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CHEST

Original Research

ASTHMA

Risk Factors and Predictive Clinical Scores for Asthma Exacerbations in Childhood

Erick Forno, MD, MPH; Anne Fuhlbrigge, MD; Manuel E. Soto-Quirós, MD, PhD; Lydiana Avila, MD; Benjamin A. Raby, MDCM, MPH; John Brehm, MD, MPH; Jody M. Sylvia, MS; Scott T. Weiss, MD; and Juan C. Celedón, MD, DrPH, FCCP

Background: **Asthma is a major public health problem that affects millions of children worldwide, and exacerbations account for most of its morbidity and costs. Primary-care providers lack efficient tools to identify children at high risk for exacerbations. We aimed to construct a clinical score to help providers to identify such children.**

Methods: **Our main outcome was severe asthma exacerbation, which was defined as any hospitalization, urgent visit, or systemic steroid course for asthma in the previous year, in children. A clinical score, consisting of a checklist questionnaire made up of 17 yes-no questions regarding asthma symptoms, use of medications and health-care services, and history, was built and validated in a cross-sectional study of Costa Rican children with asthma. It was then evaluated using data from the Childhood Asthma Management Program (CAMP), a longitudinal trial cohort of North American children.**

Results: **Compared with children at average risk for an exacerbation in the Costa Rican validation set, the odds of an exacerbation among children in the low-risk (OR, 0.2; 95% CI, 0.1-0.4) and high-risk (OR, 5.4; 95% CI, 1.5-19.2) score categories were significantly reduced and increased, respectively. In CAMP, the hazard ratios for an exacerbation after 1-year follow-up in the low-risk and high-risk groups were 0.6 (95% CI, 0.5-0.7) and 1.9 (95% CI, 1.4-2.4), respectively, with similar results at 2 years.**

Conclusions: **The proposed Asthma Exacerbation Clinical Score is simple to use and effective at identifying children at high and low risk for asthma exacerbations. The tool can easily be used in primary-care settings.**

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Abbreviations: ATS = American Thoracic Society; AUC = area under the curve; CAMP = Childhood Asthma Management Program; EPR-3 = Expert Panel Report 3; ERS = European Respiratory Society; ISAAC = International Study for Asthma and Allergies in Childhood; NHLBI = National Heart, Lung, and Blood Institute; PCA = principal component analysis; PV = predictive value; STR = skin test reactivity

Disease exacerbations account for the majority of asthma-related costs. Among children living in the United States, >4 million asthma exacerbations occur each year, resulting in approximately 700,000 ED visits, 205,000 hospital admissions, and 200 deaths per year.[1,2] Without including prescriptions, costs related to pediatric asthma exacerbations accounted for $9.8 billion (63.2%) of the estimated $15.5 billion total asthma costs in the United States in 2002.[3] According to guidelines for the diagnosis and management of asthma from the National Heart, Lung and Blood Institute (NHLBI), two or more exacerbations requiring oral steroids per year place children in the persistent category, represent suboptimal control, and increase morbidity and mortality.[4]

The prevalence of pediatric asthma exacerbations varies widely by ethnicity. Among Hispanic children living in the United States, the prevalence ranges from 2.9% in Mexicans to 11.8% in Puerto Ricans, and the rate of ED visits is 14.1% for Hispanics vs 10.8% for non-Hispanic whites.[2] The prevalence of childhood asthma in Costa Rica, a Hispanic American country, is among the highest in the world.[5] During phase 3 of the International Study for Asthma and Allergies in Childhood (ISAAC) study, the reported current prevalence of asthma was 34.8% for 6- to 7-year-olds and 25.5% for 13- to 14-year-olds; with 9.7% and 6.7%, respectively, reporting more than four exacerbations a year. Little is known, however, about risk factors for asthma

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exacerbations in childhood in Hispanics, such as Costa Ricans.

In this study, we first identified risk factors for asthma exacerbations in Costa Rican children. Given the paucity of clinically relevant tools to predict asthma exacerbations, we then developed and validated a predictive score for asthma exacerbations that we further validated in a cohort of North American children with asthma.

Materials and Methods

Study Population

A detailed description of the study methods is provided in the e-Appendix 1 and e-Table 1. Children who participated in this study were index cases for a family-based study of the genetics of asthma in Costa Rica. Subject recruitment and study procedures have been described in detail elsewhere.[6,7] The study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San José, Costa Rica) and Brigham and Women's Hospital (Boston, MA).

Questionnaires and Laboratory Testing

Parents of the study participants completed slightly modified versions of the Collaborative Study on the Genetics of Asthma[8] and the ISAAC questionnaires.[9] Spirometry was conducted with a Survey Tach Spirometer (Warren E. Collins; Braintree, MA) following American Thoracic Society (ATS) recommendations.[10] On a subsequent visit, children with an $FEV_1 \geq 65\%$ predicted underwent methacholine challenge using a modified version of the Chatham protocol[11]; the test was terminated if the FEV_1 declined by $\geq 20\%$ from the best FEV_1 after inhalation of saline solution. Allergy skin testing was performed using the ISAAC protocol.[12] Antigens tested for were dust mite (*Dermatophagoides pteronyssinus*), cockroach (*Blatella germanica* and *Periplaneta americana*), cat dander, dog dander, mixed grass pollen, mixed tree pollen, and *Alternaria tenuis*.

Validation Population

Data for the external validation sample were taken from the Childhood Asthma Management Program (CAMP), a double-blind, placebo-controlled study of the long-term effects of budesonide and nedocromil on lung growth in children. Details on the design and methods of CAMP have been published elsewhere.[13,14] Children with asthma aged 5 to 12 years were assigned to one of three treatment arms (budesonide, nedocromil, or placebo) and followed for 4 years. The protocol for CAMP was approved by the institutional review boards of each of the participating clinical sites and by the CAMP Data Coordinating Center in Baltimore, Maryland.

Statistical Analysis

Based on recommendations from the Expert Panel Report 3 (EPR-3) from the NHLBI for the diagnosis and management of asthma,[4] we defined a severe exacerbation as any hospitalization or two or more ED or urgent care visits. Scheduled physician visits were not considered. This definition (EPR-3 outcome) was our main outcome for the exploratory phase of the present study and for the construction of the clinical score. To further assess our clinical score, we used a secondary definition of a severe asthma exacerbation (any hospitalization, ED or urgent care visit, or systemic steroid burst for asthma in the previous year) that was recently proposed by the ATS/European Respiratory Society (ERS) for clinical trials.[15]

The database for Costa Rica was randomly split in two sets: one for the exploratory analysis ($n = 465$) and one for validation of the clinical score ($n = 150$). These numbers were calculated to achieve $> 90\%$ power to detect a 20% difference in the outcome. Univariate analyses were conducted to identify variables to be included in the multivariate analysis. We then used principal component analysis (PCA) to identify clusters of variables and build a clinical score to stratify subjects by risk. Finally, we evaluated the performance of this score in the Costa Rican validation set and in CAMP.

Univariate analyses were conducted using Fisher exact tests for categorical variables and two-tailed *t* tests for categorical and continuous variables. Stepwise logistic regression was then used; initial models included variables associated with an exacerbation at $P < .20$ and potential confounders. All final models included age, sex, and parental education level as well as variables that were significant at $P < .05$ or led to a $\geq 10\%$ change in risk measures.

PCA with varimax rotation was used to explore the relationships among significant variables. PCA is a statistical technique that condenses the information from a large set of variables into a reduced number of factors that can explain the common variance of the sample. Factors with an eigenvalue > 1 were used to build the score. For ease of use, only questionnaire variables were included in the final score, which was then evaluated in the internal validation set in Costa Rica.

To assess the performance of the clinical score in a different population, we applied it to CAMP using both our main and our secondary outcomes. The score was applied at baseline (before randomization) and evaluated by Cox survival analysis adjusted for age, sex, race, and treatment arm. We limited our analysis of CAMP to the first 2 years because prediction beyond that extended past the age range of the Costa Rican children and because most exacerbations occurred in the first year of the CAMP. All analyses

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were performed with SAS, version 9.1, statistical software (SAS Institute; Cary, NC).

Results

Costa Rican Cohort

A total of 615 children with asthma enrolled in the study had information on exacerbations. There were no significant differences between the exploratory and validation data sets (e-Table 2). The baseline characteristics of the 465 children in the exploratory data set are shown in Table 1. The age of participants ranged from 6 to 14 years. Physician-diagnosed hay fever, parental history of asthma and hay fever, and skin test reactivity (STR) to one or more allergens were all common; mean total IgE level was elevated. Of the 465 participants, 367 (80%) used short-acting β2-agonists, 27 (6%) used xanthines, and 178 (38%)

Table 1—*Characteristics of Study Participants in Costa Rica Exploratory Set and Childhood Asthma Management Program*

	Costa Rica		CAMP	
Characteristic	Yes	No	Yes	No
Severe asthma exacerbation, No.	324	141	579	462
Female sex	40.7	38.3	43.2	39.0
Physician-diagnosed hay fever	28.1	25.5	75.3	67.9
Physician-diagnosed eczema	5.9	3.6	n/a	n/a
Bronchiolitis or pneumonia as infant	34.0[a]	22.0	n/a	n/a
Maternal history[b]				
Asthma	32.2	24.8	20.5	21.9
Hay fever	26.5	34.8	40.0	38.5
Eczema	3.7[a]	9.2	…	…
Paternal history[b]				
Asthma	24.0	20.9	25.4	26.1
Hay fever	27.1[a]	17.1	48.5	47.4
Eczema	5.0	1.4	…	…
Symptoms/health-care utilization last year				
Symptoms present ≥3 mo	70.1[c]	36.9	100	100
Shortness of breath with activity	82.7[a]	69.5	79.0	80.5
Physician visits (four or more)[d]	57.7[c]	8.5	93.3	90.8
Admitted to ICU (ever)	1.5	2.1	5.2	2.9
Medication use in the last year				
Short-acting β_2-agonists	85.8[c]	63.1	95.4	93.7
Inhaled steroids	40.4[a]	25.5	47.5[a]	32.9
Leukotriene inhibitors	4.6	4.3	n/a	n/a
Bronchodilator responsiveness	16.2[c]	8.2	42.2	35.9
Smoke exposure, current	28.8	24.8	42.7	42.2
Positive IgE test for dust mite (*Dermatophagoides pteronyssinus*)	79.0[a]	68.1	n/a	n/a
Positive IgE test for cockroach (*Blatella germanica*)	44.1[a]	34.0	n/a	n/a
Positive IgE test for *Ascaris lumbricoides*	42.6[a]	31.9	n/a	n/a
Positive skin test for at least one allergen	89.5[a]	81.6	n/a	n/a
Age, y	8.4[c] (7.4-9.9)	9.7 (8.1-10.9)	8.1[c] (6.6-9.6)	9.3 (7.6-11.0)
Height, in.	50.8[c] (48.1-53.9)	52.2 (49.6-55.1)	50.7[c] (47.4-54.7)	53.3 (49.0-57.5)
BMI (percentile), kg/m²	61 (29-89)	64 (36-92)	64[a] (36-86)	69 (43-91)
No. oral steroid courses last year (range)	2[c] (2-2)	1 (0-1)	0[c] (0-5)	0 (0-4)
FEV_1 prebronchodilator, L	1.6[c] (1.3-1.9)	1.8 (1.5-2.1)	1.5[c] (1.2-1.8)	1.7 (1.4-2.0)
FEV_1/FVC prebronchodilator, % (range)	82.7[a] (77.5-87.2)	84.9 (80.1-87.3)	80.2 (74.1-85.7)	80.4 (75.1-85.3)
FEV_1/FVC postbronchodilator, % change (range)	3.4[a] (0.8-6.1)	2.7 (0.4-4.9)	5.8 (3.5-8.7)	5.3 (2.9-7.9)
Eosinophils, cells/mm³[e]	580[c] (320-870)	430 (240-630)	410 (200-700)	393 (200-600)
Total IgE, IU/mL[e]	444 (150-1029)	411 (87-832)	463 (164-1388)	429 (176-1145)

Data are presented as % or median (interquartile range), unless otherwise indicated. CAMP = Childhood Asthma Management Program; n/a = not available.

[a]$P < .05$.

[b]In CAMP, maternal and parental history of eczema and hay fever was assessed as one question.

[c]$P < .001$.

[d]Nonacute (scheduled) visits.

[e]Analyzed as $\log_{10}$.

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used antiinflammatory medications (inhaled steroids [n = 157], leukotriene inhibitors [n = 11], or both [n = 21]) in the previous year.

Based on the EPR-3 and ATS/ERS definitions, 324 (69.7%) and 383 (82.4%) children had an exacerbation in the previous year, respectively. A total of 27 (5.8%) children were hospitalized in the previous year.

Predictors of Exacerbations in Costa Rica

The results of the univariate analyses of asthma exacerbations are shown in Table 1. Variables significantly associated with asthma exacerbations were age, height, bronchiolitis or pneumonia during infancy, maternal eczema, paternal history of hay fever, asthma symptoms ≥3 months/year, dyspnea when walking uphill, more than four scheduled physician visits for asthma in the previous year, and use of certain medications (short-acting β_2-agonists, antiinflammatory medications, and one or more courses of oral steroids) in the prior year. Markers of lung function and allergy that showed significant associations were baseline FEV_1 and FEV_1/FVC ratio; change in FEV_1/FVC ratio after use of a bronchodilator; airway responsiveness to methacholine challenge (as log-transformed dose-response slope); eosinophil count; positive IgE test for dust mite, cockroach, and *Ascaris lumbricoides*; and STR to one or more allergens.

The results of the multivariate analysis of asthma exacerbations are shown in Table 2. Children with an exacerbation were more likely to have paternal history of hay fever, four or more scheduled physician visits, a higher number of oral steroid bursts in the previous year, and asthma symptoms for ≥3 months/year than children without an exacerbation. Additionally, total IgE level and eosinophil count were associated with increased odds of exacerbations. (Inclusion of both variables in the same model was not possible because of high colinearity.)

Clinical Score in the Exploratory Data Set

Factor analysis identified 10 clusters of variables in the exploratory set in Costa Rica (e-Figure 1, e-Table 3) corresponding to six categories: asthma symptoms, health-care utilization, medical history, asthma medications, laboratory tests, and airway responsiveness. A scoring questionnaire was built using these categories, excluding laboratory tests and airway responsiveness for ease of use. The resulting score with 17 total points was grouped in four categories (Fig 1). In our exploratory set, the mean ± SD total score was 6.85 ± 2.25 (range, 0-14), and the median score was 7 (interquartile range, 5-8). We classified patients into three groups: low risk (score, ≤5), intermediate or average risk (score, 6-8), and high risk (score, ≥9).

The multivariate analysis in the exploratory set showed that each 1-point increment in the score resulted in a 1.75-fold increment in the odds of an exacerbation (95% CI, 1.5-2.0; $P < .0001$). The coefficient of determination for this model was $R^2 = 0.31$, and the C statistic (equivalent to the receiver operating characteristic area under the curve [AUC]) was 0.79. Based on our main outcome, children in the low-risk group had markedly reduced odds for an asthma exacerbation, whereas those in the high-risk group had greatly increased odds for an exacerbation (Table 3). Of the 93 children in the high-risk group, 87 had an exacerbation (predictive value [PV], 93.6%), with a false-positive rate (FPR) (1-specificity) of 4.2%. Of the 121 children in the low-risk group, 67 did not have an exacerbation (PV, 55.4%; FPR, 16.7%).

Table 2—*Risk Factors for Asthma Exacerbations in Costa Rica Exploratory Set*

Risk Factor	Unadjusted	Model 1	Model 2
Four or more physician visits[a] for asthma in previous year	14.7 (7.8-27.6)[b]	6.8 (3.3-13.9)[b]	6.4 (3.1-13.1)[b]
Number of oral steroid courses in the previous year	6.0 (4.0-9.0)[b]	4.1 (2.6-6.5)[b]	4.1 (2.6-6.5)[b]
Paternal history of hay fever	1.8 (1.1-3.0)[c]	1.9 (1.02-3.7)[c]	1.9 (1.02-3.7)[c]
Symptoms for ≥3 mo/y	4.0 (2.6-6.1)[b]	1.9 (1.1-3.3)[c]	1.9 (1.1-3.2)[c]
Total serum IgE level, IU/mL[d]	1.3 (0.98-1.8)	1.5 (1.03-2.3)[c]	…
Eosinophil count, cells/mm^3[d]	2.8 (1.6-5.0)[b]	…	2.7 (1.2-5.7)[c]
FEV_1 % change postbronchodilator[e]	1.03 (1.01-1.1)[c]	ns	ns
Antiinflammatory medications[e]	1.9 (1.3-3.0)[b]	ns	ns
C statistic	…	0.87	0.88
Goodness of fit	…	0.92	0.84

Data are presented as OR (95% CI), unless otherwise indicated. ns = not significant. Each model included all variables listed in the respective column; both models also was adjusted for age, sex, and parental education level.

[a]Nonacute visits.

[b]$P < .001$.

[c]$P < .05$.

[d]Analyzed as $\log_{10}$.

[e]Not statistically significant but included as confounders.

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A **Asthma Exacerbation Clinical Score**

Reported asthma symptoms	
Symptoms for ≥3 months of the year	❑
Symptoms precipitated by: -colds	❑
-cold air	❑
-exercise	❑
-dust	❑

Healthcare utilization	
Ever hospitalized for asthma	❑
Ever admitted to ICU for asthma	❑
≥2 courses of steroids last year	❑
≥2 ER visits for asthma last year	❑
Doctor visits last year*: 3 or more	❑
also 6 or more	❑

Current asthma medications	
Short-acting β_2 agonists	❑
Inhaled steroids	❑
Leukotriene inhibitors	❑

Medical history	
Personal history of eczema / hay fever	❑
Parental history of asthma or atopy	❑
Smoke exposure as infant or current	❑

Total Score =	❑ ≤ 5 (Low risk)	❑ ≥ 9 (High risk)

B **Histogram and ROC curve**

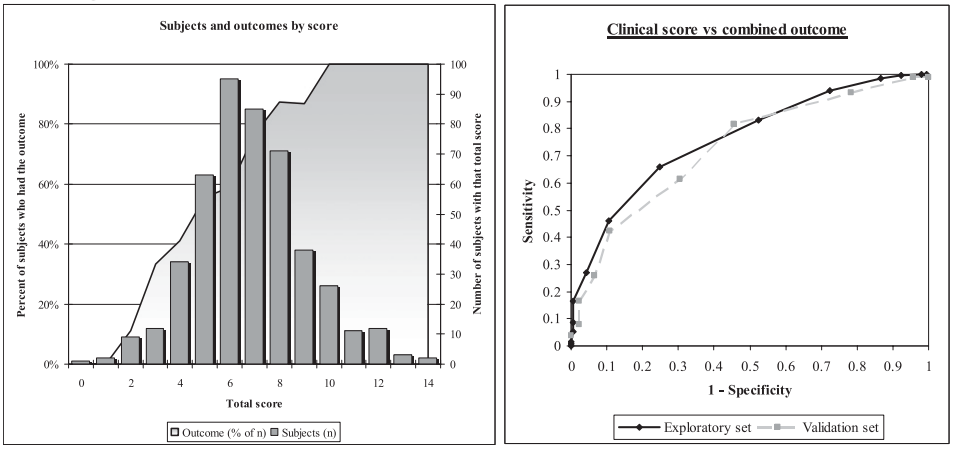

FIGURE 1. A, Clinical score instructions: One point is assigned for each question answered as yes. The score is calculated by adding all points (total score range, 0-17). For "Doctor visits last year," one point is assigned for ≥3 visits, and one more point (two total) if the patient also had ≥6 visits. B, Histogram of total clinical score with superimposed proportion of children who had the Expert Panel Report 3 (EPR-3) outcome (theoretical range, 0-17; actual range, 0-14; mean ± SD, 6.85 ± 2.5; median, 7; interquartile range, 5-8). ROC curve for the total clinical score and the EPR-3 outcome (area under the curve, 0.78 for the exploratory set and 0.76 for the validation set [dashed line]). ROC = receiver operating characteristic.

Of interest, there was only one hospitalization for asthma among children at low risk (PV for no hospitalizations, 99.2%). Similar results were obtained for our secondary outcome (Table 4).

Clinical Score in the Validation Set

The results of the multivariate analysis were similar to those in the exploratory set: each 1-point increment in the clinical score was associated with a 1.6-fold increment in the odds of an exacerbation (95% CI, 1.3-2.0; $P < .0001$); the AUC was 0.75, and the odds ratio for an exacerbation in both the low-risk and high-risk groups were similar to those in the exploratory set. Of 30 children in the high-risk group, all but three had an asthma exacerbation (PV, 90%; FPR, 14.3%). Among the 44 children in the low-risk group, 25 did not have an asthma exacerbation (PV, 56.8%; FPR, 19.3%). Only two children at low risk were hospitalized (PV, 95.4%). Similar results were obtained for our secondary outcome (Table 4).

Validation in CAMP

The characteristics of the CAMP cohort are shown in Table 1. The Costa Rican and CAMP cohorts were similar with regard to age, sex, lung function, and total IgE level. Severe exacerbations at 1 and 2 years of follow-up were less frequent in CAMP than in Costa Rica (main outcome, 33% vs 48%, respectively;

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Table 3—*Asthma Exacerbations (Expert Panel Report 3 Definition) by Score Category*

Data Set	Low Risk (≤5)	Average Risk (6-8)	High Risk (≥9)
Exploratory set (n = 465), No.	121	251	93
Subjects with outcome, No. (%)[a]	54 (44.6)	183 (72.9)	87 (93.6)
OR (95% CI)[b]	0.2 (0.1-0.3)[c]	…	8.3 (3.5-19.5)[c]
PV, %[d]	55.4	…	93.6
FPR, %[e]	16.7	…	4.3
Validation set (n = 150), No.	44	76	30
Subjects with outcome, No. (%)[a]	19 (43.2)	58 (76.3)	27 (90.0)
OR (95% CI)[b]	0.2 (0.1-0.4)[c]	…	5.4 (1.5-19.2)[f]
PV, %[d]	56.8	…	90
FPR, %[e]	18.3	…	6.5
CAMP 1 y (n = 1,041), No.[g]	371	530	140
Subjects with outcome, No. (%)[a]	92 (24.8)	185 (34.9)	67 (47.9)
HR (95% CI)[b]	0.6 (0.5-0.7)[f]	…	1.9 (1.4-2.4)[c]
PV, %[d]	75.2	…	47.9
FPR, %[e]	26.7	…	10.5
CAMP 2 y (n = 1,041), No.[h]	371	530	140
Subjects with outcome, No. (%)[a]	145 (39.1)	262 (49.4)	95 (67.9)
HR (95% CI)[b]	0.6 (0.5-0.8)[f]	…	1.9 (1.5-2.4)[c]
PV, %[d]	60.9	…	67.9
FPR, %[e]	28.9	…	8.3

FPR = false-positive rate; HR = hazard ratio; PV = predictive value. See Table 1 legend for expansion of other abbreviation.
[a]Percentage of subjects in the same score category.
[b]Adjusted for age, sex, and parental education in Costa Rica and for age, sex, race, and treatment group in CAMP.
[c]$P < .001$.
[d]PV for no exacerbation in the low-risk group and for exacerbation in the high-risk group.
[e]FPR = 1-specificity.
[f]$P < .05$.
[g]From start of cohort through 1-y follow-up.
[h]From start of cohort through 2-y follow-up.

secondary outcome, 56% vs 66%, respectively). The clinical score in CAMP had similar characteristics to that in Costa Rica (mean, 6.35 ± 1.9; range, 1-13; median, 6; interquartile range, 5-8).

At 1 and 2 years of follow-up, each 1-point increment in the score was associated with a ~25% increased risk of exacerbations (95% CI, 1.2-1.4; $P < .0001$). The AUC was 0.69 at 1 year and 0.66 at 2 years. Compared with children in the average-risk group, those in the low-risk group had a 40% reduction in the risk of exacerbations at both 1 and 2 years of follow-up, and those in the high-risk group had a 90% increase in their risk at 1 and 2 years of follow-up (Table 3). The PV for the high-risk group was 48% for year 1 and 68% for year 2, with an FPR of 10.5% and 8.3%, respectively. The PV for the low-risk group was 75% for year 1 and 61% for year 2, with an FPR of 26.7% and 28.9%, respectively. Similar to our findings in Costa Rica, the PV of the low-risk group was higher for hospitalizations (~94%). Similar results were found for our secondary outcome (Table 4).

Figure 2 and Table 5 show the Kaplan-Meier survival curves and hazard ratios for exacerbations for each of the score categories. There was a statistically significant difference among the three groups for both our main and secondary outcomes starting at the 4-month visit, which remained through to the end of our follow-up period.

Discussion

To our knowledge, this study is the first to examine risk factors for asthma exacerbations in a well-characterized cohort of Hispanic children. We constructed a checklist-type clinical score to identify Costa Rican children at low and high risk for asthma exacerbations. This score performed well in the exploratory and validation sets, indicating good reproducibility. In Costa Rica, compared with children at average risk for exacerbations, children at low risk had 0.2 times lower odds for exacerbations, and children at high risk had five to eight times higher odds for exacerbations. When applied to a cohort of North American children with asthma participating in a clinical trial (CAMP), the magnitude of the effect was attenuated, but the results were consistent: Compared with children at average risk for exacerbations, children with a low score had a 40% lower risk, and children with a high score had a 90% higher risk .

The PVs allow us to predict how many of the children in a category will have the outcome. The PV of

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Table 4—*Asthma Exacerbations (American Thoracic Society/European Respiratory Society Definition) by Score Category*

Data Set	Low Risk (≤5)	Average Risk (6-8)	High Risk (≥9)
Exploratory set (n = 465), No.	121	251	93
Subjects with outcome, No. (%)[a]	77 (63.6)	216 (86.1)	90 (96.8)
OR (95% CI)[b]	0.2 (0.1-0.4)[c]	…	7.9 (2.4-25.7)[c]
PV, %[d]	36.4	…	96.8
FPR, %[e]	20.1	…	3.7
Validation set (n = 150), No.	44	76	30
Subjects with outcome, No. (%)[a]	26 (59.1)	66 (86.4)	29 (96.7)
OR (95% CI)[b]	0.2 (0.1-0.4)[c]	…	9.7 (1.3-75.2)[f]
PV, %[d]	40.9	…	96.7
FPR, %[e]	21.5	…	3.4
CAMP 1 y (n = 1,041), No.[g]	371	530	140
Subjects with outcome, No. (%)[a]	181 (48.8)	301 (56.8)	97 (69.3)
HR (95% CI)[b]	0.7 (0.6-0.8)[c]	…	1.6 (1.2-1.9)[c]
PV, %[d]	51.2	…	69.3
FPR, %[e]	31.3	…	9.3
CAMP 2 y (n = 1041), No.[h]	371	530	140
Subjects with outcome, No. (%)[a]	220 (59.3)	358 (67.6)	109 (77.9)
HR (95% CI)[b]	0.7 (0.6-0.8)[c]	…	1.5 (1.2-1.8)[c]
PV, %[d]	40.7	…	77.9
FPR, %[e]	32.0	…	8.8

See Table 1 and 3 legends for expansion of abbreviations.
[a]Percentage of subjects in the same score category.
[b]Adjusted for age, sex, and parental education in Costa Rica and for age, gender, race, and treatment group in CAMP.
[c]$P < .001$.
[d]Predictive value for no exacerbation in the low-risk group and for exacerbation in the high-risk group.
[e]FPR = 1-specificity.
[f]$P < .05$.
[g]From start of cohort through 1-y follow-up.
[h]From start of cohort through 2-y follow-up.

the score's high-risk group was 97% in Costa Rica and 69% to 78% in CAMP, meaning that between 70% and 90% of children classified as high risk will indeed have a severe exacerbation. The usefulness of having a low-risk group was less clear cut, with the PV being 36% to 40% in Costa Rica and 51% to 61% in CAMP. The differences in PVs are expected because of the lower prevalence of exacerbations in CAMP. Importantly, the low-risk group had a very high PV for no hospitalizations in both cohorts (94%-99%). To make our results comparable for future studies, we included a second definition of an asthma exacerbation based on ATS/ERS definitions. This outcome was more prevalent in our cohorts (leading to variation in the PVs), but the overall results and risk ratios were similar and remained significant.

Several differences existed between the study cohorts. Costa Rica was a cross-sectional study, whereas CAMP was a prospective clinical trial. Participation in a clinical trial has been shown to increase adherence and improve outcomes. Whereas CAMP included children with mild to moderate persistent asthma, the Costa Rican cohort had a broader range of severity. Differences also existed between the cohorts with regard to medical history (eg, family history of atopy) and health-care utilization (eg, unscheduled visits and hospitalizations). Despite these differences, we were able to predict the risk of asthma exacerbations in CAMP after 1 and 2 years of follow-up.

Identification of risk factors for asthma morbidity (from genetics, to in utero factors, to environmental exposures[16-24]) has had limited success.[19,25] Although two computer-based models had good predictive performances for asthma morbidity (AUC, 0.70-0.78),[16,18] they required a detailed clinical record integrated with medication refill information. We obtained results similar to those of more complex models (training set AUC, 0.76; validation phases AUC, 0.65-0.73) using variables attainable in a physician's office. The performance of our score compares well with those used for other diseases.[26-28] For example, acute physiology and chronic health evaluation scores have an AUC of 0.66 to 0.79 when assessing prognosis in cirrhosis and severe sepsis.[26,27]

Factor analysis and PCA inspect multiple variables and look at interrelations and clustering to identify the underlying structure of a large set of variables.[29,30] Rather than evaluating variables in relationship to an outcome (as in regression analysis), factor analysis

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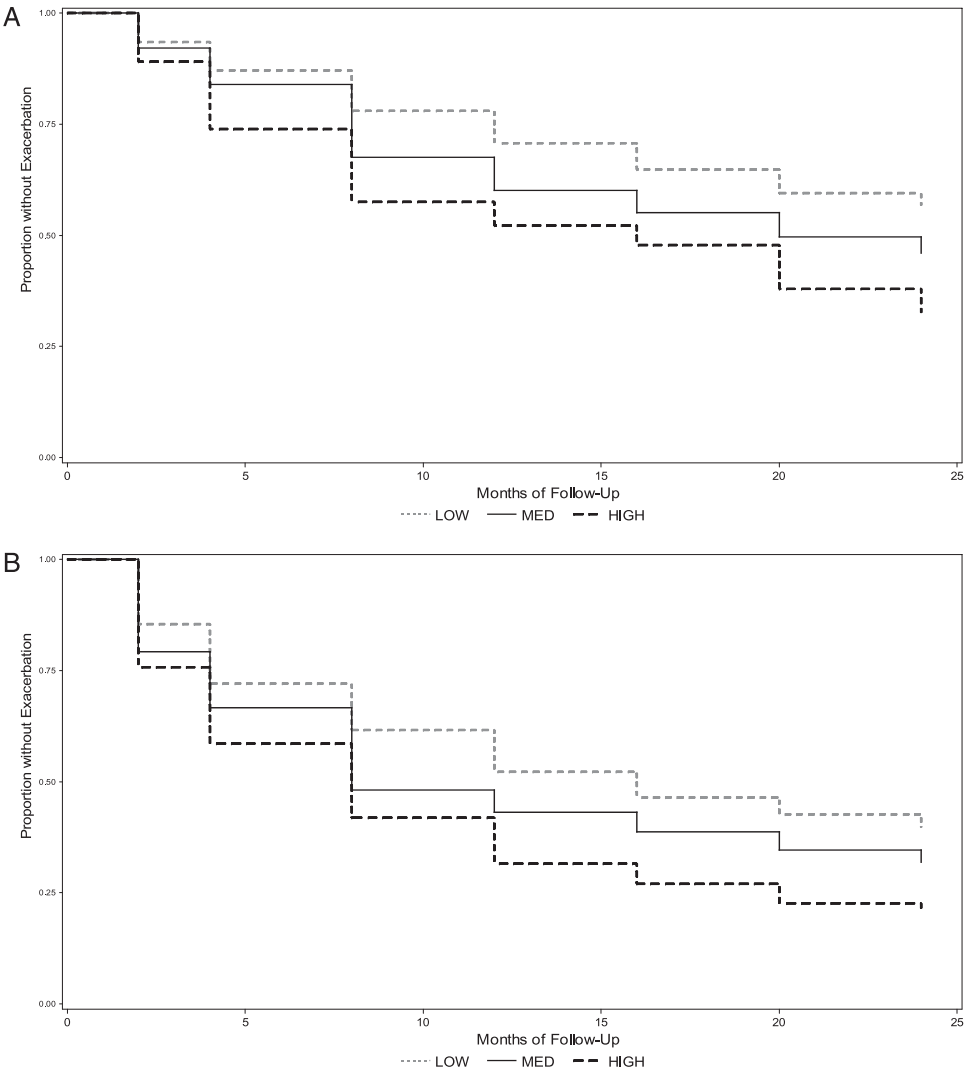

FIGURE 2. Kaplan-Meier curves of time to first exacerbation during 24 months of follow-up in the Childhood Asthma Management Program by score category. A, EPR-3. B, American Thoracic Society/European Respiratory Society. See Figure 1 legend for expansion of the abbreviation.

and PCA describe how variables are related to one another. Each resulting factor comprises several variables that may reflect a unique disease aspect. By using different factors, we aimed to cover multiple disease aspects. Although a few studies have used factor analysis and PCA to identify components of asthma morbidity and care,[31-33] none have evaluated such components in relation to clinical outcomes.[29] To our knowledge, this study is the first to build a clinical score based on factor analysis and PCA and to evaluate its performance and predictive utility both in a validation subset and in an independent cohort. Although exclusion of laboratory and pulmonary function data eliminated some of the identified clusters, we were interested in developing a predictive score for use in primary-care settings in different countries.

There are several limitations to our study. First, the predictive score was built in a cross-sectional study. Without a prospective timeline, it is difficult to assess whether the risk factors really antedated the outcomes or whether they were related, and this can lead to significant difficulties in the interpretation of the results. However, we were able to evaluate outcomes over 2 years of follow-up by applying the score to CAMP, where the score's predictive utility remained significant over time. Second, there was an appreciable reduction in risk ratios and PVs in CAMP compared with Costa Rica, which likely reflects the different characteristics described previously. Costa Rica had a higher prevalence of exacerbations and a broader spectrum of disease severity, and importantly, the score was originally designed using this cohort. Third, the PCA technique shows correlations

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Table 5—*Hazard Ratios of Time to First Exacerbation During 24 Months of Follow-up in the CAMP*

Category	No.	1-Year Follow-up		2-Year Follow-up	
		Events, %[a]	HR (95% CI)[b]	Events, %[a]	HR (95% CI)[b]
EPR-3 definition					
Low risk	371	24.8	0.6 (0.5-0.7)[c]	39.1	0.6 (0.5-0.8)[c]
High risk	140	47.9	1.9 (1.4-2.4)[d]	67.9	1.9 (1.5-2.4)[d]
ATS/ERS definition					
Low risk	341	48.8	0.7 (0.6-0.8)[d]	59.3	0.7 (0.6-0.9)[d]
High risk	140	69.3	1.6 (1.3-2.0)[d]	77.9	1.5 (1.2-1.9)[d]

ATS = American Thoracic Society; EPR-3 = Expert Panel Report 3; ERS = European Respiratory Society; See Table 1 and 3 legends for expansion of other abbreviations.
[a]Percentage of subjects in each category that had asthma exacerbations during the follow-up period.
[b]HR adjusted for age, sex, race, and treatment group.
[c]$P < .05$.
[d]$P < .001$.

among the variables introduced, but it does not indicate whether using more variables would improve the results. Finally, the goodness of fit for Costa Rica and the first year of CAMP were high, indicating a very good calibration of the score, but it was lower in year 2 (e-Table 4), which may imply that the instrument is not as accurate that far out.

Developing an effective predictive score for clinical practice is potentially important for identifying patients at high or low risk for asthma exacerbations and would allow providers to improve management, better allocate treatment, and make referrals when necessary. The practical usefulness of such a score, on the other hand, depends on its ease of use and interpretability. Including more variables and components may yield a more accurate tool, but the trade-off would be to produce an instrument that is too lengthy and, thus, too cumbersome for clinical practice.

In summary, we present a clinical score that is effective at identifying groups of children with asthma at high risk for exacerbations. The score is designed as a checklist questionnaire and excludes laboratory data in order to be easily used in primary-care settings, particularly in areas with few resources or where access to subspecialty care is difficult. Ideally, this tool should be prospectively assessed in a cohort in this type of population. If validated, a next step would be to evaluate whether it is useful in guiding or adjusting therapy. To ensure generalizability, we recommend using the ATS/ERS definitions for mild, moderate, and severe asthma exacerbations in future prospective studies assessing this score.

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Dr Soto-Quirós: contributed to the data collection and the drafting of the manuscript and review of its final version.
Dr Avila: contributed to the data collection and the drafting of the manuscript and review of its final version.
Dr Raby: contributed to the data analysis and the drafting of the manuscript and review of its final version.
Dr Brehm: contributed to the data analysis and the drafting of the manuscript and review of its final version.
Ms Sylvia: contributed to the data collection and the drafting of the manuscript and review of its final version.
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References

1. Asher MI, Montefort S, Björkstén B, et al; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat

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multicountry cross-sectional surveys. *Lancet*. 2006;368(9537): 733-743.
2. 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.
3. Dilley JA, Pizacani BP, Macdonald SM, Bardin J. *The Burden of Asthma in Washington State*. Olympia, WA: State Department of Health; 2005. DOH publication 345-201.
4. 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(5 suppl):S94-S138.
5. Pearce N, Aït-Khaled N, Beasley R, et al; ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007;62(9):758-765.
6. Hunninghake GM, Soto-Quiros ME, Avila L, et al. Sensitization to Ascaris lumbricoides and severity of childhood asthma in Costa Rica. *J Allergy Clin Immunol*. 2007;119(3): 654-661.
7. Ly NP, Soto-Quirós ME, Avila L, et al. Paternal asthma, mold exposure, and increased airway responsiveness among children with asthma in Costa Rica. *Chest*. 2008;133(1): 107-114.
8. Blumenthal MN, Banks-Schlegel S, Bleecker ER, Marsh DG, Ober C. Collaborative studies on the genetics of asthma–National Heart, Lung and Blood Institute. *Clin Exp Allergy*. 1995;25(suppl 2):29-32.
9. ISAAC. Phase II modules of the International Study of Asthma and Allergies in Childhood. http://www.uni-ulm.de/med/med-epidemiologie/forschung-in-der-epidemiologie/isaac.html. Modified March 6, 2009. Accessed May 14, 2010.
10. American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med*. 1995;152(3): 1107-1136.
11. Chatham M, Bleecker ER, Smith PL, Rosenthal RR, Mason P, Norman PS. A comparison of histamine, methacholine, and exercise airway reactivity in normal and asthmatic subjects. *Am Rev Respir Dis*. 1982;126(2):235-240.
12. Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP; International Study of Asthma and Allergies in Childhood Phase II Study Group. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J*. 2004; 24(3):406-412.
13. 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.
14. Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. *Control Clin Trials*. 1999;20(1): 91-120.
15. 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.
16. Schatz M, Cook EF, Joshua A, Petitti D. Risk factors for asthma hospitalizations in a managed care organization: development of a clinical prediction rule. *Am J Manag Care*. 2003;9(8):538-547.
17. Celedón JC, Soto-Quiros ME, Silverman EK, Hanson L, Weiss ST. Risk factors for childhood asthma in Costa Rica. *Chest*. 2001;120(3):785-790.
18. 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.
19. Berger WE, Legorreta AP, Blaiss MS, et al. The utility of the Health Plan Employer Data and Information Set (HEDIS) asthma measure to predict asthma-related outcomes. *Ann Allergy Asthma Immunol*. 2004;93(6):538-545.
20. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000; 162(4 pt 1):1403-1406.
21. Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bever HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy*. 2000;30(11):1547-1553.
22. Kumar R. Prenatal factors and the development of asthma. *Curr Opin Pediatr*. 2008;20(6):682-687.
23. Carroll KN, Hartert TV. The impact of respiratory viral infection on wheezing illnesses and asthma exacerbations. *Immunol Allergy Clin North Am*. 2008;28(3):539-561.
24. Shore SA, Johnston RA. Obesity and asthma. *Pharmacol Ther*. 2006;110(1):83-102.
25. Taylor BW. The identification of high risk asthmatic children using the emergency department asthma visit count. *J Emerg Med*. 1999;17(6):953-956.
26. Cholongitas E, Senzolo M, Patch D, Shaw S, Hui C, Burroughs AK. Review article: scoring systems for assessing prognosis in critically ill adult cirrhotics. *Aliment Pharmacol Ther*. 2006; 24(3):453-464.
27. Johnston JA. Determinants of mortality in patients with severe sepsis. *Med Decis Making*. 2005;25(4):374-386.
28. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558): 283-292.
29. Riekert KA, Eakin M. Factor analysis: a primer for asthma researchers. *J Allergy Clin Immunol*. 2008;121(5):1181-1183.
30. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning*. Stanford, CA: Springer; 2001.
31. Leung TF, Wong GW, Ko FW, Lam CW, Fok TF. Clinical and atopic parameters and airway inflammatory markers in childhood asthma: a factor analysis. *Thorax*. 2005;60(10): 822-826.
32. Holt EW, Cook EF, Covar RA, Spahn J, Fuhlbrigge AL. Identifying the components of asthma health status in children with mild to moderate asthma. *J Allergy Clin Immunol*. 2008;121(5):1175-1180.
33. Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J*. 2004; 23(2):287-291.

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CHEST Online Supplement

Risk Factors and Predictive Clinical Scores for Asthma Exacerbations in Childhood

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e-Appendix

Methods

Study Population

Children who participated in this study were index cases for a family-based study of the genetics of asthma in Costa Rica. Of 7,130 schoolchildren whose parents returned the screening survey, 2,594 (36.4%) had asthma (physician-diagnosed asthma and at least 2 respiratory symptoms or an asthma attack in the previous year). Of these, 616 (23.6%) unrelated children had Costa Rican ancestry and were willing to participate in the study. There was no significant difference in sex or grade in school for children who did and did not participate. Written parental consent and written assent were obtained. The study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San José, Costa Rica) and Brigham and Women's Hospital (Boston, MA).

Pulmonary function tests

Subjects were instructed to avoid short-acting bronchodilators for at least four hours before testing. After baseline spirometry, subjects were given 200μg of albuterol via metered-dose inhaler using a spacer, and spirometry was repeated 15 minutes later to assess response to bronchodilator administration.

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Methacholine challenge testing

The protocol consisted of 5 breaths of saline solution followed by one breath of a 1 mg/mL methacholine solution, 1 and 4 breaths of a 5 mg/mL methacholine solution, and one breath of a 25 mg/mL methacholine solution. Inhalations were taken from a DeVilbiss 646 nebulizer (Sunrise Medical, Carlsbad, CA). After each level, spirometry was performed at 180, 210 and 240 seconds.

IgE levels and eosinophil count

Serum total and allergen-specific IgE levels were determined using a UniCAP 250 (Pharmacia & Upjohn, Kalamazoo, MI), with samples measured in duplicate. Serum was assayed for IgE to three allergens: cockroach (*Blatella germanica*), dust mite (*Dermatophagoides pteronyssinus*), and *Ascaris lumbricoides*. Eosinophil count was measured in peripheral blood by a Coulter-counter technique. IgE levels and eosinophil counts were $\log_{10}$-transformed for data analysis.

Clinical score

Variable selection: All variables that were significantly associated with the EP3-based (main) definition of asthma exacerbations in the univariate analysis were included. Using principal components analysis (PCA), factors or clusters of variables were identified. Decision was made *a priori* to only select factors with an Eigenvalue greater than 1 (see **e-Table 3** and **e-Figure 1**). In order to create a tool applicable in any setting by general practitioners and pediatricians, we decided *a priori* to exclude pulmonary function tests and laboratory results from the clinical score. The remaining factors (factors 4-10 in the table) were used to build a clinical score.

Variable reduction: Some of the identified variables were combined into one question either to simplify the process or because separate responses would not be available for replication in CAMP: “maternal history of eczema” and “paternal history of hay fever” were combined into “parental history of atopy” (in CAMP, parental eczema and/or hay fever were asked in one question, and this was the variable included in the analysis); “current smoke exposure” and “smoke exposure during infancy” were combined into one item. While some of these steps depend on subjective decisions by the investigators, they were based on prior knowledge on the matter, and they were made before evaluating the score in the validation sets.

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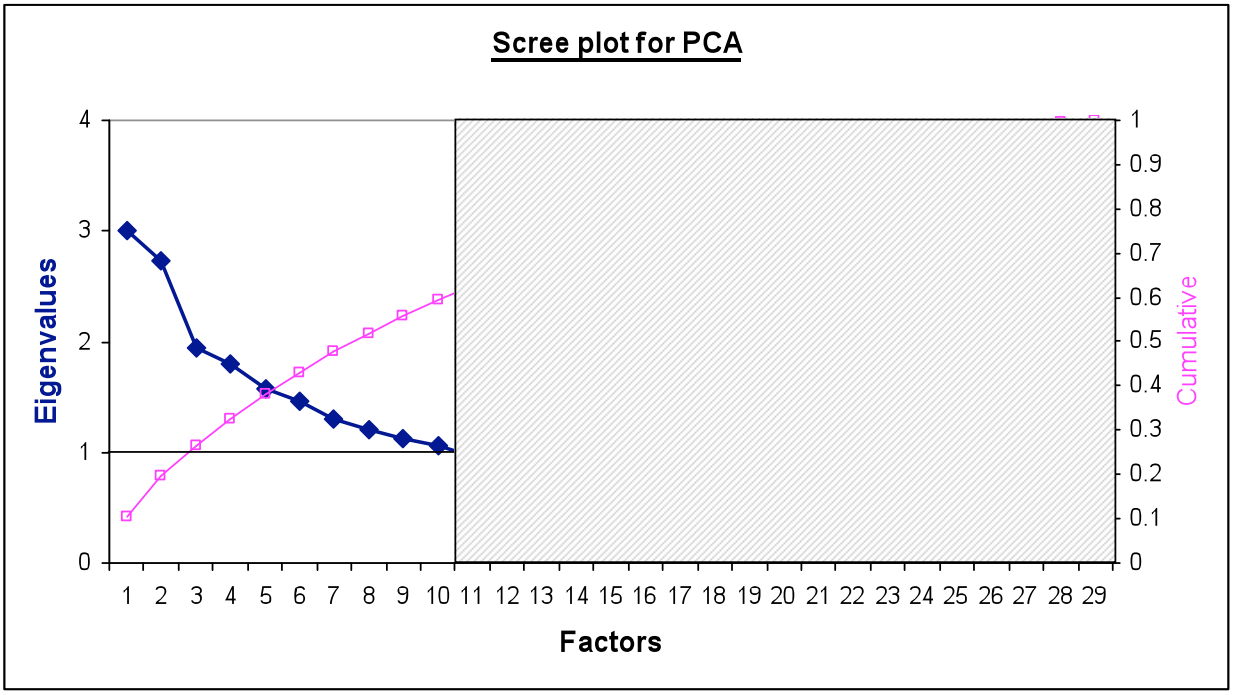
From PCA, each variable should be accompanied by a corresponding weight. However, all variables were assigned the same weight (in this case 0 for "no" and 1 for "yes") to improve simplicity and reduce the time required to administer the questionnaire. Finally, in a fashion similar to backward selection in logistic regression, the score was tested for the EP3 outcome, removing one variable at a time, and those variables found to not improve the performance or predictability were removed. The resulting 17 items for the final score are shown in **Figure 1** in the main manuscript.

Score validation: No further modifications were introduced once we moved from the exploratory subset to the validation set in Costa Rica or the CAMP trial cohort. Evaluation of the clinical score was then performed using both the EP3 and the ATS/ERS definitions in the Costa Rica validation set and in CAMP.

e-Figure 1. Scree plot for principal components analysis



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e-Table 1. Variable definitions

Variable name	*Definition*
Main outcome:	
Asthma exacerbation	1) EP3 definition: The NAEPP/NHLBI published the Expert Panel Report 3 (EP3) Guidelines for the Diagnosis and Management of Asthma in 2007. It defines several criteria for assessment of asthma control, among which is the number of exacerbations requiring systemic steroids per year: ≥2 indicates not well controlled. We therefore defined an exacerbation as any hospitalization and/or ≥ 2 acute care visits in the last 12 months. 2) ATS/ERS definition: In accordance to ATS/ERS consensus guidelines, a severe asthma exacerbation was defined as any hospital admission, acute/urgent visit, and/or oral steroid burst for asthma in the last 12 months. This definition was used only in the validation phases of the study. *Note:* Acute visits included emergency rooms, urgent care centers, and acute doctor's office visits related to exacerbations. For Costa Rica, it also included acute nebulization rooms.
Predictor variables:	
Anti-inflammatory medications	Reported use of inhaled steroids and/or leukotriene inhibitors
Bronchodilator response	FEV_1 increase ≥ 200mL or ≥ 12% over baseline
Doctor visits for asthma	Reported non-acute, scheduled doctor visits for asthma
Ever hospitalized for asthma	Ever admitted to the hospital for asthma (in Costa Rica, this variable excluded subjects admitted in the last year), as reported by the parents.
High eosinophil count	Peripheral blood eosinophil count ≥ 500 cells/mm^3
High IgE level	Serum total IgE level ≥ 100 IU/mL
Parental education level	Highest education level reported by either mother or father (highest of the two if both available)
PD_{20} / PC_{20}	Methacholine dose (for Costa Rica) or concentration (CAMP) that produced a 20% decrease in FEV_1 compared to baseline (best FEV_1 after inhalation of saline solution)
Positive methacoline test	FEV_1 decrease of 20% or more below baseline (best FEV_1 after inhalation of saline solution)
Positive allergen-specific IgE	Serum IgE ≥ 0.35 IU/mL for the specific allergen
Positive skin test	Wheal ≥ 3 mm larger than saline control
Prematurity	Birth before 37 weeks gestational age, as reported by parents
Treatment group	Treatment groups from the CAMP trial (placebo, nedocromil, or inhaled steroids)

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e-Table 2. Baseline characteristics in Costa Rica and CAMP

	Exploratory set (n=465)	*Validation set (n=150)*	*p**
Mean age in years (SD)	8.99 (1.81)	9.21 (1.90)	0.20
Male gender (%)	279 (60.0)	90 (60.0)	1.00
Parental educ. high school or higher (%)	235 (50.5)	75 (50.0)	0.93
Ever hospitalized for asthma (%)	195 (41.9)	56 (37.3)	0.34
Ever ICU for asthma (%)	8 (1.7)	2 (1.3)	1.00
Mean number of ER visits previous year	1.80	1.79	0.92
Mean number of doctor visits last yr	3.82	3.69	0.73
≥2 oral steroid bursts last year (%)	35 (7.5)	13 (8.7)	0.73
Doctor-diagnosed eczema (%)	24 (5.2)	9 (6.0)	0.68
Doctor-diagnosed hay fever (%)	127 (27.3)	42 (28.0)	0.92
High eosinophil count (%)	255 (54.9)	74 (49.3)	0.26
High IgE (%)	368 (79.1)	107 (71.3)	0.06
Short acting β_2 (%)	367 (78.9)	124 (82.7)	0.35
Inhaled steroids (%)	167 (35.9)	57 (38.0)	0.69
Leukotriene inhibitors (%)	21 (4.5)	2 (1.3)	0.08
Xanthines (%)	20 (4.3)	7 (4.7)	0.82
Father's history of: asthma (%)	106 (23.0)	31 (21.0)	0.66
eczema (%)	18 (3.9)	7 (4.7)	0.64
hay fever (%)	111 (24.1)	41 (27.5)	0.45
Mother's history of: asthma (%)	139 (30.0)	48 (32.0)	0.68
eczema (%)	25 (5.4)	12 (8.0)	0.24
hay fever (%)	135 (29.0)	40 (26.9)	0.68
Dyspnea walking up slight level (%)	366 (78.7)	124 (82.7)	0.35
Tightness walking up slight level (%)	332 (71.4)	115 (76.7)	0.25
Symptoms ≥ 3 months/year (%)	279 (60.0)	90 (60.0)	1.00
Smoke exposure, before 2yrs of age (%)	142 (30.6)	50 (33.6)	0.54
Smoke exposure, current (%)	128 (27.6)	41 (27.5)	1.00
Mean FEV_1/FVC pre-albuterol (SD)	82.5 (7.4)	82.4 (7.1)	0.86
Post-albuterol FEV_1 % increase (SD)	6.1 (9.9)	5.1 (8.5)	0.29
Mean PD_{20}/PC_{20}[c] from saline (SD)	2.42 (2.92)	2.50 (3.16)	0.82
Mean total clinical score (SD)	6.85 (2.2)	6.82 (2.1)	0.90
-Reported symptoms	3.8	3.8	0.26
-Healthcare utilization	1.1	1.0	0.10
-Medical history	0.8	0.8	0.61
-Current medications	1.2	1.2	0.70
Hospitalization and/or ≥2 acute visits (%)	324 (69.7)	104 (69.3)	0.94
-Any hospitalization (%)	27 (5.8)	8 (5.3)	0.83

*P-value for comparison between exploratory and validation sets in Costa Rica; Fisher's exact test (binary variables) or t-test (continuous variables).

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e-Table 3. Principal components analysis: Factor loadings of clinical variables in Costa Rica[a]

	Factor[b]									
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Height (cm)	**0.94***	0.05	0.05	-0.01	-0.04	0.03	0.07	0.10	0.00	0.00
FEV_1 pre-bronchodilator (L)	**0.88***	-0.21	0.02	-0.01	-0.05	0.05	-0.03	0.00	0.08	0.06
Age (yrs)	**0.88***	0.04	0.08	-0.03	-0.07	0.04	0.06	-0.01	-0.13	-0.03
FEV_1/FVC (% change)	-0.04	**0.80***	0.04	-0.08	-0.02	0.03	0.11	0.02	0.06	0.09
Bronchodilator response	-0.05	**0.72***	0.12	-0.12	0.18	-0.03	0.08	-0.04	-0.04	0.07
Gender	0.19	0.32	0.08	0.23	0.01	-0.04	-0.28	-0.31	0.13	-0.20
FEV_1/FVC pre-bronchodilator (L)	0.03	**-0.77***	-0.07	-0.17	0.02	-0.01	-0.02	-0.14	0.07	0.16
Positive IgE to dust mite	0.07	0.10	**0.77***	0.00	-0.07	-0.03	0.01	0.15	0.04	0.04
Eosinophils (cells/mm^3)	-0.05	0.03	**0.75***	-0.05	0.11	-0.02	0.04	-0.01	0.12	0.08
Positive IgE to ascaris	0.14	0.09	**0.62***	0.07	0.08	-0.01	0.06	0.05	-0.18	-0.06
Symptoms with exercise	0.04	-0.02	0.02	**0.73***	0.03	-0.02	0.16	0.00	-0.13	0.05
Shortness of breath with activity	-0.01	-0.02	-0.03	**0.66***	0.00	0.09	0.03	0.20	-0.22	0.07
Symptoms with cold air	-0.08	0.04	0.20	**0.60***	0.02	0.00	0.10	-0.21	0.09	0.08
Symptoms with colds or flu	-0.01	-0.01	-0.08	**0.51***	0.08	0.02	-0.07	0.02	0.16	-0.03
Courses of steroids last year	0.05	0.08	0.09	0.00	**0.84***	-0.01	0.02	-0.04	-0.04	0.03
Doctor visits last year	-0.19	0.08	0.09	0.16	**0.81***	0.03	0.11	0.10	0.05	0.09
Smoke exposure, current	0.03	0.02	-0.04	0.05	0.01	**0.90***	0.03	0.02	-0.02	-0.02
Smoke exposure, infancy	0.07	-0.01	-0.03	0.02	-0.04	**0.86***	-0.04	0.00	-0.11	0.01
History of bronchiolitis or	0.05	0.16	-0.12	0.07	0.08	-0.05	**0.67***	-0.03	-0.02	0.00
Ever hospitalized for asthma	-0.01	0.11	0.26	0.10	0.11	0.09	**0.57***	-0.01	-0.10	0.03
Ever ICU for asthma	0.10	-0.09	0.22	0.07	-0.13	0.00	**0.47***	-0.07	0.28	-0.03
Short-acting β_2 agonists	0.01	0.09	0.21	0.15	0.01	-0.05	0.09	**0.70***	0.13	-0.13
Maternal history of eczema	-0.12	0.00	-0.03	0.11	-0.03	-0.04	0.18	**-0.64***	0.12	-0.10
Parental education	0.01	-0.02	0.05	-0.05	-0.05	-0.15	-0.03	-0.09	**0.77***	0.18
Inhaled steroids	-0.12	0.17	-0.02	0.07	0.17	0.13	0.26	0.31	**0.43***	-0.15
Leukotriene inhibitors	-0.05	-0.11	-0.16	-0.04	**0.38***	-0.11	-0.07	0.07	**0.39***	-0.14
Symptoms with dust	0.04	-0.03	0.15	0.11	0.05	0.05	0.01	-0.04	0.04	**0.79***
Paternal history of hay fever	0.03	-0.01	-0.19	-0.04	-0.07	-0.22	**0.40***	0.00	0.02	**0.44***
Symptoms over 3 months per year	-0.19	0.17	-0.05	0.17	0.28	0.04	-0.22	0.32	0.09	**0.41***
Variance	2.630	2.063	1.903	1.828	1.739	1.687	1.487	1.374	1.288	1.201

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Laboratory values and pulmonary function tests obtained by research team during study visit. Past family, medical, and respiratory histories as reported by parents in study questionnaire; unless specifically stated, questions referred to the 12 months prior to the interview. [a]Principal components analysis with varimax (orthogonal) rotation. [b]Factors 4-10 used in clinical score. [c]Reported history of bronchiolitis and/or pneumonia during the first 2 years of life. [*]Significant loading.

e-Table 4. Score model characteristics in both samples

	Costa Rica[a]	CAMP 1-year	CAMP 2-years
Odds / risk ratio (95%CI)[b]	1.71 (1.5-1.9)	1.24 (1.2-1.3)	1.25 (1.2-1.3)
P-value	<0.0001	<0.0001	<0.0001
C-statistic[c]	0.78	0.69	0.66
Goodness of fit[d]	0.61	0.70	0.11

[a]Costa Rica sample as a whole (n=615). [b]Adjusted logistic regression using score as a continuous variable rather than categories. Costa Rica adjusted for age, gender, and parental education. CAMP adjusted for age, gender, race, and treatment arm. [c]C-statistic is equivalent to the area under the curve (AUC) in an ROC curve. [d]Hosmer-and-Lemeshow goodness of fit (GOF).

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Risk Factors and Predictive Clinical Scores for Asthma Exacerbations in Childhood

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e-Appendix

Methods

Study Population

Children who participated in this study were index cases for a family-based study of the genetics of asthma in Costa Rica. Of 7,130 schoolchildren whose parents returned the screening survey, 2,594 (36.4%) had asthma (physician-diagnosed asthma and at least 2 respiratory symptoms or an asthma attack in the previous year). Of these, 616 (23.6%) unrelated children had Costa Rican ancestry and were willing to participate in the study. There was no significant difference in sex or grade in school for children who did and did not participate. Written parental consent and written assent were obtained. The study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San José, Costa Rica) and Brigham and Women's Hospital (Boston, MA).

Pulmonary function tests

Subjects were instructed to avoid short-acting bronchodilators for at least four hours before testing. After baseline spirometry, subjects were given 200μg of albuterol via metered-dose inhaler using a spacer, and spirometry was repeated 15 minutes later to assess response to bronchodilator administration.

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Methacholine challenge testing

The protocol consisted of 5 breaths of saline solution followed by one breath of a 1 mg/mL methacholine solution, 1 and 4 breaths of a 5 mg/mL methacholine solution, and one breath of a 25 mg/mL methacholine solution. Inhalations were taken from a DeVilbiss 646 nebulizer (Sunrise Medical, Carlsbad, CA). After each level, spirometry was performed at 180, 210 and 240 seconds.

IgE levels and eosinophil count

Serum total and allergen-specific IgE levels were determined using a UniCAP 250 (Pharmacia & Upjohn, Kalamazoo, MI), with samples measured in duplicate. Serum was assayed for IgE to three allergens: cockroach (*Blatella germanica*), dust mite (*Dermatophagoides pteronyssinus*), and *Ascaris lumbricoides*. Eosinophil count was measured in peripheral blood by a Coulter-counter technique. IgE levels and eosinophil counts were $\log_{10}$-transformed for data analysis.

Clinical score

Variable selection: All variables that were significantly associated with the EP3-based (main) definition of asthma exacerbations in the univariate analysis were included. Using principal components analysis (PCA), factors or clusters of variables were identified. Decision was made *a priori* to only select factors with an Eigenvalue greater than 1 (see **e-Table 3** and **e-Figure 1**). In order to create a tool applicable in any setting by general practitioners and pediatricians, we decided *a priori* to exclude pulmonary function tests and laboratory results from the clinical score. The remaining factors (factors 4-10 in the table) were used to build a clinical score.

Variable reduction: Some of the identified variables were combined into one question either to simplify the process or because separate responses would not be available for replication in CAMP: “maternal history of eczema” and “paternal history of hay fever” were combined into “parental history of atopy” (in CAMP, parental eczema and/or hay fever were asked in one question, and this was the variable included in the analysis); “current smoke exposure” and “smoke exposure during infancy” were combined into one item. While some of these steps depend on subjective decisions by the investigators, they were based on prior knowledge on the matter, and they were made before evaluating the score in the validation sets.

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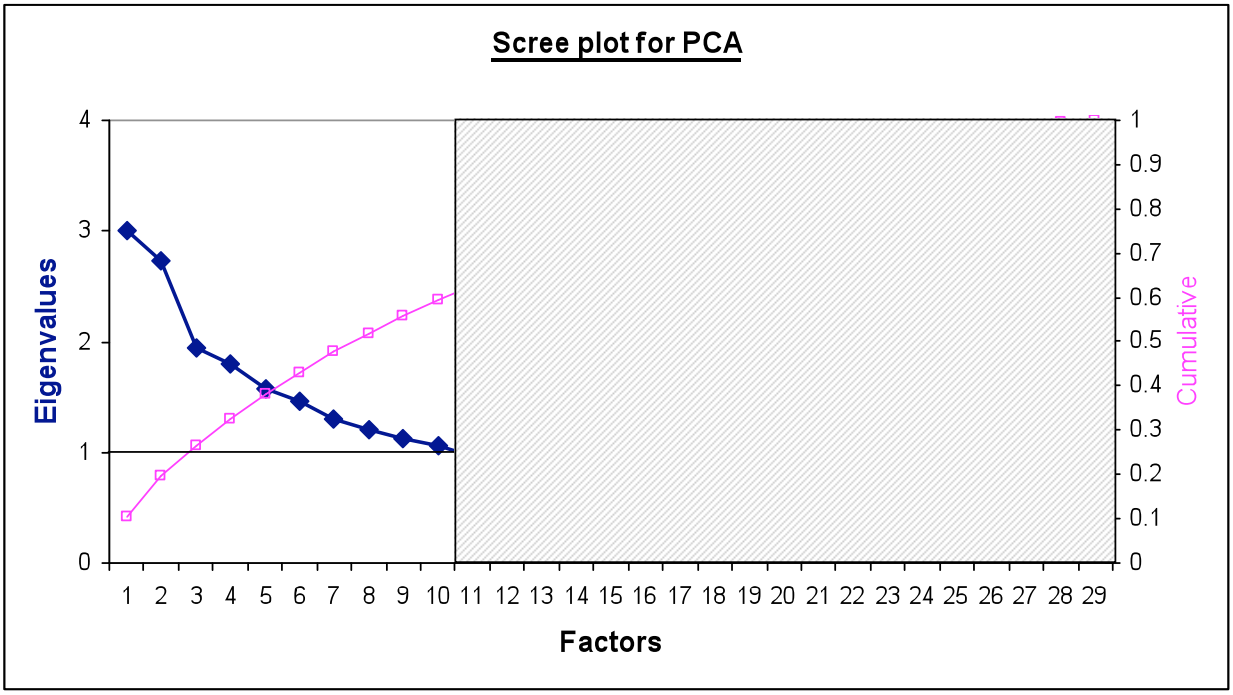
From PCA, each variable should be accompanied by a corresponding weight. However, all variables were assigned the same weight (in this case 0 for "no" and 1 for "yes") to improve simplicity and reduce the time required to administer the questionnaire. Finally, in a fashion similar to backward selection in logistic regression, the score was tested for the EP3 outcome, removing one variable at a time, and those variables found to not improve the performance or predictability were removed. The resulting 17 items for the final score are shown in **Figure 1** in the main manuscript.

Score validation: No further modifications were introduced once we moved from the exploratory subset to the validation set in Costa Rica or the CAMP trial cohort. Evaluation of the clinical score was then performed using both the EP3 and the ATS/ERS definitions in the Costa Rica validation set and in CAMP.

e-Figure 1. Scree plot for principal components analysis



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e-Table 1. Variable definitions

Variable name	*Definition*
Main outcome:	
Asthma exacerbation	1) EP3 definition: The NAEPP/NHLBI published the Expert Panel Report 3 (EP3) Guidelines for the Diagnosis and Management of Asthma in 2007. It defines several criteria for assessment of asthma control, among which is the number of exacerbations requiring systemic steroids per year: ≥2 indicates not well controlled. We therefore defined an exacerbation as any hospitalization and/or ≥ 2 acute care visits in the last 12 months. 2) ATS/ERS definition: In accordance to ATS/ERS consensus guidelines, a severe asthma exacerbation was defined as any hospital admission, acute/urgent visit, and/or oral steroid burst for asthma in the last 12 months. This definition was used only in the validation phases of the study. *Note:* Acute visits included emergency rooms, urgent care centers, and acute doctor's office visits related to exacerbations. For Costa Rica, it also included acute nebulization rooms.
Predictor variables:	
Anti-inflammatory medications	Reported use of inhaled steroids and/or leukotriene inhibitors
Bronchodilator response	FEV_1 increase ≥ 200mL or ≥ 12% over baseline
Doctor visits for asthma	Reported non-acute, scheduled doctor visits for asthma
Ever hospitalized for asthma	Ever admitted to the hospital for asthma (in Costa Rica, this variable excluded subjects admitted in the last year), as reported by the parents.
High eosinophil count	Peripheral blood eosinophil count ≥ 500 cells/mm^3
High IgE level	Serum total IgE level ≥ 100 IU/mL
Parental education level	Highest education level reported by either mother or father (highest of the two if both available)
PD_{20} / PC_{20}	Methacholine dose (for Costa Rica) or concentration (CAMP) that produced a 20% decrease in FEV_1 compared to baseline (best FEV_1 after inhalation of saline solution)
Positive methacoline test	FEV_1 decrease of 20% or more below baseline (best FEV_1 after inhalation of saline solution)
Positive allergen-specific IgE	Serum IgE ≥ 0.35 IU/mL for the specific allergen
Positive skin test	Wheal ≥ 3 mm larger than saline control
Prematurity	Birth before 37 weeks gestational age, as reported by parents
Treatment group	Treatment groups from the CAMP trial (placebo, nedocromil, or inhaled steroids)

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e-Table 2. Baseline characteristics in Costa Rica and CAMP

	Exploratory set (n=465)	*Validation set (n=150)*	*p**
Mean age in years (SD)	8.99 (1.81)	9.21 (1.90)	0.20
Male gender (%)	279 (60.0)	90 (60.0)	1.00
Parental educ. high school or higher (%)	235 (50.5)	75 (50.0)	0.93
Ever hospitalized for asthma (%)	195 (41.9)	56 (37.3)	0.34
Ever ICU for asthma (%)	8 (1.7)	2 (1.3)	1.00
Mean number of ER visits previous year	1.80	1.79	0.92
Mean number of doctor visits last yr	3.82	3.69	0.73
≥2 oral steroid bursts last year (%)	35 (7.5)	13 (8.7)	0.73
Doctor-diagnosed eczema (%)	24 (5.2)	9 (6.0)	0.68
Doctor-diagnosed hay fever (%)	127 (27.3)	42 (28.0)	0.92
High eosinophil count (%)	255 (54.9)	74 (49.3)	0.26
High IgE (%)	368 (79.1)	107 (71.3)	0.06
Short acting β_2 (%)	367 (78.9)	124 (82.7)	0.35
Inhaled steroids (%)	167 (35.9)	57 (38.0)	0.69
Leukotriene inhibitors (%)	21 (4.5)	2 (1.3)	0.08
Xanthines (%)	20 (4.3)	7 (4.7)	0.82
Father's history of: asthma (%)	106 (23.0)	31 (21.0)	0.66
eczema (%)	18 (3.9)	7 (4.7)	0.64
hay fever (%)	111 (24.1)	41 (27.5)	0.45
Mother's history of: asthma (%)	139 (30.0)	48 (32.0)	0.68
eczema (%)	25 (5.4)	12 (8.0)	0.24
hay fever (%)	135 (29.0)	40 (26.9)	0.68
Dyspnea walking up slight level (%)	366 (78.7)	124 (82.7)	0.35
Tightness walking up slight level (%)	332 (71.4)	115 (76.7)	0.25
Symptoms ≥ 3 months/year (%)	279 (60.0)	90 (60.0)	1.00
Smoke exposure, before 2yrs of age (%)	142 (30.6)	50 (33.6)	0.54
Smoke exposure, current (%)	128 (27.6)	41 (27.5)	1.00
Mean FEV_1/FVC pre-albuterol (SD)	82.5 (7.4)	82.4 (7.1)	0.86
Post-albuterol FEV_1 % increase (SD)	6.1 (9.9)	5.1 (8.5)	0.29
Mean PD_{20}/PC_{20}[c] from saline (SD)	2.42 (2.92)	2.50 (3.16)	0.82
Mean total clinical score (SD)	6.85 (2.2)	6.82 (2.1)	0.90
-Reported symptoms	3.8	3.8	0.26
-Healthcare utilization	1.1	1.0	0.10
-Medical history	0.8	0.8	0.61
-Current medications	1.2	1.2	0.70
Hospitalization and/or ≥2 acute visits (%)	324 (69.7)	104 (69.3)	0.94
-Any hospitalization (%)	27 (5.8)	8 (5.3)	0.83

*P-value for comparison between exploratory and validation sets in Costa Rica; Fisher's exact test (binary variables) or t-test (continuous variables).

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e-Table 3. Principal components analysis: Factor loadings of clinical variables in Costa Rica[a]

	Factor[b]									
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Height (cm)	**0.94***	0.05	0.05	-0.01	-0.04	0.03	0.07	0.10	0.00	0.00
FEV_1 pre-bronchodilator (L)	**0.88***	-0.21	0.02	-0.01	-0.05	0.05	-0.03	0.00	0.08	0.06
Age (yrs)	**0.88***	0.04	0.08	-0.03	-0.07	0.04	0.06	-0.01	-0.13	-0.03
FEV_1/FVC (% change)	-0.04	**0.80***	0.04	-0.08	-0.02	0.03	0.11	0.02	0.06	0.09
Bronchodilator response	-0.05	**0.72***	0.12	-0.12	0.18	-0.03	0.08	-0.04	-0.04	0.07
Gender	0.19	0.32	0.08	0.23	0.01	-0.04	-0.28	-0.31	0.13	-0.20
FEV_1/FVC pre-bronchodilator (L)	0.03	**-0.77***	-0.07	-0.17	0.02	-0.01	-0.02	-0.14	0.07	0.16
Positive IgE to dust mite	0.07	0.10	**0.77***	0.00	-0.07	-0.03	0.01	0.15	0.04	0.04
Eosinophils (cells/mm^3)	-0.05	0.03	**0.75***	-0.05	0.11	-0.02	0.04	-0.01	0.12	0.08
Positive IgE to ascaris	0.14	0.09	**0.62***	0.07	0.08	-0.01	0.06	0.05	-0.18	-0.06
Symptoms with exercise	0.04	-0.02	0.02	**0.73***	0.03	-0.02	0.16	0.00	-0.13	0.05
Shortness of breath with activity	-0.01	-0.02	-0.03	**0.66***	0.00	0.09	0.03	0.20	-0.22	0.07
Symptoms with cold air	-0.08	0.04	0.20	**0.60***	0.02	0.00	0.10	-0.21	0.09	0.08
Symptoms with colds or flu	-0.01	-0.01	-0.08	**0.51***	0.08	0.02	-0.07	0.02	0.16	-0.03
Courses of steroids last year	0.05	0.08	0.09	0.00	**0.84***	-0.01	0.02	-0.04	-0.04	0.03
Doctor visits last year	-0.19	0.08	0.09	0.16	**0.81***	0.03	0.11	0.10	0.05	0.09
Smoke exposure, current	0.03	0.02	-0.04	0.05	0.01	**0.90***	0.03	0.02	-0.02	-0.02
Smoke exposure, infancy	0.07	-0.01	-0.03	0.02	-0.04	**0.86***	-0.04	0.00	-0.11	0.01
History of bronchiolitis or	0.05	0.16	-0.12	0.07	0.08	-0.05	**0.67***	-0.03	-0.02	0.00
Ever hospitalized for asthma	-0.01	0.11	0.26	0.10	0.11	0.09	**0.57***	-0.01	-0.10	0.03
Ever ICU for asthma	0.10	-0.09	0.22	0.07	-0.13	0.00	**0.47***	-0.07	0.28	-0.03
Short-acting β_2 agonists	0.01	0.09	0.21	0.15	0.01	-0.05	0.09	**0.70***	0.13	-0.13
Maternal history of eczema	-0.12	0.00	-0.03	0.11	-0.03	-0.04	0.18	**-0.64***	0.12	-0.10
Parental education	0.01	-0.02	0.05	-0.05	-0.05	-0.15	-0.03	-0.09	**0.77***	0.18
Inhaled steroids	-0.12	0.17	-0.02	0.07	0.17	0.13	0.26	0.31	**0.43***	-0.15
Leukotriene inhibitors	-0.05	-0.11	-0.16	-0.04	**0.38***	-0.11	-0.07	0.07	**0.39***	-0.14
Symptoms with dust	0.04	-0.03	0.15	0.11	0.05	0.05	0.01	-0.04	0.04	**0.79***
Paternal history of hay fever	0.03	-0.01	-0.19	-0.04	-0.07	-0.22	**0.40***	0.00	0.02	**0.44***
Symptoms over 3 months per year	-0.19	0.17	-0.05	0.17	0.28	0.04	-0.22	0.32	0.09	**0.41***
Variance	2.630	2.063	1.903	1.828	1.739	1.687	1.487	1.374	1.288	1.201

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Laboratory values and pulmonary function tests obtained by research team during study visit. Past family, medical, and respiratory histories as reported by parents in study questionnaire; unless specifically stated, questions referred to the 12 months prior to the interview. [a]Principal components analysis with varimax (orthogonal) rotation. [b]Factors 4-10 used in clinical score. [c]Reported history of bronchiolitis and/or pneumonia during the first 2 years of life. [*]Significant loading.

e-Table 4. Score model characteristics in both samples

	Costa Rica[a]	CAMP 1-year	CAMP 2-years
Odds / risk ratio (95%CI)[b]	1.71 (1.5-1.9)	1.24 (1.2-1.3)	1.25 (1.2-1.3)
P-value	<0.0001	<0.0001	<0.0001
C-statistic[c]	0.78	0.69	0.66
Goodness of fit[d]	0.61	0.70	0.11

[a]Costa Rica sample as a whole (n=615). [b]Adjusted logistic regression using score as a continuous variable rather than categories. Costa Rica adjusted for age, gender, and parental education. CAMP adjusted for age, gender, race, and treatment arm. [c]C-statistic is equivalent to the area under the curve (AUC) in an ROC curve. [d]Hosmer-and-Lemeshow goodness of fit (GOF).

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