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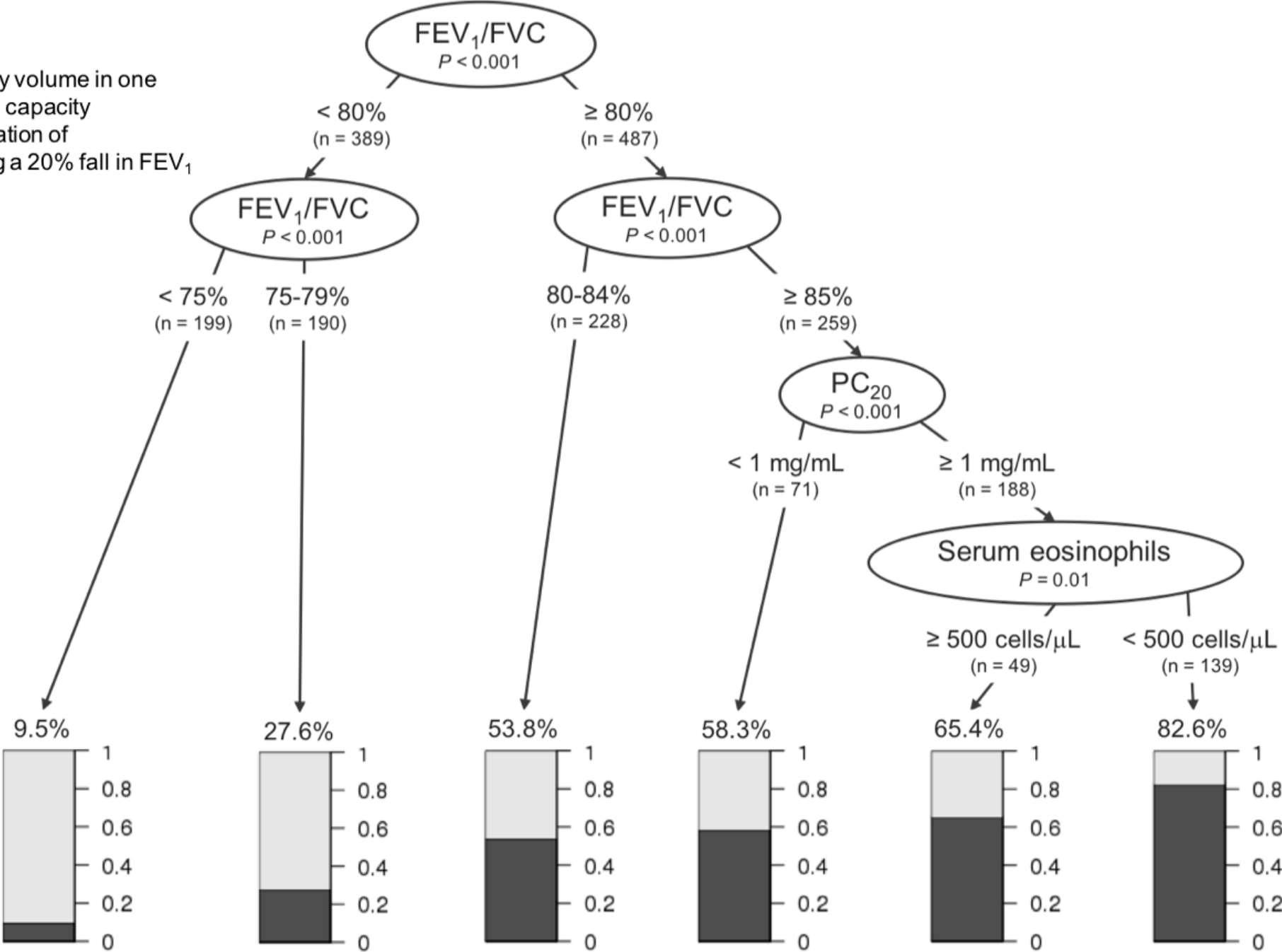
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Baseline clinical measurements in childhood asthma at age 8 years can predict remission of disease by early adulthood (age 18-23 years):

Abbreviations

FEV₁/FVC: forced expiratory volume in one second to forced vital capacity
PC₂₀: provocative concentration of methacholine causing a 20% fall in FEV₁



Predicted probability of childhood asthma remission

Remission of persistent childhood asthma: early predictors of adult outcomes

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ABSTRACT

BACKGROUND: Few data exist on the predictors of asthma remission by early adulthood in North America.

OBJECTIVE: The predictors of adult asthma remission were determined in a multiethnic population of mild-to-moderate persistent childhood asthmatics.

METHODS: Asthma remission in early adulthood was measured using two definitions, a clinical and a strict definition. Both included normal lung function and the absence of symptoms, exacerbations, and medication use. The strict definition also included normal airways responsiveness. Predictors were identified from 23 baseline measures using multivariate logistic regression. The probability of remission was modeled using decision tree analysis.

RESULTS: In 879 subjects, mean baseline age was 8.8 years ($SD \pm 2.1$), 59.4% were males, and 68.7% were Caucasian. By adulthood, 229 (26.0%) of 879 participants were in clinical remission and 111 (15.0%) of 741 participants were in strict remission. The degree of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) impairment was the largest predictor of asthma remission. Over half of boys and two-thirds of girls with baseline $FEV_1/FVC \geq 90\%$ were in remission at adulthood. Decreased airways responsiveness was also a predictor for both remission definitions (clinical remission OR 1.23, 95% CI 1.09-1.39; strict remission OR 1.52, 95% CI 1.26-1.84). The combination of normal FEV_1/FVC , airways responsiveness, and serum eosinophil count at baseline yielded $> 80\%$ probability of remission by adulthood.

CONCLUSION: A considerable minority of persistent childhood asthmatics will develop disease remission by adulthood. Clinical prognostic indicators of asthma remission, including baseline lung function, can be seen from an early age.

CLINICAL IMPLICATIONS

Lung function measurements and serum eosinophil count obtained in early childhood predict asthma remission in early adulthood. Spirometry should be obtained in all childhood asthmatics for clinical prognostication.

CAPSULE SUMMARY

Adult asthma remission can be predicted using baseline clinical measurements obtained in early childhood. Persistent childhood asthmatics with normal baseline measurements of airway obstruction, airways responsiveness, and serum eosinophil count have greater than 80% probability of remission.

KEY WORDS

Pediatric asthma, asthma remission, prognostication

ABBREVIATIONS

CAMP: Childhood Asthma Management Program

FEV₁/FVC: forced expiratory volume in one second to forced vital capacity

PC₂₀: provocative concentration causing a 20% fall in FEV₁

BHR: bronchial hyperresponsiveness

AUC: area under the curve

SD: standard deviation

OR: odds ratio

CI: confidence interval

IQR: interquartile range

INTRODUCTION

Predicting the clinical trajectory of childhood asthma has important prognostic implications for patients, parents, clinicians, and researchers. Prior longitudinal studies have estimated between 15% to 64% of childhood asthmatics go into asthma remission by early adulthood^{1, 2}. In those studies, asthma remission rates have been noted to vary widely by population, and remission has been associated with less allergic sensitization, milder initial asthma severity, and male sex²⁻⁴. Asthma remission occurs most commonly between the ages 14 to 21 years². Studies characterizing asthma remission to date have emphasized epidemiologic associations, rather than clinical translation and prognostication. Furthermore, limited data exist on asthma remission in multiethnic cohorts representative of the North American population and in cohorts with mild-to-moderate persistent asthma, whose remission rates would be expected to differ from those with either intermittent or severe disease. In this study, we determined which baseline characteristics in early childhood can predict asthma remission by adulthood in a multiethnic cohort of mild-to-moderate persistent asthmatics. Cross-sectional baseline characteristics representative of a snapshot obtained at a physician's visit were examined that can be used for individualized prognostication.

The Childhood Asthma Management Program (CAMP) was a four-year randomized, placebo-controlled trial of inhaled anti-inflammatory treatments for mild-to-moderate persistent asthma in children followed by an additional 13 years of detailed longitudinal follow-up⁵. As such, this cohort is well suited to evaluate the natural history of childhood asthma. After the first eight years of CAMP, 6% of patients developed clinical asthma remission in adolescence⁶. We now study asthma remission at the onset of adulthood in CAMP using definitions for asthma

remission that include both clinical and pulmonary function measurements. Asthma remission was measured at the first CAMP continuation study visit following the age of 18 years with an average follow-up of 12 years. In addition to determining the prevalence of asthma remission in early adulthood, we specifically investigated early childhood factors to prognosticate future asthma outcomes.

METHODS

A longitudinal study was performed with 879 participants from CAMP who had asthma remission outcomes available at their first follow-up visit on or after age 18 years (range 18 to 23 years). The details of CAMP have been described elsewhere^{5,7}. Briefly, 1041 children with mild-to-moderate persistent asthma and significant airways responsiveness to methacholine between the ages 5 to 12 years were enrolled from December 1993 to September 1995. Participants were randomized to receive inhaled budesonide, nedocromil, or placebo for a mean 4.3 years, and observational follow-up continued for an additional 13 years. Parental informed consent with subject assent was obtained, and the study was approved by each CAMP study center institutional review board. More than 80% of individuals participated through the entire duration of observational follow-up⁷.

Asthma remission at early adulthood was defined in two ways, a clinical primary definition and a strict secondary definition. Clinical asthma remission was defined as: 1) no evidence of airflow obstruction with a ratio of forced expiratory volume in one second to forced vital capacity ($FEV_1/FVC \geq 80\%$), 2) no asthma exacerbations in the prior year, 3) no use of asthma medications in the prior year, and 4) no reported asthma symptoms in the prior year. Strict

asthma remission was defined as the above four criteria in addition to having negative bronchoprovocation testing by methacholine challenge with a provocative concentration (PC_{20}) greater than or equal to 25 mg/mL. The absence of bronchial hyperresponsiveness (BHR) in CAMP was defined as a $PC_{20} \geq 25$ mg/mL, and thus, this cutoff was used for the strict asthma remission definition. FEV_1/FVC was included in the remission definitions to include both objective and subjective criteria from the impairment and risk domains of National Asthma Education and Prevention Program guidelines, and the use of the absolute ratio was chosen according to American Thoracic Society guidelines^{8,9}. The clinical remission definition was considered the primary definition as PC_{20} is not typically measured longitudinally in the clinical setting.

Potential baseline predictors of asthma remission were selected based on previously published associations with asthma susceptibility and/or remission¹⁰. Twenty-three baseline measures collected at the time of enrollment into CAMP were selected: age at asthma diagnosis, sex, ethnicity, household income, parental education, history of parental asthma, body mass index, history of wheezing (with and without colds), asthma exacerbations after exercise, physician diagnosed atopic dermatitis or allergies, aeroallergen skin test positivity (as an indicator of allergic sensitization with or without symptoms), exposure to home tobacco smoke, history of maternal smoking during pregnancy, use of wood stove, any pet ownership, asthma severity classified by a physician, PC_{20} , FEV_1 percentage predicted, FEV_1/FVC , serum IgE level, and serum eosinophil count.

Statistical analyses

The characteristics of the 162 subjects missing the primary remission outcome were compared to the 879 subjects who had the outcome. T-tests were used to compare continuous parametric variables, Wilcoxon rank-sum tests for continuous non-parametric variables, and χ^2 and Fisher's exact tests for categorical variables. Most variables in the loss to follow-up analysis were not statistically significant ($P > 0.05$), and significant variables were adjusted for in the multivariate models (**Supplemental Table I**). R version 3.3.2 was used.

Cross-validated stepwise logistic regression was performed to determine predictors for each asthma remission outcome. Variables that were statistically significant on univariate analyses were placed into a 5-fold cross-validated stepwise logistic regression model with 100 cross-validation repeats using the caret package¹¹. Cross-validation was used to reduce overfitting and improve precision and accuracy. In addition to the statistically significant variables from the loss to follow-up analysis, age, sex, CAMP treatment group, and clinic site were controlled for in all models. Prior to model building, continuous variables that had a non-linear relationship with the log odds of remission were log transformed. FEV₁/FVC and PC₂₀ were modeled as continuous variables in the main clinical and strict asthma remission models. Model selection was determined by Akaike information criterion, and Wald tests were used to evaluate individual variables. Analyses were restricted to complete cases. The models were then stratified by sex, and the statistically significant variables that differed across sexes were tested as interaction terms.

Sex stratified analyses for the primary clinical asthma remission definition were planned *a priori* because asthma persistence has been shown to vary by sex^{1, 2, 4, 12}. Sex stratified models were

built using cross-validated stepwise logistic regression. To increase clinical interpretability in the sex stratified models, baseline FEV₁/FVC was divided into 4 categories to reflect spirometric categorizations used in the Global Initiative for Asthma Report (i.e., < 70%, 70-80%, 80-90%, > 90%), and baseline PC₂₀ was divided into 3 categories (i.e., moderate to severe BHR: < 1 mg/mL, mild BHR: 1-4 mg/mL, borderline BHR: > 4 mg/mL) per American Thoracic Society guidelines^{13, 14}. Receiver operating characteristic curves and the area under the curve (AUC) were obtained using the pROC, plotROC, and ggplot2 packages¹⁵⁻¹⁷. The probability of asthma remission was modeled using conditional inference trees with case weights from the party package¹⁸.

A sensitivity analysis of the primary clinical asthma remission definition was performed to examine the effect of the FEV₁/FVC criterion. FEV₁/FVC was removed from the definition, and a cross-validated stepwise logistic regression model was built as specified above (**Supplemental Table II**). Since airflow obstruction is one of the hallmarks of asthma, FEV₁/FVC was retained in the primary clinical asthma remission definition.

RESULTS

Of the 879 participants, 229 (26.0%) individuals were in asthma remission and 650 (73.9%) individuals were not, using the primary clinical definition (**Table I**). The mean baseline age at study entry was 8.8 years (standard deviation SD $\pm$ 2.1), 59.4% were males, and 68.7% were Caucasian. Within the 879 participants, 741 (84.3%) individuals had PC₂₀ measurements, permitting analysis of the secondary strict asthma remission definition. Of these, 111 (15.0%)

individuals were in strict asthma remission and 630 (85.0%) individuals were not (**Supplemental Table III**).

Clinical Asthma Remission Predictors

For the entire cohort, sex, baseline history of wheezing with and without colds, exacerbations after exercise, aeroallergen sensitization, physician classified asthma severity, PC₂₀, FEV₁ percentage predicted, FEV₁/FVC, serum IgE level, and serum eosinophil count were significant predictors of asthma remission on univariate analyses (**Table I**). In the multivariate model, only FEV₁/FVC and PC₂₀ remained significant. Each 10% increase in baseline FEV₁/FVC was associated with a 4.62 times odds of asthma remission (95% CI 3.35-6.50, $P < 0.001$), and each two-fold increase in PC₂₀ was associated with 23% increase in the odds of asthma remission (OR 1.23, 95% CI 1.09-1.39, $P = 0.001$) (**Table II**). The AUC of the cross-validated model was 0.81 (95% CI 0.77-0.84) (**Supplemental Figure 1a**).

Predictors of Clinical Asthma Remission by Sex

^{1, 2, 4, 12}The severity of airflow obstruction was the strongest predictor of clinical asthma remission in both males and females (**Figure 1a**). Within the subset of individuals with mild baseline airway obstruction, females were more likely to develop asthma remission than males (**Figure 1b**). Females had 8.03 times odds (95% CI 4.60-14.93, $P < 0.001$) whereas males had 3.88 times odds (95% CI 2.62-5.92, $P < 0.001$) of asthma remission with each 10% increase in FEV₁/FVC (interaction $P = 0.04$). A FEV₁/FVC less than 70% was strongly indicative of asthma persistence, particularly in males where only 1.4% of subjects developed remission (**Figure 1a**).

In addition, in the sex specific models of clinical asthma remission, males without peripheral eosinophilia had 1.79 times odds (95% CI 1.02-3.21, $P = 0.045$) of asthma remission compared to males with peripheral eosinophilia (**Table IIIa**). Treatment during the first four years of CAMP with inhaled budesonide was also associated with higher odds of remission in males. In females, Hispanic race and airway hyperresponsiveness were additional predictors of asthma remission (**Table IIIb and Supplemental Figure 2**). The odds of asthma remission decreased 63% (OR 0.37, 95% CI 0.15-0.89, $P = 0.03$) in females with moderate airway hyperresponsiveness and 76% (OR 0.24, 95% CI 0.09-0.64, $P = 0.005$) in females with severe airway hyperresponsiveness. The AUC of the cross-validated models were 0.79 (95% CI 0.75-0.84) for males and 0.85 (95% CI 0.80-0.89) for females (**Supplemental Figures 1b and 1c**).

Strict Asthma Remission Predictors

Similar to the primary remission analysis, history of wheezing with and without colds, exacerbations after exercise, aeroallergen sensitization, physician classified asthma severity, PC₂₀, FEV₁ percentage predicted, FEV₁/FVC, serum IgE level, and serum eosinophil count were significant predictors of strict asthma remission status on univariate analyses, along with baseline age at study entry and physician diagnosed allergies (**Supplemental Table III**). In the multivariate model, each 10% increase in baseline FEV₁/FVC was associated with 5.71 times odds (95% CI 3.58-9.45, $P < 0.001$) of strict asthma remission, and each two-fold increase in baseline PC₂₀ was associated with a 1.52 times odds (95% CI 1.26-1.84, $P < 0.001$) of strict asthma remission (**Supplemental Table IV**). Furthermore, each two-fold increase in serum IgE level was associated with a 12% decrease in the odds of strict remission (OR 0.88, 95% CI 0.78-1.00, $P = 0.047$), and aeroallergen sensitization was associated with a 52% decrease in the odds

of strict remission (OR 0.48, 95% CI 0.24-0.97, $P = 0.04$). The AUC of the cross-validated model was 0.86 (95% CI 0.83-0.90) (**Supplemental Figure 1d**). Predictors of strict asthma remission did not differ between sexes.

Asthma Remission Decision Tree

A decision tree classifying the predicted probability of clinical asthma remission was constructed (**Figure 2**). The probability of asthma remission was lowest (9.5%) in individuals with baseline FEV₁/FVC less than 75%. Conversely, individuals with the combination of baseline FEV₁/FVC greater than or equal to 85%, PC₂₀ of at least 1 mg/mL, and absence of peripheral eosinophilia had 82.6% probability of asthma remission.

DISCUSSION

Prognostication of asthma remission at adulthood can be performed from an early age in childhood. We followed 879 children with mild-to-moderate persistent asthma for an average of 12 years until early adulthood and found 26% had asthma remission focusing on clinical parameters and 15% had asthma remission using a strict definition that additionally included normal bronchoprovocation testing. Thus, a sizeable proportion of childhood asthmatics develop complete remission with no residual evidence of ongoing disease. Decreased airway obstruction and lower airways responsiveness in childhood were strongly associated with both definitions of asthma remission. While research in other populations have demonstrated associations between higher childhood lung function, less severe airway obstruction, and absence of airway hyperresponsiveness with improved asthma prognosis, prior studies have not yielded prognostic strata related to these measures^{1, 4, 19, 20}. The single greatest predictor of asthma remission was the

severity of airflow obstruction. Fewer than 10% of children with a baseline FEV₁/FVC less than 80% “outgrew” their asthma, whereas each 10% increase in baseline FEV₁/FVC was associated with a 4.62 times higher odds of asthma remission (**Table II**).

For asthmatics with well-preserved lung function at baseline (FEV₁/FVC $\geq$ 90%), over 54% of boys and 70% of girls were in remission by early adulthood (**Figure 1a**). Baseline FEV₁/FVC is an excellent predictor of future asthma remission and lung function, which is consistent with research showing the tracking of lung function growth over time^{1, 21}. Gains in baseline FEV₁/FVC beyond the threshold of 80% used in current guidelines continued to increase the probability of asthma remission, indicating that higher cut-offs within “normal” FEV₁/FVC values continue to stratify pediatric asthmatics (**Figure 1b**)⁸. In the United States general population, the reference FEV₁/FVC for healthy pre-adolescent children approaches 90%²². Therefore, the cut-off for normal FEV₁/FVC in children regardless of asthma status is likely higher than indicated in current guidelines and has direct implications on future health status. Our findings further emphasize the importance of obtaining baseline spirometry in pediatric asthmatics, which is recommended in current guidelines but not routinely obtained in all pediatric practices^{8, 14}.

From a clinical perspective, the probability of asthma remission can be estimated based on baseline FEV₁/FVC, PC₂₀, and serum eosinophil count (**Figure 2**). Specifically, our decision tree analysis indicated that in children with mild-to-moderate persistent asthma, the predicted probability of adult clinical remission exceeds 80% when FEV₁/FVC is normal, PC₂₀ is higher (lower airways responsiveness), and peripheral eosinophilia is absent at baseline. The asthma

remission decision tree can be used as a clinical tool for physicians to prognosticate childhood asthmatics. Each of the three prognostic components is readily available to most pediatric care providers, and several asthma guidelines recommend measuring these components^{8, 14, 23}.

In addition to these overall findings, sex-specific associations with clinical asthma remission were detected. Although sex by itself was not associated with asthma remission in our main multivariable model, we noted differences related to sex in the association of FEV₁/FVC with clinical remission. For each 10% increase in FEV₁/FVC, females were more likely to develop clinical asthma remission compared to males (**Figure 1b**). This contrasts with previous studies that have found either no association between sex and asthma remission or an association between female sex and asthma persistence^{1-4, 12, 20, 24-26}. Females with less severe early onset asthma are more likely to develop remission than males, which suggests that early increases in FEV₁/FVC in females that run counter to the decrements expected from dysynapsis in lung growth may disproportionately affect lung preservation²⁷. Within females, Hispanics were more likely to develop asthma remission compared to other races, which may reflect ethnic subgroup specific risks within and between races²⁸. In males, the absence of peripheral eosinophilia and use of inhaled corticosteroid treatment in early childhood (i.e., during the clinical trial phase of CAMP) were associated with increased odds of asthma remission (**Table IIIa**). Inhaled corticosteroid use does not alter the development of asthma in at risk pre-school children, and CAMP treatment group assignment has not been shown to affect lung growth²⁹⁻³¹. At this juncture, it is not clear if early inhaled corticosteroids have the potential for a previously undescribed latent effect, and further research is needed to definitively determine the long-term effects of early ICS use.

The remission of childhood asthma by adulthood has not been widely studied, and the determination of asthma remission during adolescence may not capture all events. Even fewer studies have defined asthma remission using both clinical and pulmonary function measurements^{19, 20, 25}. In the Netherlands, 22% of 119 asthmatic children followed to ages 32 to 42 years were in complete remission, as defined by having no wheeze or asthma attacks in the previous three years, no use of inhaled corticosteroids, normal lung function ($FEV_1 > 90\%$ predicted), and no airway hyperresponsiveness¹⁹. In a separate cohort from the Netherlands, Panhuysen et al. reported 11% of 181 childhood asthmatics to be in asthma remission at adulthood as defined by normal lung function ($FEV_1 > 90\%$ predicted), absence of airway hyperresponsiveness ($PC_{20} \geq 16$ mg/mL), and absence of respiratory symptoms²⁰. Our study had a larger, multiethnic population and included more frequent follow-up and comprehensive detailing of baseline characteristics compared to prior studies.

The strict remission criteria included normal airways responsiveness and was additionally associated with decreases in baseline serum IgE level and the absence of aeroallergen sensitization. These results suggest that atopic inflammation may modulate airway smooth muscle physiology, resulting in persistent asthma and airways hyperresponsiveness³². A limited number of studies have examined atopic factors as predictors of asthma remission. One study demonstrated an inverse association with allergic sensitization to animals, and a second study did not find an association between atopy and remission^{3, 20}. Conversely, asthma persistence has been associated with aeroallergen sensitization and history of atopy^{1, 2, 24, 26}. The predictors of

strict asthma remission did not differ by sex, suggesting that the baseline predictors of airways hyperresponsiveness are not sex-specific.

A higher proportion of individuals went into asthma remission by early adulthood in our study compared to a prior study of asthma outcomes at adolescence in this population⁶. Previously, Covar et al. found only 6% of individuals had clinical remission of asthma at adolescence based on symptoms, health care utilization, and medication use after the first four years of observational follow-up⁶. The difference in asthma remission rates between the two studies is likely due to a combination of different asthma remission definitions and the continued development of asthma remission in subjects followed from late adolescence to early adulthood across the entire 13-year observational follow-up. Covar et al. included the absence of local medical provider contact and school absenteeism into their asthma remission definition, whereas we did not include these criteria because their causes are not specific to asthma. Our definitions used criteria specific for asthma remission and thus, may have captured subjects who were previously labeled as persistent asthmatics by Covar et al.

Currently, there is no consensus on the definition of asthma remission. Pulmonary function measurements are used to diagnose asthma and are obtained during follow-up for clinical monitoring per guidelines; hence, pulmonary function measurements should bear some relevance in determining remission^{8,14}. When FEV₁/FVC was removed from the clinical asthma remission definition on sensitivity analysis, sex, baseline asthma severity, and serum IgE level became additional predictors of remission (**Supplemental Table II**). These additional predictors are likely a proxy for future lung function, since sex, disease severity, and allergic sensitization are

associated with changes in FEV_1/FVC ³³. Spirometry measurements were included in our asthma remission definitions to ensure the accurate classification between persistent and remitted asthma. The primary clinical remission definition reflects current clinical guidelines and practices where serial methacholine challenge tests are not routinely performed. However, methacholine challenge is the definitive test for airway hyperresponsiveness and was therefore included in the strict definition.

This study had several unique strengths. The CAMP population was ethnically diverse, and over 84% of the 1041 subjects had longitudinal follow-up. The detailed long-term follow-up from the CAMP study minimized information bias, and variables associated with loss to follow-up were controlled for to reduce selection bias. Severe asthma in childhood is uncommon. This study included only mild-to-moderate persistent childhood asthmatics, so our results may not be generalizable to mild intermittent or severe childhood asthmatics. The cut-off for normal airways responsiveness was 25 mg/mL in CAMP, and more participants would have met strict remission criteria had a less conservative cutoff been used. This study examined asthma remission at early adulthood. CAMP subjects were followed until a mean age of 26 years, and the conclusion of CAMP precluded follow-up of asthma outcomes later in life.

In summary, in a multiethnic clinical trial population from North America, a considerable minority (15-26%) of children with mild-to-moderate persistent asthma outgrew their disease by early adulthood. Our asthma remission definitions utilized clinical measurements readily available in most patients and can be applied to future studies and clinical settings. The clinical trajectory of childhood asthmatics can be predicted using baseline FEV_1/FVC , PC_{20} , and serum

eosinophil measurements. Moderate to severe decrements in FEV₁/FVC during early childhood asthma, whether due to increased disease severity or abnormal lung development, imply lifelong persistence of disease. In contrast, the majority of childhood asthmatics with well-preserved lung function will develop remission by adulthood. Our results also suggest that the increases in FEV₁/FVC above the current normal threshold of 80% are informative in childhood asthmatics, and further characterization of FEV₁/FVC above this threshold is meaningful for clinical prognostication. Together these findings strongly support the use of baseline spirometry in childhood asthma as an easily measurable and important prognostic component.

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Table I. Baseline characteristics for all participants in the study stratified by clinical asthma remission status (n = 879)

	No asthma remission (n = 650)	Asthma remission (n = 229)	P-value
Baseline age (mean $\pm$ SD)	8.8 ($\pm$ 2.1)	8.6 ($\pm$ 1.9)	0.07
Age at asthma diagnosis (mean $\pm$ SD)	3.8 ($\pm$ 2.5)	4.1 ($\pm$ 2.5)	0.07
Sex			0.001
Males	407 (62.6%)	115 (50.2%)	
Females	243 (37.4%)	114 (49.8%)	
Ethnicity			0.90
Caucasian	450 (69.2%)	154 (67.2%)	
Black	89 (13.7%)	35 (15.3%)	
Hispanic	57 (8.8%)	22 (9.6%)	
Other	54 (8.3%)	18 (7.9%)	
Baseline household income (USD)			0.95
< 29,999	140 (22.3%)	48 (22.3%)	
30,000-49,999	215 (34.2%)	71 (33.0%)	
50,000 or more	274 (43.6%)	96 (44.7%)	
Parental highest education			0.38
High school or less	116 (17.8%)	35 (15.3%)	
Some college or higher	534 (82.2%)	194 (84.7%)	
CAMP treatment group			0.15
Budesonide	178 (27.4%)	78 (34.1%)	
Nedocromil	204 (31.4%)	63 (27.5%)	
Placebo	268 (41.2%)	88 (38.4%)	
Parental history of asthma	270 (44.3%)	94 (45.2%)	0.82
Body mass index (mean $\pm$ SD)	18.2 ($\pm$ 3.6)	17.9 ($\pm$ 3.1)	0.33
Wheezes with colds	601 (92.6%)	199 (86.9%)	0.009
Wheezes apart from colds	524 (80.7%)	168 (73.4%)	0.02
Exacerbations after exercise	527 (81.1%)	164 (71.9%)	0.004
Aeroallergen sensitization on skin testing	584 (89.8%)	190 (83.0%)	0.006
History of physician diagnosed allergies	445 (68.5%)	152 (66.4%)	0.56
Exposure to home tobacco smoke	256 (39.6%)	97 (42.7%)	0.45
Baseline asthma severity			0.01
Mild	296 (45.5%)	117 (55.5%)	
Moderate	354 (54.5%)	102 (44.5%)	
Baseline PC ₂₀ (mg/mL) (median $\pm$ IQR)	0.9 ($\pm$ 1.6)	1.7 ($\pm$ 3.6)	< 0.001
Baseline FEV ₁ % predicted (mean $\pm$ SD)	92.2 ($\pm$ 14.1)	99.0 ($\pm$ 12.7)	< 0.001
Baseline FEV ₁ /FVC % (mean $\pm$ SD)	77.9 ($\pm$ 7.9)	85.6 ($\pm$ 6.3)	< 0.001
Baseline serum IgE level (ng/mL) (median $\pm$ IQR)	516.0 ($\pm$ 1166.0)	343.0 ($\pm$ 924.5)	< 0.001
Baseline eosinophil count (cells/ μ L) (median $\pm$ IQR)	422.0 ($\pm$ 493.5)	320.5 ($\pm$ 327.3)	< 0.001
Atopic dermatitis	145 (76.7%)	44 (74.6%)	0.74
Mother smoked while pregnant	90 (13.9%)	31 (13.5%)	0.88
Used wood stove for heating or cooking	67 (10.3%)	16 (7.0%)	0.14
Pet ownership	51 (7.8%)	12 (5.2%)	0.19
Clinic site			0.06
Albuquerque	77 (11.8%)	23 (10.0%)	
Baltimore	75 (11.5%)	33 (14.4%)	
Boston	73 (11.2%)	39 (17.0%)	
Denver	90 (13.8%)	19 (8.3%)	
San Diego	70 (10.8%)	27 (11.8%)	
Seattle	91 (14.0%)	32 (14.0%)	
St. Louis	101 (15.5%)	25 (10.9%)	
Toronto	73 (11.2%)	31 (13.5%)	

Table II. Baseline predictors of clinical asthma remission^{a,b}

Variable	OR	OR 95% CI	P-value
10% increase in FEV ₁ /FVC	4.62	3.35, 6.50	< 0.001
Two-fold increase in PC ₂₀	1.23	1.09, 1.39	0.001

^aCovariates included in the cross-validated model: age, sex, race, CAMP treatment group, clinic site, household income level, history of wheezing with colds, history of exacerbations after exercise, history of exposure to home tobacco smoke

^bQuantitative variables were modeled continuously

Table IIIa. Baseline predictors of clinical asthma remission in males^{a,b}

Clinical phenotype	OR	OR 95% CI	P-value
Serum eosinophil count < 500 cells/mcl	1.79	1.02-3.21	0.045
Inhaled budesonide treatment ^c	2.05	1.11-3.83	0.02
Inhaled nedocromil treatment ^c	1.30	0.70-2.42	0.41
FEV ₁ /FVC ≥ 90% ^d	73.81	13.07-1404.13	< 0.001
FEV ₁ /FVC 80-89% ^d	25.10	5.16-453.35	0.002
FEV ₁ /FVC 70-79% ^d	6.59	1.28-120.93	0.07

^aCovariates included in the cross-validated model: age, race, CAMP treatment group, clinic site, household income level, history of wheezing with colds, history of exacerbations after exercise, history of exposure to home tobacco smoke, baseline asthma severity, serum IgE level

^bQuantitative variables were modeled categorically

^cReference group is placebo treatment

^dReference level is FEV₁/FVC < 70%

Table IIIb. Baseline predictors of clinical asthma remission in females^{a,b}

Clinical phenotype	OR	OR 95% CI	P-value
Hispanic race	9.84	2.60-39.39	< 0.001
Moderate airway hyperresponsiveness (PC ₂₀ 1-4 mg/mL) ^c	0.37	0.15-0.89	0.03
Severe airway hyperresponsiveness (PC ₂₀ < 1 mg/mL) ^c	0.24	0.09-0.64	0.005
FEV ₁ /FVC ≥ 90% ^d	54.76	7.56-1166.80	< 0.001
FEV ₁ /FVC 80-89% ^d	12.13	2.00-239.14	0.02
FEV ₁ /FVC 70-79% ^d	1.44	0.20-29.90	0.75

^aCovariates included in the cross-validated model: age, CAMP treatment group, clinic site, household income level, history of wheezing with colds, history of exacerbations after exercise, history of exposure to home tobacco smoke, serum IgE level

^bQuantitative variables were modeled categorically

^cReference level is PC₂₀ > 4 mg/mL

^dReference level is FEV₁/FVC < 70%

Figure 1.

a) The proportion of childhood asthmatics who had asthma remission in early adulthood increased as baseline FEV_1/FVC increased. b) Females with higher baseline FEV_1/FVC were more likely to have remission than their male counterparts. For each 10% increase in FEV_1/FVC , females had 8.03 times odds (95% CI 4.60-14.93) of asthma remission, whereas males had 3.88 times odds (95% CI 2.62-5.92) of asthma remission (interaction $P = 0.04$).

Figure 2.

The probability of asthma remission by adulthood increases as baseline FEV_1/FVC increases. When baseline FEV_1/FVC was at least 85%, the probability of asthma remission is dependent of baseline PC_{20} and serum eosinophil count. In this subgroup, the probability of asthma remission was 58.3% when baseline PC_{20} was less than 1 mg/mL. When baseline PC_{20} was greater than or equal to 1 mg/mL, the probability of asthma remission was 65.4% in those with peripheral eosinophilia and 82.6% in those without peripheral eosinophilia.

Figure 1. Differential effect of baseline FEV₁/FVC on adult clinical asthma remission status in girls compared to boys

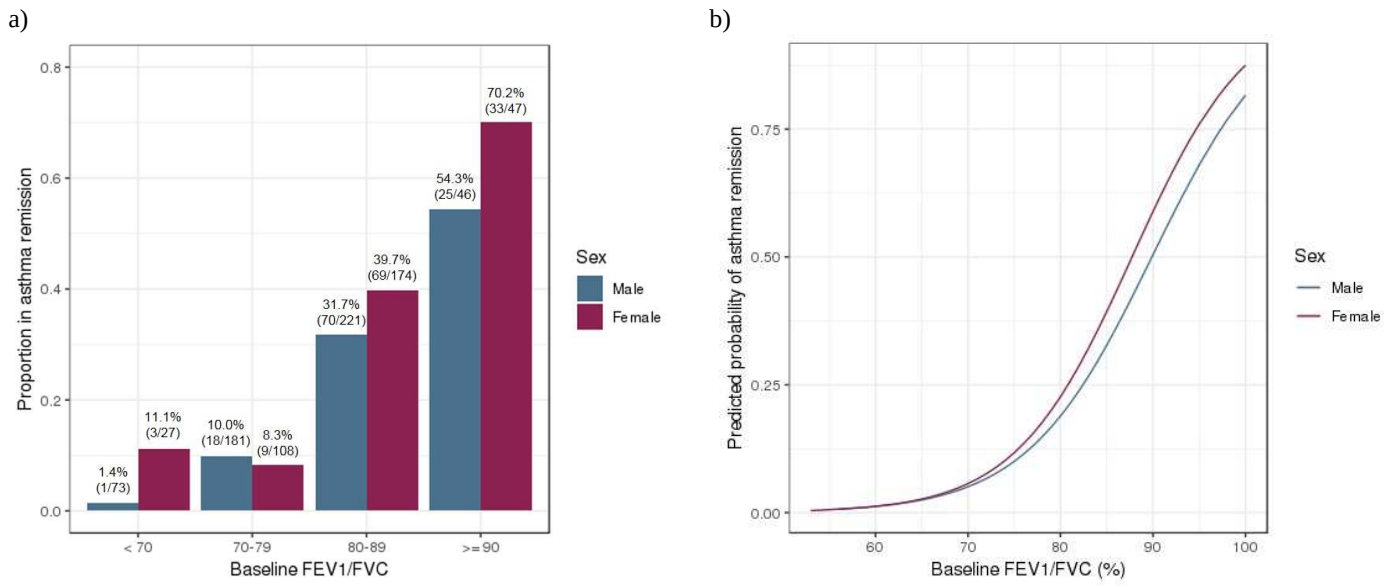
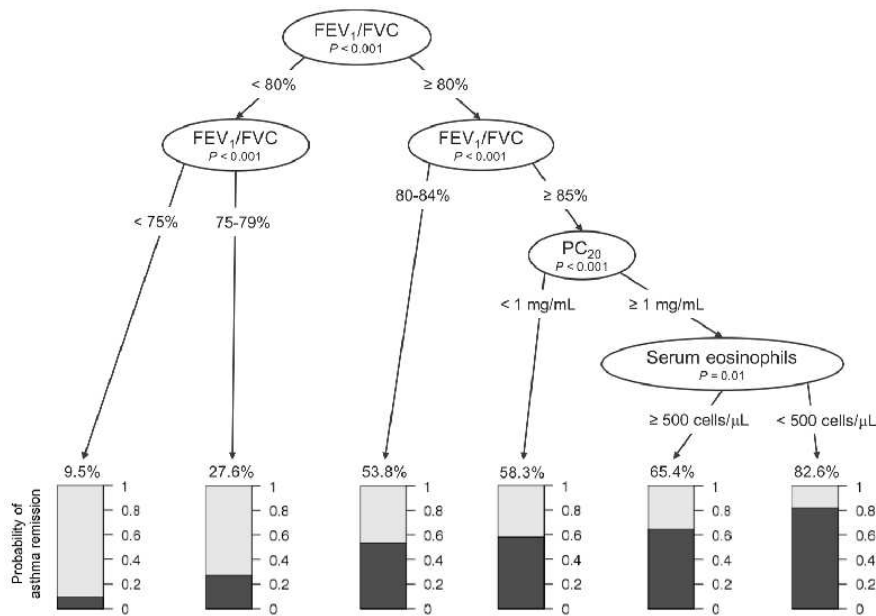


Figure 2. Decision tree classifying the probability of adult clinical asthma remission using baseline childhood predictors

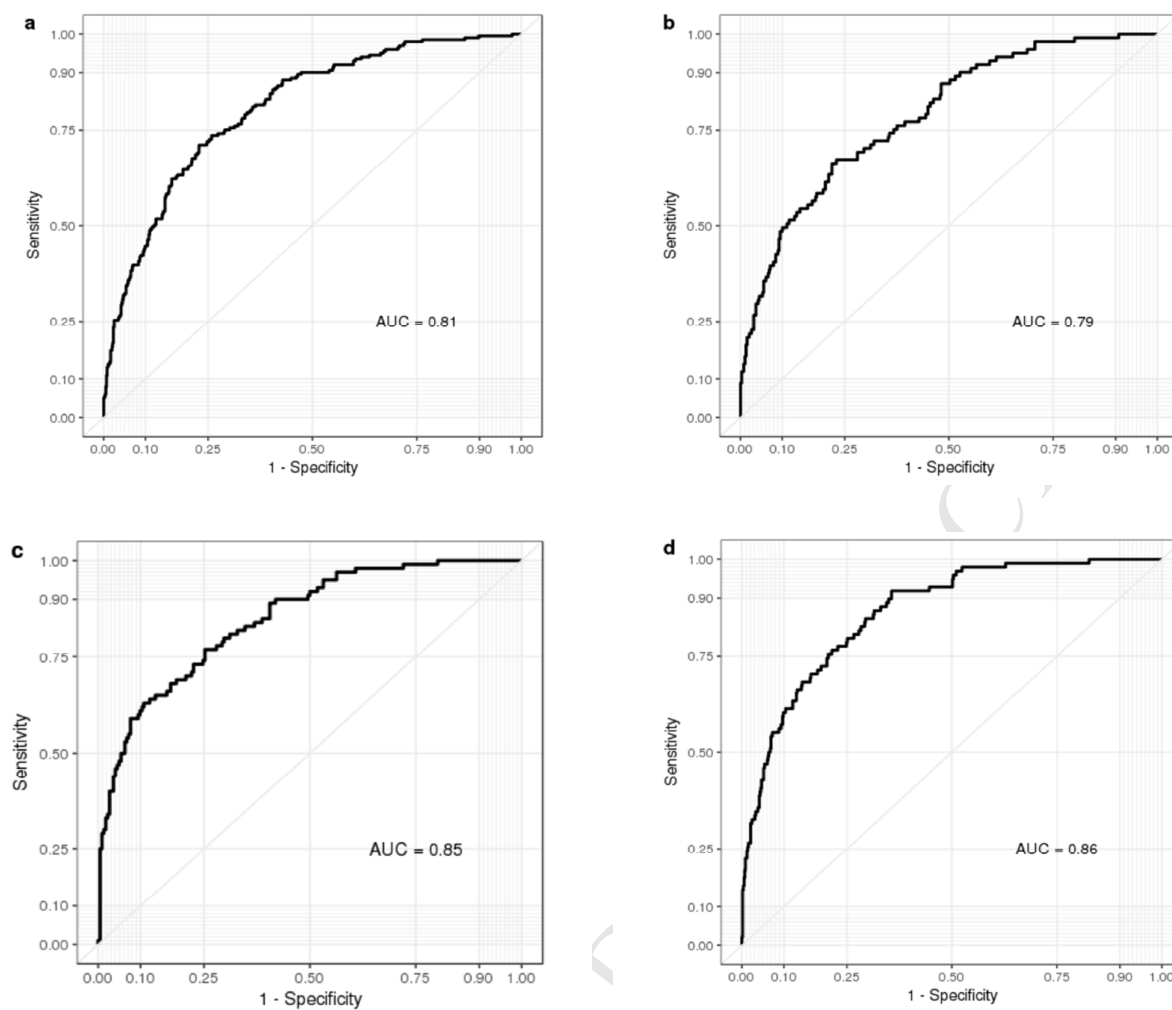


Supplemental Figure 1.

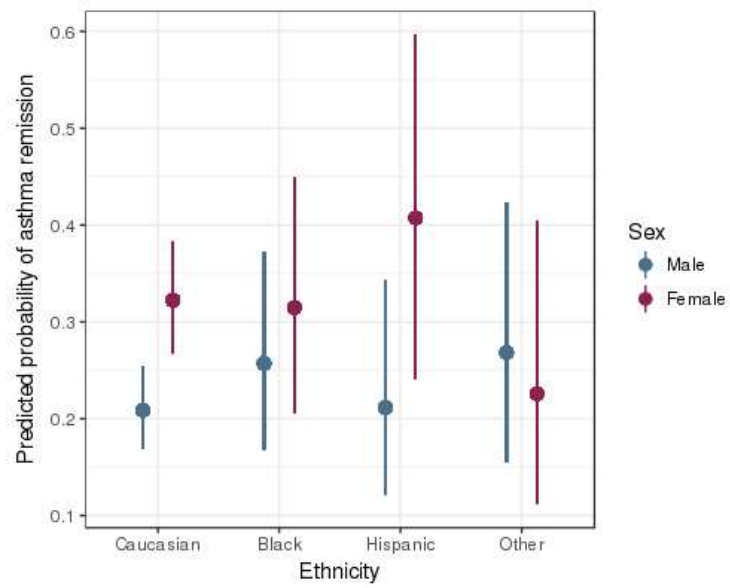
a) ROC curve for clinical asthma remission with an area under the curve (AUC) of 0.81 (95% CI 0.77-0.84), b) ROC curve for clinical asthma remission in males with an AUC of 0.79 (95% CI 0.75-0.84), c) ROC curve for clinical asthma remission in females with an AUC of 0.85 (95% CI 0.80-0.89), d) ROC curve for strict asthma remission with an AUC of 0.86 (95% CI 0.83-0.90)

Supplemental Figure 2.

Among females, the predicted probability of asthma remission was higher in Hispanics compared to Caucasians (OR 5.67, 95% CI 1.57-21.28, $P = 0.009$), Blacks (OR 8.45, 95% CI 1.99-38.93, $P = 0.005$), and other ethnicities (OR 13.89, 95% CI 2.83-76.24, $P = 0.003$). Race was not associated with asthma remission status in males.

Supplemental Figure 1. Receiver operating characteristic (ROC) curves for the cross-validated models

Supplemental Figure 2. Differential effect of race on clinical asthma remission status in girls compared to boys



Supplemental Table I. Baseline characteristics of participants in the Childhood Asthma Management Program stratified by adult clinical asthma remission follow-up status

	Participants with adult asthma remission follow-up (n = 879)	Participants lost to adult asthma remission follow-up (n = 162)	P-value
Baseline age (mean $\pm$ SD)	8.8 ($\pm$ 2.1)	9.7 ($\pm$ 2.2)	< 0.001
Age at asthma diagnosis (mean $\pm$ SD)	3.8 ($\pm$ 2.5)	4.2 ($\pm$ 2.9)	0.12
Sex			0.68
Males	522 (59.4%)	99 (61.1%)	
Females	357 (40.6%)	63 (38.9%)	
Ethnicity			< 0.001
Caucasian	604 (68.7%)	0 (0.0%)	
Black	124 (14.1%)	107 (76.4%)	
Hispanic	79 (9.0%)	14 (10.0%)	
Other	72 (8.2%)	19 (13.6%)	
Baseline household income			0.004
< 29,999	188 (22.3%)	54 (34.6%)	
30,000-49,999	286 (33.9%)	48 (30.8%)	
50,000 or more	370 (43.8%)	54 (34.6%)	
Parental highest education			0.23
High school or less	151 (17.2%)	34 (21.1%)	
Some college or higher	728 (82.8%)	127 (78.9%)	
CAMP treatment group			0.46
Budesonide	256 (29.1%)	55 (34.0%)	
Nedocromil	267 (30.4%)	45 (27.8%)	
Placebo	356 (40.5%)	62 (38.3%)	
Parental history of asthma	364 (44.5%)	63 (40.9%)	0.41
Body mass index (mean $\pm$ SD)	18.1 ($\pm$ 3.4)	18.6 ($\pm$ 3.9)	0.07
Wheezes with colds	800 (91.1%)	149 (92.0%)	0.72
Wheezes apart from colds	692 (78.8%)	136 (84.0%)	0.14
Exacerbations after exercise	691 (78.7%)	140 (87.0%)	0.02
Aeroallergen sensitization on skin testing	774 (88.1%)	140 (86.4%)	0.56
History of physician diagnosed allergies	597 (67.9%)	121 (75.2%)	0.07
7	353 (40.4%)	86 (53.1%)	0.003
Baseline asthma severity			0.67
Mild	423 (48.1%)	75 (46.3%)	
Moderate	456 (51.9%)	87 (53.7%)	
Baseline PC ₂₀ (mg/mL) (median $\pm$ IQR)	1.1 ($\pm$ 2.1)	1.1 ($\pm$ 3.0)	0.36
Baseline FEV ₁ % predicted (mean $\pm$ SD)	93.9 ($\pm$ 14.1)	92.9 ($\pm$ 15.3)	0.32
Baseline FEV ₁ /FVC % (mean $\pm$ SD)	79.9 ($\pm$ 8.3)	78.6 ($\pm$ 8.9)	0.09
Baseline serum IgE level (ng/mL) (median $\pm$ IQR)	460.0 ($\pm$ 1094.8)	393.0 ($\pm$ 874.0)	0.32
Baseline eosinophil count (cells/ μ L) (median $\pm$ IQR)	400.0 ($\pm$ 440.0)	388.5 ($\pm$ 429.5)	0.74
Atopic dermatitis	145 (76.7%)	44 (74.6%)	0.15
Mother smoked while pregnant	90 (13.9%)	31 (13.5%)	0.17
Used wood stove for heating or cooking	67 (10.3%)	16 (7.0%)	0.94
Pet ownership	51 (7.8%)	12 (5.2%)	0.14
Clinic site			< 0.001
Albuquerque	100 (11.4%)	12 (13.0%)	
Baltimore	108 (12.3%)	20 (12.3%)	
Boston	112 (12.7%)	12 (7.4%)	
Denver	109 (12.4%)	35 (21.6%)	
San Diego	97 (11.0%)	25 (15.4%)	
Seattle	123 (14.0%)	21 (13.0%)	
St. Louis	126 (14.3%)	7 (4.3%)	
Toronto	104 (11.8%)	21 (13.0%)	

Supplemental Table II. Baseline predictors of clinical asthma remission with FEV₁/FVC excluded from the definition^{a,b}

Variable	OR	OR 95% CI	P-value
Female sex	0.62	0.45, 0.86	0.004
Moderate baseline asthma severity ^c	0.71	0.51, 0.99	0.04
10% increase in FEV ₁ /FVC	1.39	1.12, 1.72	0.003
Two-fold increase in baseline PC ₂₀	1.22	1.10, 1.37	< 0.001
Two-fold increase in serum IgE level	0.82	0.75, 0.89	< 0.001

^aCovariates included in the cross-validated model: age, race, CAMP treatment group, clinic site, household income level, history of exacerbations after exercise, history of exposure to home tobacco smoke, serum eosinophil count

^bQuantitative variables were modeled continuously

^cReference level: Mild baseline physician classified asthma severity

Supplemental Table III. Baseline characteristics for the participants included in the secondary strict asthma remission outcome analysis stratified by asthma remission status (n = 741)

	No asthma remission (n = 630)	Strict asthma remission (n = 111)	P-value
Baseline age (mean $\pm$ SD)	8.7 ($\pm$ 2.1)	8.2 ($\pm$ 1.8)	0.01
Age at asthma diagnosis (mean $\pm$ SD)	3.8 ($\pm$ 2.5)	4.1 ($\pm$ 2.5)	0.16
Sex			0.09
Males	388 (61.6%)	59 (53.2%)	
Females	242 (38.4%)	52 (46.8%)	
Ethnicity			0.83
Caucasian	430 (68.3%)	79 (71.2%)	
Black	92 (14.6%)	15 (13.5%)	
Hispanic	53 (8.4%)	10 (9.0%)	
Other	55 (8.7%)	7 (6.3%)	
Baseline household income (USD)			0.61
< 29,999	134 (22.1%)	26 (24.5%)	
30,000-49,999	212 (35.0%)	32 (30.2%)	
50,000 or more	259 (42.8%)	48 (45.3%)	
Parental highest education			0.82
High school or less	102 (16.2%)	17 (15.3%)	
Some college or higher	528 (83.8%)	94 (84.7%)	
CAMP treatment group			0.29
Budesonide	169 (26.8%)	36 (32.4%)	
Nedocromil	201 (31.9%)	28 (25.2%)	
Placebo	260 (41.3%)	47 (42.3%)	
Parental history of asthma	259 (43.9%)	39 (40.2%)	0.50
Body mass index (mean $\pm$ SD)	18.1 ($\pm$ 3.4)	18.0 ($\pm$ 3.1)	0.85
Wheezes with colds	579 (92.1%)	93 (83.8%)	0.005
Wheezes apart from colds	505 (80.3%)	69 (62.2%)	< 0.001
Exacerbations after exercise	503 (79.8%)	76 (69.1%)	0.01
Aeroallergen sensitization on skin testing	571 (90.6%)	82 (73.9%)	< 0.001
History of physician diagnosed allergies	439 (69.7%)	62 (55.9%)	0.004
Exposure to home tobacco smoke	252 (40.3%)	47 (42.3%)	0.68
Baseline asthma severity			0.003
Mild	290 (46.0%)	68 (61.3%)	
Moderate	340 (54.0%)	43 (38.7%)	
Baseline PC ₂₀ (mg/mL) (median $\pm$ IQR)	1.0 ($\pm$ 1.6)	2.8 ($\pm$ 4.5)	< 0.001
Baseline FEV ₁ % predicted (mean $\pm$ SD)	93.1 ($\pm$ 13.9)	102.7 ($\pm$ 11.3)	< 0.001
Baseline FEV ₁ /FVC % (mean $\pm$ SD)	78.8 ($\pm$ 8.1)	87.2 ($\pm$ 4.9)	< 0.001
Baseline serum IgE level (ng/mL) (median $\pm$ IQR)	527.5 ($\pm$ 1207.0)	191.5 ($\pm$ 629.5)	< 0.001
Baseline eosinophil count (cells/ μ L) (median $\pm$ IQR)	440.0 ($\pm$ 471.0)	240.0 ($\pm$ 310.0)	< 0.001
Atopic dermatitis	146 (76.8%)	20 (76.9%)	0.99
Mother smoked while pregnant	82 (13.1%)	12 (10.8%)	0.51
Used wood stove for heating or cooking	58 (9.2%)	7 (6.3%)	0.32
Pet ownership	48 (7.6%)	4 (3.6%)	0.13
Clinic site			0.09
Albuquerque	77 (12.2%)	13 (11.7%)	
Baltimore	68 (10.8%)	14 (12.6%)	
Boston	76 (12.1%)	16 (14.4%)	
Denver	90 (14.3%)	8 (7.2%)	
San Diego	70 (11.1%)	6 (5.4%)	
Seattle	90 (14.3%)	18 (16.2%)	
St. Louis	90 (14.3%)	15 (13.5%)	
Toronto	69 (11.0%)	21 (18.9%)	

Supplemental Table IV. Baseline predictors of strict asthma remission^{a,b}

Variable	OR	OR 95% CI	P-value
10% increase in FEV ₁ /FVC	5.71	3.58, 9.45	< 0.001
Two-fold increase in PC ₂₀	1.52	1.26, 1.84	< 0.001
Two-fold increase in serum IgE level	0.88	0.78, 1.00	0.047
Aeroallergen sensitization on skin testing	0.48	0.24, 0.97	0.04

^aCovariates included in the cross-validated model: age, sex, race, CAMP treatment group, clinic site, household income level, history of exacerbations after exercise, history of exposure to home tobacco smoke

^bQuantitative variables were modeled continuously