CHEST

Original Research

ASTHMA

Predictors of Symptoms Are Different From Predictors of Severe Exacerbations From Asthma in Children

*Ann Chen Wu, MD, MPH; Kelan Tantisira, MD, MPH; Lingling Li, PhD; Brooke Schuemann, BS; Scott T. Weiss, MD; and Anne L. Fuhlbrigge, MD; for the Childhood Asthma Management Program Research Group**

Background: **Asthma therapy is typically prescribed and titrated based on patient or parent self-report of symptoms. No longitudinal studies have assessed the relationship between symptoms and severe asthma exacerbations in children. The goal of our study was (1) to assess the association of asthma symptoms with severe asthma exacerbations and (2) to compare predictors of persistent asthma symptoms and predictors of severe asthma exacerbations.**

Methods: **The Childhood Asthma Management Program was a multicenter clinical trial of 1,041 children randomized to receive budesonide, nedocromil, or placebo (as-needed β-agonist). We conducted a post hoc analysis of diary cards that were completed by subjects on a daily basis to categorize subjects as having persistent vs intermittent symptoms. We defined a severe asthma exacerbation as an episode requiring ≥ 3 days use of oral corticosteroids, hospitalization, or ED visit due to asthma based on self-report at study visits every 4 months.**

Results: **While accounting for longitudinal measures, having persistent symptoms from asthma was significantly associated with having severe asthma exacerbations. Predictors of having persistent symptoms compared with intermittent symptoms included not being treated with inhaled corticosteroids, lower FEV_1/FVC ratio, and a lower natural logarithm of provocative concentration of methacholine producing a 20% decline in FEV_1 ($lnPC_{20}$). Predictors of having one or more severe asthma exacerbations included younger age, history of hospitalization or ED visit in the prior year, ≥ 3 days use of oral corticosteroids in the prior 3 months, lower FEV_1/FVC ratio, lower $lnPC_{20}$, and higher logarithm to the base 10 eosinophil count; treatment with inhaled corticosteroids was predictive of having no severe asthma exacerbations.**

Conclusions: **Patients with persistent symptoms from asthma were more likely to experience severe asthma exacerbations. Nevertheless, demographic and laboratory predictors of having persistent symptoms are different from predictors of severe asthma exacerbations. Although symptoms and exacerbations are closely related, their predictors are different. The current focus of the National Asthma Education and Prevention Program guidelines on the two separate domains of asthma control, impairment and risk, are supported by our analysis.**

CHEST 2011; 140(1):100–107

Abbreviations: CAMP = Childhood Asthma Management Program; GEE = generalized estimating equation; $lnPC_{20}$ = natural logarithm of provocative concentration of methacholine producing a 20% decline in FEV_1; log_{10} = logarithm to the base 10; NAEPP = National Asthma Education and Prevention Program; PC_{20} = provocative concentration of methacholine producing a 20% decline in FEV_1

Asthma is the most common chronic illness in children, affecting approximately 8.5% of children in the United States.[1] According to the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines, prevention of asthma morbidity requires assessment of asthma severity and control, which include two domains: (1) impairment, which includes an evaluation of the frequency and intensity of symptoms; and (2) risk, which includes an assessment of the likelihood of asthma exacerbations.[2] The risk of exacerbation is correlated with both health-related quality of life as measured by the Asthma Quality of

Life Questionnaire, an asthma-specific instrument, and with the level of asthma control as measured by the Asthma Therapy Assessment Questionnaire.[3-5] Both of these instruments include asthma symptoms in their assessment, suggesting increased symptoms are associated with increased risk of exacerbations.[3-5] Symptoms increase in adults prior to onset of acute exacerbations,[5-7] even though symptoms may have poor specificity for predicting severe exacerbations.[7] Similarly, a 1-year pediatric trial found that symptom scores worsened before an exacerbation, but the best predictor of an exacerbation is a past history of an exacerbation.[8] Nevertheless, the relationship between symptoms and severe exacerbations from asthma in children is unknown over a longer time period, and scarce data are available to support the NAEPP guidelines for children. Children who are at risk for exacerbations from asthma may not experience greater asthma symptoms before the onset of the severe exacerbation.[9]

To our knowledge, no studies have examined both the predictors of asthma symptoms and the predictors of severe exacerbations using longitudinal data in children. Predictors of asthma symptoms in adults include use of oral corticosteroids, comorbid illnesses, higher BMI, and low income.[10] Predictors that are associated with increased risk of exacerbations in adults include being female, nonwhite, poor, a current smoker, or having had two or more ED visits or hospitalizations for asthma in the past year.[11-14] In children, predictors of being at risk for severe exacerbations include having severe and persistent airflow obstruction based on spirometry and any history of intubation or admission to the ICU.[15-19] The strongest predictor for risk of exacerbations is a history of previous exacerbation.[8,16] The objectives of this study were (1) to assess the association of asthma symptoms with severe asthma exacerbations, and (2) to compare predictors of persistent asthma symptoms and predictors of severe exacerbations in children with asthma.

The Bottom Line

How does this work advance the field?

This study provides support of national asthma guidelines. Patients with asthma who have persistent symptoms may be at greater risk of experiencing an ED visit or hospitalization or requiring at least 3 days' use of systemic corticosteroids. In making clinical decisions for asthma management, assessment of both symptoms and exacerbations is important.

What are the clinical implications?

Although symptoms and exacerbations are closely related, their predictors are different. The goals of asthma therapy include reducing impairment by preventing symptoms and reducing risk by preventing exacerbations.

Material and Methods

Design

We conducted an analysis using data from the Childhood Asthma Management Program (CAMP), a multicenter trial of 1,041 children with mild to moderate persistent asthma between the ages of 5 and 12 years who were randomly assigned to receive budesonide, nedocromil, or placebo.[20] Details of the CAMP protocol have been previously published.[20] The institutional review board at each of the eight participating institutions approved the study, and parents or guardians of the subjects gave informed consent.[20]

Data Collection

Parents or subjects recorded information on symptoms on a daily basis in diary cards for the 4 years of the study. Subjects assigned a code from 0 to 3 for each day, representing an assessment of the severity and frequency of asthma episodes for the day. A "0" indicated no asthma episodes during the day; a "1" indicated they had one to three intermittent asthma episodes, each lasting ≤ 2 h; a "2" indicated they had four or more intermittent asthma episodes or one or more asthma episodes that temporarily interfered with activity, play, school, or sleep; and a "3" indicated they experienced one or more asthma episodes that lasted ≥ 2 h or resulted in shortened normal activity, seeing a doctor for acute care, or going to a hospital for acute care. At each research study visit, parents reported whether the subjects had been seen in the ED or hospitalized for asthma since the prior visit. Parents also reported the number of days since the prior visit that subjects had been given oral corticosteroids.

Manuscript received October 28, 2010; revision accepted January 3, 2011.
Affiliations: From the Center for Child Health Care Studies (Drs Wu and Li), Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School; the Department of Pediatrics (Dr Wu), Children's Hospital; Harvard Medical School (Drs Wu, Tantisira, Li, Weiss, and Fuhlbrigge); the Channing Laboratory (Drs Tantisira, Weiss, and Fuhlbrigge and Ms Schuemann) and the Center for Genomic Medicine (Drs Tantisira and Weiss), Department of Medicine, Brigham and Women's Hospital, Boston, MA.
*A complete list of participants is located in e-Appendix 1.
Funding/Support: The Childhood Asthma Management Program (CAMP) is supported by the National Heart, Lung, and Blood Institute [Contracts NO1-HR-16044, 16045, 16046, 16047, 16048, 16049, 16050, 16051, and 16052] and General Clinical Research Center [Grants M01RR00051, M01RR0099718-24, M01RR02719-14, and RR00036] from the National Center for Research Resources. The CAMP Continuation Study/Phases 2 and 3 were supported by the National Heart, Lung, and Blood Institute [Grants U01HL075232, U01HL075407, U01HL075408, U01HL075409, U01HL075415, U01HL075416, U01HL075417, U01HL075419, U01HL075420, and U01HL075408].
Correspondence to: Ann Wu, MD, MPH, Department of Population Medicine, 133 Brookline Ave, 6th Floor, Boston, MA 02215-5301; e-mail: ann.wu@childrens.harvard.edu

DOI: 10.1378/chest.10-2794

Research coordinators obtained spirometry measurements on the subjects both before and after a bronchodilator at study visits. The subjects' airway responsiveness to methacholine was measured by calculating the provocative concentration of methacholine that caused a 20% decrease in the FEV_1 (PC_{20}). Additional demographic information was obtained at an initial prerandomization study visit. Race/ethnicity, family income, and parental education were determined by parental self-report. Height, weight, blood samples including measurement of eosinophil and IgE counts, and skin-prick testing were obtained at baseline, just prior to randomization.

Measures

Our main outcome measures were experiencing intermittent or persistent symptoms from asthma and occurrence of one or more severe exacerbations from asthma. Subjects returned the diary cards at routine study visits; thus, we developed a symptom score for each 4-month period. Subjects who recorded a 1 or more for a mean of ≥ 2 days per week of symptoms during each 4-month block were considered to have persistent symptoms for the time block. Subjects who had 4 weeks of persistent symptoms within a 4-month period were considered to have persistent symptoms for the 4-month period. Our inclusion criteria for having completed diary cards regularly included subjects who recorded their symptoms at least 6 out of 7 days per week in 3 out of 4 weeks. We limited our study population to those who were followed in the study for 4 years and had completed the last visit at 48 months.

We defined severe exacerbations according to the Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations.[21] A severe exacerbation included an episode that required at least 3 days' use of systemic corticosteroids, an ED visit, or hospitalization[21] and was based on a previous study that examined recurrent severe exacerbations.[22]

Statistical Analyses

Analyses were conducted in SAS, version 9.1 (SAS Institute; Cary, North Carolina). In order to study the outcome of intermittent vs persistent symptoms, we first conducted bivariate analyses to evaluate the association of candidate variables with persistent symptoms. The candidate variables included demographic variables, pulmonary function tests, and biologic markers in the 4 years of the study. In order to determine our potential confounding variables, we created a symptom category (intermittent vs persistent) for each 4-month block. If a subject had a mean of ≥ 2 days of symptoms per week, the subject was categorized as having persistent symptoms for that 4-month block, in order to be consistent with national guidelines. Our longitudinal analysis accounted for subjects' symptoms category over all 4 years of the study; thus, each subject had a symptom category for each of 12 blocks. We started with a comprehensive model including all the covariates significantly correlated ($P < .10$) with persistent symptoms in the bivariate analyses. Generalized estimating equation (GEE) models[23] were used to study the predictors of persistent symptoms using repeated measurements.

We studied our second outcome, severe exacerbations, with similar methodology. We conducted bivariate analyses to evaluate the association of the same candidate variables and severe exacerbations. For each of the 12 4-month blocks of the 4 years of the trial, subjects were assessed as having severe exacerbations or not. Covariates correlated at $P < .10$ in bivariate analyses were included in the multivariate model. GEE models[23] were used to determine the predictors of severe exacerbations with repeated measurements.

To assess the association of asthma symptoms with severe asthma exacerbations, we determined whether the number of blocks of persistent symptoms was associated with the number of severe exacerbations using a χ^2 test over 4 years. Next, we fit a GEE model with persistent symptoms as the outcome and severe exacerbations as the predictor. We fit a second GEE model with severe exacerbations as the outcome and persistent symptoms as the predictor. We studied this association in both directions because it is unclear which measure should be the outcome. For each of these two GEE models, we attempted to adjust for confounding by including all of the covariates that are significantly correlated ($P < .10$) with either outcome in the bivariate analyses. In addition, we included whether the subject was treated with inhaled corticosteroids (budesonide group) vs not treated with inhaled corticosteroids (placebo and nedocromil groups) to account for the positive effect of inhaled corticosteroids on exacerbations and symptoms. The final multivariate model presented in this article retains those covariates with $P < .1$.

Results

Of the 1,041 subjects in the trial, 1,019 met our inclusion criteria for having completed daily diary cards regularly. As shown in Table 1, the subjects in the budesonide group were less likely to have persistent symptoms. In the budesonide group, 26% (78) of subjects had persistent symptoms compared with 37% (115) in the nedocromil group and 44% (179) in the placebo group ($P < .0001$). Forty percent (197) of subjects who had a history of previous ED visit or hospitalization visit had persistent symptoms, whereas 33% (175) of subjects who did not have a previous history of ED visit or hospitalization had persistent symptoms ($P = .016$). There were no significant differences between intermittent and persistent symptom category groups with respect to race/ethnicity, gender, parental education, exposure to smoking while in utero, or family history of asthma (Table 1). Twenty-one percent (66) of subjects in the budesonide group experienced one or more severe exacerbations compared with 30% (95) in the nedocromil group and 37% (154) in the placebo group ($P < .0001$). Subjects with a previous history of ED visits or hospitalizations vs subjects without such history were more likely to have one or more severe exacerbations during the first year of the study (39% vs 22%, $P < .0001$). Similarly, subjects with a history of treatment with oral corticosteroids for ≥ 3 days in the 6 months prior to randomization were more likely to experience a severe exacerbation (48% vs 22%, $P < .0001$). There were no significant differences between subjects who had no severe exacerbations vs subjects who experienced one or more severe exacerbations during the first year of the study with respect to race/ethnicity, gender, household education, parental education, smoke exposure in utero, or family history of asthma.

Between subjects who were in the intermittent vs persistent symptom categories, there was a significant difference in the FEV_1/FVC ratio, FEV_1 % predicted,

Table 1—*Demographic Factors and Information on Medical History at Baseline Stratified by Symptom Category and Number of Severe Exacerbations During the 4 y of the Study*

	Symptom Category (No. = 1,019)			Severe Exacerbations (No. = 1,041)		
Demographic or Medical History	Intermittent	Persistent	*P* Value	0	≥ 1	*P* Value
Treatment group			< .0001			< .0001
Budesonide	226 (74)	78 (26)		245 (79)	66 (21)	
Nedocromil	193 (63)	115 (37)		217 (70)	95 (30)	
Placebo	228 (56)	179 (44)		264 (63)	154 (37)	
Race/ethnicity			.46			.53
White	443 (63)	255 (37)		506 (71)	205 (29)	
Black	94 (68)	44 (32)		93 (67)	45 (33)	
Hispanic	58 (62)	35 (38)		65 (66)	33 (34)	
Other	52 (58)	38 (42)		62 (66)	32 (34)	
Gender			.63			.90
Male	389 (64)	218 (36)		434 (70)	187 (30)	
Female	258 (63)	154 (37)		292 (70)	128 (30)	
Household income			.019			.94
< $30,000	131 (57)	100 (43)		168 (69)	74 (31)	
≥ $30,000	488 (65)	260 (35)		528 (70)	230 (30)	
Parental education			.70			.17
High school or less	116 (65)	63 (35)		137 (74)	48 (26)	
Some college	531 (63)	308 (37)		589 (69)	266 (31)	
Intrauterine smoke exposure			.19			.31
Present	101 (68)	47 (32)		110 (73)	40 (27)	
Absent	542 (63)	324 (37)		613 (69)	273 (31)	
Family history of asthma			.21			.41
Present	347 (62)	214(38)		391 (68)	183 (32)	
Absent	286 (66)	149 (34)		313 (71)	131 (30)	
History of ED visit or hospitalization in year prior to randomization			.016			< .0001
Present	292 (60)	197 (40)		305 (61)	197 (39)	
Absent	355 (67)	175 (33)		421 (78)	118 (22)	
History of oral corticosteroids for ≥ 3 d in 6 mo prior to randomization			.032			< .0001
Present	184 (59)	130 (41)		166 (52)	154 (48)	
Absent	461 (66)	239 (34)		557 (78)	159 (22)	

Data are presented as No. (%) unless indicated otherwise.

natural logarithm of PC_{20} ($lnPC_{20}$), logarithm to the base 10 (log_{10}) IgE count, log_{10} eosinophil count, and number of positive skin tests (Table 2). Age, FEV_1, and BMI *z* score were not significantly different between the two groups. Age at randomization, FEV_1/FVC ratio, FEV_1 % predicted, FEV_1, ln PC_{20}, log_{10} IgE count, BMI *z* score, log_{10} eosinophil count, and number of positive skin tests at randomization

Table 2—*Mean Values for Clinical Factors at Randomization, Stratified by Symptom Category and Number of Severe Exacerbations in the 4 y of the Study*

	Symptom Category (No. = 1,019)			Severe Exacerbations (No. = 1,038)		
Clinical Factor at Randomization, mean	Intermittent	Persistent	*P* Value (Intermittent vs Persistent)	0	≥ 1	*P* Value (0 vs ≥ 1)
Age, y	8.9	9.0	.26	9.0	8.3	< .0001
FEV_1/FVC ratio, %	80.9	77.6	< .0001	79.5	77.8	.01
FEV_1, % predicted	95.0	91.5	.0001	93.5	90.2	.009
FEV_1, L	1.66	1.61	.13	1.67	1.47	< .0001
$lnPC_{20}$	0.31	−0.28	< .0001	0.10	−0.21	.0007
Log_{10} IgE count	2.56	2.76	< .0001	2.52	2.67	.0002
BMI *z* score	0.50	0.44	.41	0.46	0.22	.0033
Log_{10} eosinophil count	2.46	2.58	.0007	2.43	2.52	.0014
No. positive skin tests	4.91	6.32	< .0001	5.82	5.57	.0011

$lnPC_{20}$ = natural logarithm of provocative concentration of methacholine producing a 20% decline in FEV_1; log_{10} = logarithm to the base 10; PC_{20} = provocative concentration of methacholine producing a 20% decline in FEV_1.

Table 3—*Number of 4-mo Periods of Persistent Symptoms Stratified by Number of Severe Exacerbations During the 4 y of the Study*

No. Blocks of Persistent Symptoms[a]	No Severe Exacerbations, No. (%)	≥ 1 Severe Exacerbations, No. (%)	Total, No.
0	190 (86)	32 (14)	222
1	139 (81)	33 (19)	172
2	95 (70)	41 (30)	136
3	60 (67)	30 (33)	90
4	41 (59)	28 (41)	69
5	41 (60)	27 (40)	68
6	34 (68)	16 (32)	50
7	22 (50)	22 (50)	44
8	16 (46)	19 (54)	35
9	14 (56)	11 (44)	25
10	13 (41)	19 (59)	32
11	19 (54)	16 (46)	35
12	13 (41)	19 (59)	32
Total	697 (69)	313 (31)	1,010

Subjects were classified as having persistent symptoms for a 4-month period if they had a mean of ≥ 2 days per week of symptoms.
[a]$P < .0001$. The proportion of subjects having one or more severe exacerbations was compared with those with no severe exacerbations at each study visit using a χ^2 test.

were significantly different between subjects who had no severe exacerbations vs at least one severe exacerbation.

Subjects with more blocks of persistent symptoms were more likely to experience one or more severe exacerbations during the 4 years of the study ($P < .0001$) (Table 3); out of a maximum of 12 4-month blocks during the trial, 14% of subjects with no blocks of persistent symptoms had one or more severe exacerbations, whereas 59% of subjects with 12 blocks of persistent symptoms had one or more severe exacerbations.

While accounting for longitudinal measures, symptom category is associated with severe exacerbations, even after adjusting for the following covariates: age, treatment with inhaled corticosteroids, family history of asthma, previous history of ED visit or hospitalization in prior year, previous history of ≥ 3 days of treatment with oral corticosteroids in prior 6 months, FEV_1/FVC ratio, FEV_1 % predicted, $lnPC_{20}$, log_{10} IgE count, BMI *z* score, log_{10} eosinophil count, and number of positive skin tests ($P < .0001$). We also studied whether the reverse hypothesis could be true, that having one or more severe exacerbations could be a predictor of subjects who are more likely to have persistent symptoms. We found that this hypothesis was also true, even after adjusting for treatment with inhaled corticosteroids, history of ED visits or hospitalization in the prior year, history of ≥ 3 days of treatment with oral corticosteroids in prior 3 months, FEV_1/FVC ratio, FEV_1 % predicted, $lnPC_{20}$, log_{10} IgE count, log_{10} eosinophil count, and number of positive skin tests ($P < .0001$).

Predictors of Symptoms vs Predictors of Exacerbation

On multivariate analysis, predictors of having persistent symptoms compared with intermittent symptoms included not being treated with inhaled corticosteroids, lower FEV_1/FVC ratio, and a lower $lnPC_{20}$. Predictors of having one or more severe exacerbations included younger age, history of ED visits or hospitalization in the prior year, history of ≥ 3 days of treatment with oral corticosteroids in prior 3 months, lower FEV_1/FVC ratio, lower $lnPC_{20}$, and higher log_{10} eosinophil count; being treated with inhaled corticosteroids was predictive of having no exacerbations (Table 4).

Discussion

Our study suggests that experiencing persistent symptoms from asthma is closely associated with having severe exacerbations from asthma. The following predictors of experiencing persistent symptoms are similar to the predictors of experiencing severe exacerbations: (1) treatment with inhaled corticosteroids is protective against experiencing persistent symptoms and severe exacerbations, (2) lower $lnPC_{20}$ is associated with both persistent symptoms and severe exacerbations, and (3) lower FEV_1/FVC ratio is associated with persistent symptoms and severe exacerbations. Nevertheless, our study found predictors of severe exacerbations that were not also predictors of persistent symptoms: younger age, history of ED visits or hospitalizations in prior year, history of ≥ 3 days use of oral corticosteroids in prior 3 months, and log_{10} eosinophil count. Our study results provide support for current national guidelines for asthma in recommending the assessment of both symptoms and history of exacerbations when determining severity and control of asthma in children.

This study is unique in that we were able to prospectively monitor exacerbations and symptoms along with lung function measures and other clinical factors at study visits every 4 months. To our knowledge, our study is the first to examine predictors of symptoms while accounting for repeated measures over a longitudinal timeframe of 4 years in children.

Studies in adults suggest that symptoms from asthma increase prior to severe exacerbations,[5] and we found that persistent symptoms are associated with severe exacerbations in children. Our finding that predictors of persistent symptoms are different from predictors of severe exacerbations supports the

Table 4—*Predictors of Persistent Symptoms and of Having One or More Severe Exacerbations From Asthma During the 4 y of the Study*

Predictors	β Estimate	CI	*P* Value
Predictors of persistent symptoms			
Inhaled corticosteroid group (budesonide)	**−0.32**	**−0.55 to −0.099**	**.0045**
Income	−0.036	−0.27 to 0.20	.76
History of ED visits/hospitalization	0.13	−0.07 to 0.32	.21
History of ≥ 3 d use of oral corticosteroids	0.20	−0.0033 to 0.39	.054
FEV_1/FVC ratio	**−0.029**	**−0.044 to −0.015**	**< .0001**
FEV_1, % predicted	0.0036	−0.0049 to 0.012	.40
$lnPC_{20}$	**−0.31**	**−0.38 to −0.24**	**< .0001**
Log_{10} IgE count	0.15	−0.030 to 0.33	.10
Log_{10} eosinophil count	0.027	−0.18 to 0.23	.80
Number of positive skin tests	0.019	−0.0066 to 0.045	.15
Predictors of severe exacerbations			
Age	**−0.10**	**−0.16 to −0.052**	**< .0001**
Inhaled corticosteroid group (budesonide)	**−0.45**	**−0.73 to −0.17**	**.0016**
Family history of asthma	0.18	−0.034 to 0.40	.10
History or ED visit/hospitalization	**0.73**	**0.50 to 0.96**	**< .0001**
History of ≥ 3 d use of oral corticosteroids	**0.40**	**0.17 to 0.62**	**.0005**
FEV_1/FVC ratio	**−0.023**	**−0.040 to −0.0061**	**.0076**
FEV_1, % predicted	0.0056	−0.0049 to 0.016	.29
$lnPC_{20}$	**−0.091**	**−0.18 to −0.0066**	**.033**
Log_{10} IgE count	0.083	−0.11 to 0.27	.39
Log_{10} eosinophil count	**0.26**	**0.019 to 0.50**	**.034**
BMI *z* score	−0.039	−0.14 to 0.067	.47
Number of positive skin tests	−0.019	−0.046 to 0.0074	.15

Boldface indicates variables that remained significantly associated with the outcome variable on multivariate analysis. N = 1,019. See Table 2 for expansion of abbreviations.

2007 NAEPP recommendations for assessing risk and impairment separately. Although we found that persistent symptoms are associated with severe exacerbations, 14% of subjects in our study never had persistent symptoms during the entire 4 years of the trial, yet experienced one or more severe exacerbations. One study, reporting similar results, found that 55% of patients admitted to the ICU for asthma had been classified as having intermittent asthma.[24] In a second study of children who were believed to have adequate symptom control based on parental report, nearly one-third had two or more ED or unscheduled outpatient visits for asthma.[25] This finding supports the 2007 NAEPP guideline recommendation; "intermittent" asthma is no longer categorized as "mild intermittent" asthma because even patients with intermittent asthma can have severe exacerbations.

The results of our analysis are different from an analysis by Covar et al,[8] who found that the only predictor of exacerbations is a previous history of exacerbations. Reasons for our contrasting findings could be that the Covar et al[8] study examined a shorter 48-week period, compared with our analysis, which examines a 4-year time frame. Similar to our study, Covar et al[8] found that symptoms increased prior to exacerbations but had poor specificity for predicting exacerbations. Our finding that $lnPC_{20}$ is associated with persistent symptoms is not surprising given previous findings that increased airway hyperresponsiveness as measured by PC_{20} is associated with a retrospective report of wheezing and chronic cough.[26,27] Our finding that $lnPC_{20}$ is associated with severe exacerbations suggests that $lnPC_{20}$ could be an important marker of risk. Although the 2007 NAEPP recommendations mention airway hyperresponsiveness as a potential biomarker for risk, it states that few studies have validated the assessment of airway hyperresponsiveness by analyzing their relationship to the rate of adverse events. We believe that future studies of PC_{20} are important because PC_{20} has value in predicting persistent symptoms and severe exacerbations, even though routine clinical testing is impractical.

Other predictors of severe exacerbations were younger age, history of ED visits or hospitalizations in prior year, history of ≥3 days of treatment with oral corticosteroids in prior 3 months, FEV_1/FVC ratio, and log_{10} eosinophil count. Younger age was also associated with severe exacerbations in the study by Covar et al.[8] Previous studies have found that predictors of experiencing severe exacerbations are being treated with inhaled corticosteroids,[28] having had previous histories of ED visits or hospitalizations,[13,29-31] or having had treatment in the past with oral corticosteroids.[30] The previous findings that treatment with inhaled corticosteroids is a predictor of severe

exacerbations has been found in observational studies and are likely due to confounding by indication; thus, this study offers the strength of being able to assess whether treatment with inhaled corticosteroids decreases the risk of exacerbations because the treatment is randomized. Our finding that having had previous histories of exacerbations or ED visits is a predictor of future severe asthma exacerbations has been found in a previous analysis.[17] In addition, we found that lower FEV_1/FVC ratio is associated with severe exacerbations, which is consistent with previous studies[32]; these results support the inclusion of FEV_1/FVC ratio as an important component of the 2007 NAEPP guidelines for asthma, which state that low FEV_1/FVC ratio indicates increased risk of future adverse events. Although FEV_1 and FEV_1/FVC were associated with both persistent symptoms and exacerbations in univariate models, in multivariable models, including both variables, only FEV_1/FVC ratio remained a significant predictor of symptoms and severe exacerbations. Strunk and colleagues[33] previously compared the CAMP cohort with children without asthma from the Harvard Six Cities Study. In both boys and girls, reductions in FEV_1/FVC were the most prominent, resulting from the combined effect of an overall reduction in FEV_1 and an increase in FVC. In pediatric populations with asthma, baseline lung function is within the normal range. Therefore, the ratio may be a more sensitive indicator of obstruction, justifying the need to assess FEV_1/FVC in addition to FEV_1. Eosinophils mediate asthma-related inflammation,[34] thus our findings that higher eosinophil counts are associated with severe exacerbations.

Limitations of our study include the subjective reporting of symptoms and, thus, recall bias. Our classification of subjects as having persistent or intermittent symptoms was based on self-report on daily diary cards. These symptom categories could potentially be inaccurate if subjects did not accurately classify their daily symptoms or if they did not complete the diary cards on a daily basis but rather completed them at the end of a week or month. Nevertheless, in the clinical setting, we make treatment decisions based on patient report of symptoms in the previous weeks or months. Additional limitations of our study are that it is based on a closely followed clinical trial; thus, the results may not be generalizable to real-world settings, and this analysis was conducted post hoc.

In conclusion, persistent symptoms from asthma are associated with severe exacerbations from asthma. Subjects who experience severe exacerbations are also more likely to have persistent symptoms. However, the demographic and clinical predictors of persistent symptoms and severe exacerbations from asthma are different. Thus, assessing both symptoms and exacerbations is necessary in determining the level of asthma control and severity.

Acknowledgments

Author contributions: *Dr Wu:* contributed to study design, data analysis, and manuscript preparation.
Dr Tantisira: contributed to study design and manuscript preparation.
Dr Li: contributed to data analysis and manuscript revision.
Ms Schuemann: contributed to data analysis and manuscript revision.
Dr Weiss: contributed to study design and manuscript preparation.
Dr Fuhlbrigge: contributed to study design and manuscript preparation.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Fuhlbrigge received research funding from the National Institutes of Health and unrestricted research support from GlaxoSmithKline and Merck; served as a consultant to GlaxoSmithKline and Merck for the design and analysis of epidemiologic studies; and served on an advisory board and has been a member of a speakers bureau for GlaxoSmithKline and Merck in the past. Drs Wu, Tantisira, Li, and Weiss and Ms Schuemann have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The National Institutes of Health, which provided grants, had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, and approval of the manuscript.
Additional information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/140/1/100/suppl/DC1.

References

1. Moorman JE, Rudd RA, Johnson CA, et al; Centers for Disease Control and Prevention (CDC). National surveillance for asthma—United States, 1980-2004. *MMWR Surveill Summ*. 2007;56(8):1-54.
2. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol*. 2007;120(suppl 5):S94-S138.
3. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measuring health-related quality of life in adults during an acute asthma exacerbation. *Chest*. 2004;125(1):93-97.
4. Peters D, Chen C, Markson LE, Allen-Ramey FC, Vollmer WM. Using an asthma control questionnaire and administrative data to predict health-care utilization. *Chest*. 2006;129(4):918-924.
5. Tierney WM, Roesner JF, Seshadri R, Lykens MG, Murray MD, Weinberger M. Assessing symptoms and peak expiratory flow rate as predictors of asthma exacerbations. *J Gen Intern Med*. 2004;19(3):237-242.
6. Chan-Yeung M, Chang JH, Manfreda J, Ferguson A, Becker A. Changes in peak flow, symptom score, and the use of medications during acute exacerbations of asthma. *Am J Respir Crit Care Med*. 1996;154(4 pt 1):889-893.
7. Tattersfield AE, Postma DS, Barnes PJ, et al; The FACET International Study Group. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. *Am J Respir Crit Care Med*. 1999;160(2):594-599.
8. Covar RA, Szefler SJ, Zeiger RS, et al. Factors associated with asthma exacerbations during a long-term clinical trial of

controller medications in children. *J Allergy Clin Immunol*. 2008;122(4):741-747.
9. Galant SP, Morphew T, Amaro S, Liao O. Current asthma guidelines may not identify young children who have experienced significant morbidity. *Pediatrics*. 2006;117(4):1038-1045.
10. Schatz M, Mosen DM, Kosinski M, et al. Predictors of asthma control in a random sample of asthmatic patients. *J Asthma*. 2007;44(4):341-345.
11. Diette GB, Krishnan JA, Dominici F, et al. Asthma in older patients: factors associated with hospitalization. *Arch Intern Med*. 2002;162(10):1123-1132.
12. Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA Jr. Asthma exacerbations in North American adults: who are the "frequent fliers" in the emergency department? *Chest*. 2005;127(5):1579-1586.
13. Eisner MD, Katz PP, Yelin EH, Shiboski SC, Blanc PD. Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. *Respir Res*. 2001;2(1):53-60.
14. Cowie RL, Underwood MF, Revitt SG, Field SK. Predicting emergency department utilization in adults with asthma: a cohort study. *J Asthma*. 2001;38(2):179-184.
15. Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax*. 2000;55(7):566-573.
16. Fuhlbrigge AL, Kitch BT, Paltiel AD, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol*. 2001;107(1):61-67.
17. Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD; CAMP Research Group. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics*. 2006;118(2):e347-e355.
18. Kitch BT, Paltiel AD, Kuntz KM, et al. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest*. 2004;126(6):1875-1882.
19. Belessis Y, Dixon S, Thomsen A, et al. Risk factors for an intensive care unit admission in children with asthma. *Pediatr Pulmonol*. 2004;37(3):201-209.
20. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med*. 2000;343(15):1054-1063.
21. Reddel HK, Taylor DR, Bateman ED, et al; American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180(1):59-99.
22. Rogers AJ, Tantisira KG, Fuhlbrigge AL, et al. Predictors of poor response during asthma therapy differ with definition of outcome. *Pharmacogenomics*. 2009;10(8):1231-1242.
23. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73(1):13-22.
24. Carroll CL, Schramm CM, Zucker AR. Severe exacerbations in children with mild asthma: characterizing a pediatric phenotype. *J Asthma*. 2008;45(6):513-517.
25. Dell SD, Foty R, Becker A, Franssen E, Chapman KR. Parent-reported symptoms may not be adequate to define asthma control in children. *Pediatr Pulmonol*. 2007;42(12):1117-1124.
26. Gautrin D, Lapierre JG, Malo JL, Infante-Rivard C. Airway hyperresponsiveness and symptoms of asthma in a six-year follow-up study of childhood asthma. *Chest*. 1999;116(6):1659-1664.
27. Weiss ST, Van Natta ML, Zeiger RS. Relationship between increased airway responsiveness and asthma severity in the childhood asthma management program. *Am J Respir Crit Care Med*. 2000;162(1):50-56.
28. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA*. 1997;277(11):887-891.
29. Adams RJ, Fuhlbrigge A, Finkelstein JA, et al. Use of inhaled anti-inflammatory medication in children with asthma in managed care settings. *Arch Pediatr Adolesc Med*. 2001;155(4):501-507.
30. Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB. Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med*. 1998;157(4 pt 1):1173-1180.
31. Haselkorn T, Fish JE, Zeiger RS, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol*. 2009;124(5):895-902.
32. Kim TB, Park CS, Bae YJ, Cho YS, Moon HB; COREA Study Group. Factors associated with severity and exacerbation of asthma: a baseline analysis of the cohort for reality and evolution of adult asthma in Korea (COREA). *Ann Allergy Asthma Immunol*. 2009;103(4):311-317.
33. Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ; for the CAMP Research Group. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol*. 2006;118(5):1040-1047.
34. Prussin C, Metcalfe DD. 5. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2006;117(Suppl 2 Mini-Primer):S450-S456.