagnosis represent only one of several measures that can be used to assess severity and control.^{1,3} We chose it as our benchmark in the SARP III prospective study because of its widespread use and acceptance and because of its incorporation of previous guidelines.¹ Clearly, by all criteria, there remain adolescents and young adults who have severe refractory symptoms,³ and studies of improved treatment strategies are needed. However, the outcome measures and power analyses used for these studies will need to account for the fact that symptoms, medication requirements, exacerbations, and proportions of children classified as having severe asthma all decreased during adolescence, whereas lung function did not change.

Several caveats merit discussion. First, as is typical of longitudinal assessment of adolescents, some participants dropped out of the study. However, there was no difference in the rate of dropout between patients with severe asthma at the outset compared with those without severe asthma.

Second, biologic therapies were not excluded. However, there was no difference between subjects whose severe asthma did and did not resolve with regard to use of anti-IgE or anti-IL-5, and only one subject was enrolled in experimental protocols.

Third, 5 (3%) subjects stopped meeting severe asthma criteria by year 3 in part because they did not require an increase in ICS dose when they became 12 years old. However, adults require higher doses, and we believe that not requiring an adult dose is a legitimate measure of improvement.

Fourth, study participation can improve outcomes, but this was not the principal driver of resolution because severe asthma did not resolve in most adult subjects in the cohort (see Fig E1).

Finally, the first year of improvement in symptom score could be explained in part by recall bias at study entry. However, steady improvement in subjective and objective measures associated with severe asthma in subsequent years of longitudinal follow-up argues against recall bias being the driver of resolution. Furthermore, participant report of exacerbations in the prior year is a consistent entry criterion for studies of severe asthma, and therefore our findings are relevant to planning clinical trials in this population irrespective of the role of recall bias.

Four central findings from this cohort of children with severe asthma will likely be relevant in designing future clinical trials. First, fully half of children with severe asthma no longer qualified as having severe asthma 3 years later, and there was a year-to-year, stepwise decrease in the proportion meeting severe asthma criteria. Second, asthma severity decreased equally in male and female subjects during longitudinal follow-up in adolescence; this was surprising given cross-sectional evidence that children with severe asthma are disproportionately male and that adults with severe asthma are disproportionately female. Third, children with a peripheral eosinophil count of greater than 436 cells/ μ L had increased odds of no longer having severe asthma after 3 years. Finally, neither low lung function nor high BMI were observed in the children whose asthma severity classification did not improve, nor did lung function or BMI change significantly in association with decreased symptoms, exacerbations, and medication requirements.

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Key messages

- Half of children with severe asthma initially no longer had severe asthma after 3 years.
- Asthma severity decreased equally in male and female subjects.
- Peripheral eosinophilia predicted resolution.

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	Pitt Peds 822	Juan C. Celedón, MD Allyson Larkin, MD
UCSF	UCSF Adult 841/UCSF Peds 842	John Fahy, MD
University of Wisconsin–Madison	Madison 811	Nizar Jarjour, MD
Virginia/Ohio	UVA 851	Gerry Teague (subcontract investigator)
	Rainbow Babies 852	Benjamin Gaston, MD
	Cleveland Clinic/Case Western Reserve University 853	Serpil Erzurum (subcontract investigator)
	VCU 854	Anne Marie Irani (subcontract investigator)
Wake Forest/Emory	Wake Forest 861	Wendy Moore, MD Eugene Bleeker, MD (remote)
	Emory 862	Anne Fitzpatrick (subcontract investigator)
Washington University (St Louis)	St Louis 831	Mario Castro, MD

PI, Principal investigator; *UCSF*, University of California–San Francisco; *UVA*, University of Virginia.

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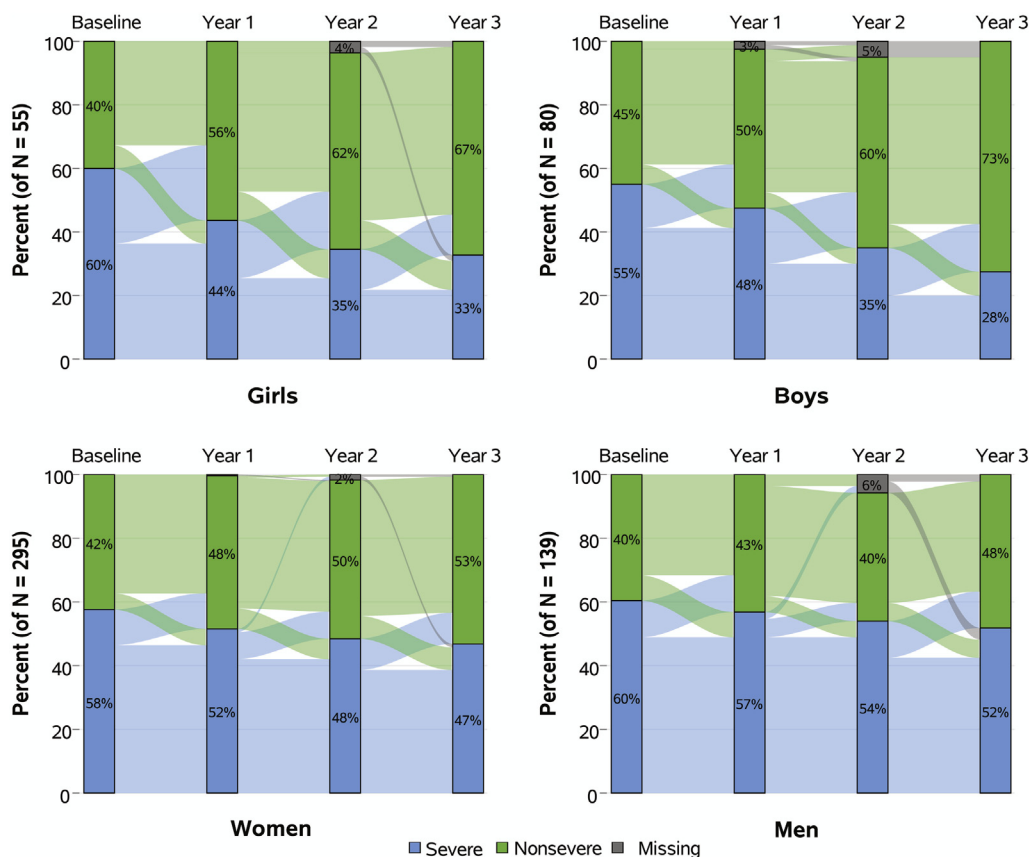


FIG E1. Sankey plot showing year-to-year change in asthma severity in the SARP III pediatric cohort (*top*) and SARP III adult cohort (*bottom*), each stratified by sex, for those subjects who completed all 3 years of the study. *Stacked bars* show percentages of participants with severe and nonsevere asthma at each yearly visit, and *connecting regions* show the proportion that changed categories from one year to the next.

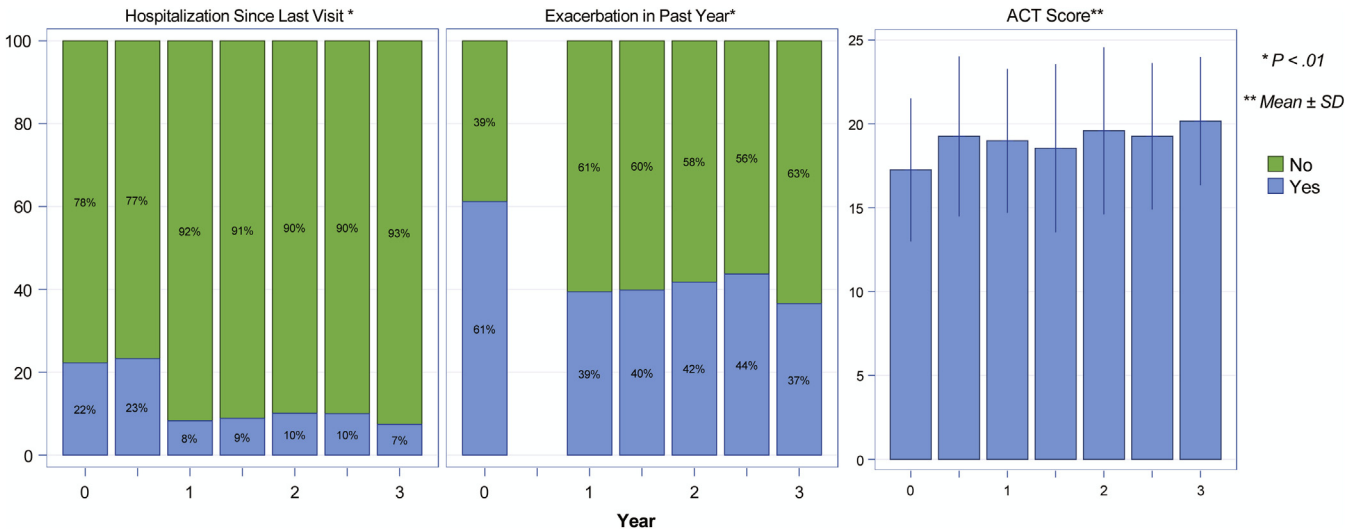


FIG E2. Longitudinal analysis of severe asthma hospitalizations, exacerbation, and Asthma Control Test (ACT) scores (including the results of telephone follow-up) among children with severe asthma at the first visit. **A and B,** Percentages of the subset of pediatric participants with severe asthma at baseline who reported hospitalization since the last visit (Fig E2, A) and exacerbation since the last visit (Fig E2, B). **C,** ACT score at each time point is shown. A linear trend test accounting for repeated measures is significant at a *P* value of less than .01.

TABLE E1. ATS/ERS consensus statement definition of severe asthma (from Ref 1)

Asthma that requires treatment with guidelines-suggested medications for GINA step 4-5 asthma (high-dose ICS* and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy
Uncontrolled asthma is defined as at least 1 of the following:
1. Poor symptom control: ACQ score consistently ≥ 1.5, ACT score < 20 (or “not well controlled” by NAEPP/GINA guidelines)
2. Frequent severe exacerbations: 2 or more bursts of systemic CS (≥3 days each) in the previous year
3. Serious exacerbations: ≥1 hospitalization, ICU stay, or mechanical ventilation in the previous year
4. Airflow limitation: FEV ₁ of <80% of predicted value after appropriate bronchodilator withhold (in the face of reduced FEV ₁ /FVC ratio defined as less than the lower limit of normal)
5. Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CS, corticosteroids; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICU, intensive care unit; LABA, long-acting β₂-agonist; NAEPP, National Asthma Education and Prevention Program.
*The definition of high-dose ICS is age specific.

TABLE E2. Annual asthma severity classification and termination status

Assessment timing	Severity classification	Not terminated, no. (%)	Terminated before year 3, no. (%)	<i>P</i> value
Baseline	Severe	88 (79)	23 (21)	.26
	Nonsevere	66 (86)	11 (14)	
Year 1	Severe	69 (85)	12 (15)	.67
	Nonsevere	83 (87)	12 (13)	
Year 2	Severe	54 (90)	6 (10)	.56
	Nonsevere	92 (93)	7 (7)	

P values were determined by using χ^2 tests for baseline and year 1 and Fisher exact tests for year 2.

TABLE E3. Characteristics of participants by termination status

Characteristic	Terminated early	Not terminated early	P value
No.	34	154	
Severe asthma (%)	23 (67.6)	88 (57.1)	.260
Age at enrollment (y), mean $\pm$ SD	10.9 $\pm$ 2.8	11.6 $\pm$ 2.9	.171
Age at asthma diagnosis (y), mean $\pm$ SD	3.2 $\pm$ 2.9	3.1 $\pm$ 2.7	.857
Female sex (%)	13 (38.2)	58 (37.7)	.950
Male sex (%)	21 (61.8)	96 (62.3)	.950
White (%)	10 (29.4)	62 (40.3)	.462
African American (%)	16 (47.1)	65 (42.2)	
Other race (%)	8 (23.5)	27 (17.5)	
Hispanic (%)	6 (17.6)	22 (14.3)	.618
BMI percentile, mean $\pm$ SD	83.6 $\pm$ 25.3	74 $\pm$ 26.7	.056

TABLE E4. Characteristics at enrollment in participants with severe asthma at baseline whose symptoms resolved or did not resolve at year 3

Variable	Severe asthma persisted (n = 30)	Severe asthma resolved (n = 47)	P value
Age (y)	11.9 (3.3)	11.5 (2.7)	.569
Race/ethnicity			.360
White, non-Hispanic	12 (46)	14 (54)	
African American, non-Hispanic	12 (46)	14 (54)	
Hispanic	3 (25)	9 (75)	
Other	3 (23)	10 (77)	
BMI percentile	73.8 (28.7)	77.7 (23.5)	.871
Total IgE	855.5 (1490.6)	839.1 (1017.2)	.277
Log IgE	2.4 (0.73)	2.6 (0.60)	.277
No. of positive specific IgE test results	6.6 (5.2)	6.7 (4.5)	.785
FENO	42.1 (52.7)	33.0 (33.1)	.469
Log FENO	1.4 (0.4)	1.34 (0.4)	.469
Total eosinophils	315.4 (250.3)	428.8 (334.0)	.084
Total neutrophils	3495.6 (2844.2)	3686.2 (2116.1)	.433
Pre-BD FEV ₁ /FVC ratio	75.5 (9.2)	77.3 (11.0)	.263
Pre-BD FEV ₁ percent predicted	87.5 (14.2)	90.2 (17.6)	.427
Pre-BD FVC percent predicted	102.0 (13.2)	102.1 (14.1)	.946
Maximum post-BD FEV ₁ /FVC ratio	94.7 (9.7)	96.6 (8.8)	.415
Maximum post-BD FEV ₁ percent predicted	102.6 (13.5)	103.8 (15.8)	.644
Maximum post-BD FVC percent predicted	108.9 (12.7)	108.0 (14.4)	.767
Maximum reversibility (relative difference)	18.4 (11.6)	17.2 (18.5)	.206
MARS	21.7 (2.9)	21.4 (3.4)	.854
Mother smoked during pregnancy	4 (13.3)	4 (8.5)	.704
Exposed to smoking in the home	5 (16.7)	2 (4.3)	.103
MARS score	21.7 ± 2.9	21.4 ± 3.4	.85
Immunotherapy	1	2	1.0

Continuous variables are shown as means ($\pm$ SDs), and categorical variables are shown as numbers (percentages). *P* values for the Wilcoxon rank-sum test are shown for continuous variables, and those for the Fisher exact test are shown for categorical variables.

BD, Bronchodilator; FENO, Fraction of exhaled nitric oxide; FVC, forced vital capacity; MARS, Medication Adherence Rating Scale.

TABLE E5. Positive aeroallergen ImmunoCAP results stratified according to those whose severe asthma did and did not resolve by year 3

Aeroallergen	Severe asthma persisted (n = 30)	Severe asthma resolved (n = 47)
Alt_tenuis_Pos	13 (43)	22 (47)
Asp_fumigatus_pos	12 (40)	16 (34)
Cat_pos	15 (50)	29 (62)
Cladosporium_pos	11 (37)	17 (36)
Roach_pos	11 (37)	14 (30)
Ragweed_pos	12 (43)	17 (37)
Dfarinae_pos	18 (60)	30 (64)
Dpteron_pos	17 (57)	29 (62)
Dog_pos	18 (60)	30 (64)
Grass_pos	16 (53)	24 (51)
Mouse_pos	7 (23)	13 (28)
Rat_pos	7 (23)	14 (30)
Treemix4_pos	15 (50)	22 (47)
Treemix6_pos	13 (43)	19 (40)
Weedmix_pos	13 (43)	19 (41)
Any 1 specific IgE	28 (93)	44 (94)

Results are shown as numbers (percentages). *P* values are not significant for each result.