Airway Responsiveness in Mild to Moderate Childhood Asthma

Sex Influences on the Natural History

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Rationale: Airway responsiveness is a prognostic marker for asthma symptoms in later life.

Objectives: To evaluate characteristics responsible for persistence of airway responsiveness in children with asthma.

Methods: A total of 1,041 children, initially aged 5–12 years, with mild to moderate persistent asthma enrolled in the Childhood Asthma Management Program (CAMP) were studied prospectively for 8.6 ± 1.8 years with methacholine challenges yearly.

Measurements and Main Results: Least squares geometric mean models were fit to determine effects of sex and age on airway responsiveness (provocative concentration producing 20% decrease in FEV₁ [PC₂₀]). Multiple linear regression analysis was performed to determine factors at baseline and over time, which were associated with PC₂₀ at end of follow-up. A total of 7,748 methacholine challenges were analyzed. PC₂₀ increased with age, with boys having greater increase after age 11 years than girls ($P < 0.001$). The divergence coincided with the mean age for Tanner stage 2. Postpubertal girls had greater airway responsiveness, even after adjustment for FEV₁ and other potential confounders. Although multivariable regression analyses noted a variety of factors that influenced airway responsiveness in both sexes, a history of hay fever ($\beta = -0.30$, $P = 0.005$), respiratory allergy ($\beta = -0.32$, $P = 0.006$), or recent inhaled corticosteroid usage ($\beta = -0.18$, $P = 0.02$) were associated with decrements in final log PC₂₀ only in girls.

Conclusions: Airway responsiveness (PC₂₀) is more severe in the postpubertal female with asthma than in males. Although there are factors associated with airway responsiveness in both males and females, sex-specific factors may contribute to new insights into asthma pathogenesis.

Keywords: methacholine; PC₂₀; FEV₁; bronchoconstriction

Increased airway responsiveness is a hallmark of asthma (1, 2). In addition to being used as a diagnostic criterion, the presence

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Although asthma affects mainly males in early childhood, it is a disease primarily of females beginning with adolescence. Longitudinal studies of airway responsiveness in asthma spanning puberty are needed.

What This Study Adds to the Field

We demonstrate that, in comparison with males, airway responsiveness persists in females during maturation; sex-specific risk factors associated with this persistence exist. Understanding of these factors may lead to novel preventative and therapeutic strategies.

of airway responsiveness in childhood asthma is of prognostic significance in the persistence and severity of symptoms in later life (3–6). These symptoms may, in turn, be related to the longitudinal decrements in pulmonary function that are also associated with increasing levels of airway responsiveness (6–9). Thus, understanding the factors influencing the level of airway responsiveness over time is crucial in the prediction of long-term asthma outcomes.

In studies of the natural history of asthma, female sex has also been cited as a risk factor for persistence of symptoms from childhood to adulthood (3, 4, 10–12). Although a variety of mechanisms have been proposed to explain the increased prevalence of asthma symptoms in teenage and adult females (13), increased airway responsiveness has consistently been noted in adult females when compared with age-matched males (5, 14–16). Therefore, factors that influence level of airway responsiveness may also help explain the reasons that asthma prevalence is greater in the postpubertal female.

In this study, we sought to ascertain the natural history of airway responsiveness as it pertains to the developing child with asthma. Specifically, the present study examines the PC₂₀ (provocative concentration necessary to cause a 20% decrement in FEV₁) results to methacholine (Mch) challenge obtained over 8.6 years to determine factors predicting change over time in a population of children with well-characterized mild to moderate asthma enrolled in the Childhood Asthma Management Program (CAMP). We focused on predictors of airway responsiveness over time, particularly during the crucial transition period surrounding adolescence. Because the natural history of asthma may vary by sex, we evaluated both the natural history of PC₂₀ values and the factors associated with degree of airway responsiveness over time in sex-specific analyses.

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*Members of the CAMP Research Group are detailed in the online supplement.

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METHODS

Detailed methods are provided in the online supplement.

CAMP and CAMP Continuation Study

CAMP design and methods have been described previously (17). Briefly, CAMP was a prospective, randomized, double-masked, multicenter clinical trial comprising 1,041 children aged 5 to 12 years with mild to moderate asthma demonstrated during a screening period and a positive Mch challenge (mean PC₂₀, 1.1 ± 3.3 mg/ml, all ≤12.5 mg/ml). The treatment phase (budesonide at 400 µg daily or nedocromil sodium at 16 mg daily) was 4 to 6 years, from 1993 to 1999. The observational phase, known as the CAMP Continuation Study (CAMPCS), began in 1999 and continued into 2004, with patient asthma care based on national guidelines directed by each patient's personal physicians (18). Informed consent and assent were obtained from all guardians and participants at the start of both CAMP and CAMPCS.

Mch testing was performed before randomization, 8 months after randomization, and then yearly throughout both the double-blind treatment and observation phases of the study. The challenge procedure was modified from the methods of Cockcroft and colleagues and Juniper and coworkers (19, 20); detailed descriptions of the procedure, preparation of Mch reagent, and safety of the procedure are available elsewhere (17). The concentration that provoked a 20% fall from postdiluent FEV₁ was obtained by linear interpolation of the logarithmic dose-response curve expressed as PC₂₀. Participants completing the challenge without a 20% drop in FEV₁ were assigned a value of 37.5 mg/ml. Tanner staging was done by physician examination during visits.

Statistical Analyses

All analyses were limited to children 5 through 18 years of age at Mch testing. Within-patient correlation was accounted for using generalized estimating equations in all analyses. With the exception of IgE levels and eosinophil counts, which were analyzed using Wilcoxon rank sum tests, unadjusted comparisons of characteristics by sex were conducted using either *t* tests (measured variables) or chi-square tests (categorical variables).

Multivariable analyses included baseline covariates (parent education level, family income, age at asthma diagnosis, asthma severity, family history of asthma, history of hay fever, food allergies, eczema, positive skin test, IgE level, eosinophil count, sensitivity and exposure to perennial allergens, presence of furry or feathered pet in the home, water damage, mold or mildew in home, passive smoking, bronchodilator response) and time-varying covariates (body mass index, weight, Tanner stage, duration of asthma, recent inhaled corticosteroid [ICS] usage, prebronchodilator FEV₁ and FVC percent predicted, and FEV₁/FVC at challenge). Linear spline terms for age, height, clinic, and race were included in all regression models. Backward stepwise selection (*P* = 0.05 for removal) was used to select characteristics. Differential effects of characteristics by sex were tested by adding interaction terms to the regression models.

The natural history of PC₂₀ was evaluated by obtaining geometric mean PC₂₀ values for each age or Tanner stage for males and females. *P* values for differences between sexes in PC₂₀ by age and Tanner stage were determined by conducting Wald *F* tests on age by sex and age by Tanner stage linear spline terms. All analyses were conducted using SAS (version 8; SAS Institute, Cary, NC) and STATA (version 9; Stata Corp., College Station, TX).

RESULTS

Population

A total of 1041 children enrolled in the CAMP clinical trial. After a mean clinical trial duration of 4.6 years, 941 of the 1,041 CAMP participants subsequently enrolled in the 4-year observational study. Study participants were predominantly male and white (Table 1; Table E1 of the online supplement). A number of characteristics varied by sex. When compared with males, at the time of challenge CAMP female participants were, on

average, shorter, older when initially diagnosed with asthma, and matured more quickly, as evidenced by the greater proportion of females at or above Tanner stage 3 over the entire set of measurements. Females also had higher baseline IgE levels, but lower eosinophil counts. Finally, females had higher average values for prechallenge FEV₁ and FVC as a percentage of predicted values, as well as a greater FEV₁/FVC ratio.

Effects of Sex and Age on Airway Responsiveness

There were 7,748 Mch challenges performed over a 10-year period and included in this analysis. Average PC₂₀ values from age 5 to 18 years for boys and girls are shown in Figure 1. All 7,748 challenges are included, with each child contributing multiple results to a curve. PC₂₀ values increased in boys and girls similarly from age 5 to 11 years. After age 11 years, PC₂₀ in boys continued to increase but in girls had minimal change from age 11 to 18 years. Overall, after adjustment for race, clinic, duration of asthma at enrollment, positive skin test reactivity, baseline asthma severity, and ongoing ICS usage, the curve for boys was significantly different from that of girls (*P* < 0.0001).

Because the sex-specific differences in PC₂₀ have been hypothesized to be related to the tight correlation between PC₂₀ and level of lung function (21), we specifically evaluated PC₂₀ values in the context of FEV₁. After adjustment for level of FEV₁ at the time of each challenge (Figure 1B), we observed that the average PC₂₀ after age 11 years remained significantly higher for males than for females (*P* < 0.0001). From about the age 14 years onward, however, although the FEV₁-adjusted PC₂₀ curves were different for girls compared with boys, the curves are reasonably parallel (Figure 1B), suggesting that the effect modification due to sex may be a relatively constant one in later adolescence.

Effects of Sex and Tanner Stage on Airway Responsiveness

Given the age-related divergence in PC₂₀ by sex, we sought to evaluate the role of Tanner stage on this relationship. Figure 2 shows the mean PC₂₀ values for boys and girls by Tanner stage. Boys demonstrated a gradual increase in PC₂₀ with each Tanner stage, compared with no apparent change in average PC₂₀ by Tanner stage in girls. The mean age at the beginning of Tanner stage 2, the point of the initial increase in PC₂₀ in boys relative to girls, across the entire cohort was 11 years, corresponding well with the age-specific analyses noted above.

Factors that Influence Airway Responsiveness over 8.6 Years of Follow-up

Table 2 shows the multivariable analysis of those factors significantly associated with PC₂₀ at end of the time points examined, stratified by sex. Lower PC₂₀ (increased airway responsiveness over time) is indicated by negative signs preceding the β -coefficients. Baseline factors associated with lower PC₂₀ at follow-up in both sexes included variables reflecting lower age at asthma diagnosis, higher objective measures of atopy (IgE level and eosinophil count), and higher bronchodilator response. In addition, several factors measured at each PC₂₀ visit over time, including lower body mass index, decreased duration of asthma, and lower level of lung function, were consistently associated with increased airway responsiveness in both sexes.

Sex-specific predictors of PC₂₀ over time are also shown in Table 2; significance is indicated by interaction *P* values < 0.05. Predictors of lower PC₂₀ that were stronger in males than females included positive skin test reactivity and decreased height, although the direction of the effect of both of these predictors was similar in both sexes. In contrast, there were

TABLE 1. SEX-SPECIFIC CHARACTERISTICS OF THE CHILDHOOD ASTHMA MANAGEMENT PROGRAM POPULATION OF CHILDREN* WITH MILD TO MODERATE ASTHMA

	Male	Female	<i>P</i> [†]
Children, n	621	420	
Methacholine challenges, n	4,685	3,063	
Mean number of challenges per child	7.5 ± 2.1	7.3 ± 2.2	0.06
Demographics			
Race/ethnicity, n (%)			0.32
White, non-Hispanic	416 (67.0)	295 (70.2)	
Black, non-Hispanic	82 (13.2)	56 (13.3)	
Hispanic	67 (10.8)	31 (7.4)	
Other	56 (9.0)	38 (9.1)	
Physical characteristics			
Tanner stage at challenge ^{‡§} , n (%)			<0.001
Stage 1	1,950 (42.6)	1,045 (34.7)	
Stage 2	912 (19.9)	557 (18.5)	
Stage 3	414 (9.1)	442 (14.7)	
Stage 4	490 (10.7)	377 (12.5)	
Stage 5	807 (17.7)	590 (19.6)	
Asthma characteristics			
Mean age at diagnosis, yr	3.4 ± 2.4	4.2 ± 2.3	<0.001
Mean age at challenge [‡] , yr	11.7 ± 3.2	11.8 ± 3.2	0.72
Recent ICS usage at each challenge [‡] , yes vs. no, n (%)	1,735 (37.1)	1,143 (37.5)	0.88
Atopy at baseline			
Any positive skin test, yes vs. no, n (%)	552 (88.9)	362 (86.2)	0.19
Mean IgE, ng/ml	1,104 ± 1,898	1,280 ± 3,030	0.16
Mean eosinophil count, cells/ml	490 ± 399	476 ± 455	0.22
Lung function			
Mean BD response at baseline (%)	11.1 ± 10.9	10.1 ± 9.3	0.13
Mean pre-BD FEV ₁ % predicted at challenge [‡]	94.4 ± 12.3	98.5 ± 12.7	<0.001
Mean pre-BD FVC % predicted at challenge [‡]	104.7 ± 11.5	107.1 ± 12.9	0.001
Mean pre-BD FEV ₁ /FVC ratio* at challenge [‡]	78.6 ± 8.0	81.4 ± 7.9	<0.001
PC ₂₀ > 25 mg/ml among subjects ≥18 yr, n (%)	38 (27.0)	14 (14.9)	0.03

Definition of abbreviations: BD = bronchodilator; ICS = inhaled corticosteroid; PC₂₀ = provocative concentration producing 20% decrease in FEV₁.

Plus-minus values are means ± SD.

* Observations on children ≤18 years of age.

† Wilcoxon rank sum test used to calculate *P* values for IgE levels and eosinophil counts. All other *P* values calculated using Student's *t* test or chi-square test. Within-patient repeated measures for time-dependent variables were accounted for using generalized estimating equations.

‡ Time-dependent variables measured across all challenges. All other variables measured at baseline.

§ Genital stage for males and breast stage for females. Tanner stage was recorded annually at non-methacholine challenge visits and carried forward. Stage is allowed to fluctuate in this analysis.

several multivariable predictors of increased airway responsiveness that were significant only in females, including any history of hay fever (interaction *P* = 0.02), respiratory allergy (interaction *P* = 0.002), or recent ICS usage (interaction *P* = 0.01). *In utero* smoking was also noted to be a predictor of lower PC₂₀ in females but not males, but the direction of the association was similar in both sexes. Of note, level of lung function as measured by FEV₁ as a percentage of predicted, while closely associated with level of PC₂₀, did not demonstrate a differential effect by sex (interaction *P* = 0.89).

DISCUSSION

Following a large cohort of children with mild to moderate persistent asthma for an extended period of time with yearly Mch challenges has allowed for a detailed description of the natural history of airway responsiveness and determination of factors related to airway responsiveness over time. On average, airway responsiveness was in the moderate range on entry into CAMP when the children were 5 to 12 years of age. Eight years later, airway responsiveness had improved to the mild range on average. The effect of sex on the evolution to airway responsiveness was striking, with males becoming much less responsive after age 11 years, but females having minimal change from age 11 to 18 years (Figure 1). Most prior studies of the natu-

ral history of airway responsiveness have focused on general population samples and contained a preponderance of non-responsive and nonasthmatic subjects. Therefore, the detailed elucidation of the natural history of airway responsiveness within asthma is unique to this longitudinal cohort.

The identification of sex-specific differences in PC₂₀ in relation to age and Tanner stage has important implications for both the mechanistic basis and the prognosis of asthma in young adults. In contrast to some prior studies (21–23), our data demonstrate that sex differences in PC₂₀ are present even after adjustment for level of FEV₁ and other confounders. This is consistent with several other population-based surveys of Mch responsiveness that also demonstrated increased airway responsiveness in females, even after adjustment for level of lung function (14–16). It should be noted that the studies that demonstrated no sex differences after adjustment for FEV₁ were relatively small, with a low prevalence of significant airway responsiveness (21–23), suggesting that those studies may have been insufficiently powered to detect a sex-specific association. With nearly 8,000 Mch challenges administered in an asthmatic cohort initially recruited based on a positive response to Mch (17), the current CAMP study has much greater statistical power than any prior study.

Although we noted several sex-specific risk factors for lower PC₂₀ in girls, including a history of hay fever, respiratory allergy,

Figure 1. Adjusted geometric mean FEV₁ PC₂₀ (provocative concentration producing 20% decrease in FEV₁) (mg/ml) by sex and age. Males are represented by squares and females by circles. Geometric means were adjusted for clinic, race, duration and severity of asthma at baseline, positive skin test at baseline, and recent inhaled corticosteroid usage (A), with additional adjustment for prebronchodilator FEV₁ percent predicted (B) using multiple linear regression. Within-patient repeated measures were accounted for using generalized estimating equations. *P* values for the age course of FEV₁ PC₂₀ by sex were determined by conducting a Wald *F* test on an age-by-sex linear spline term. Error bars are 95% confidence limits.

or recent ICS usage, neither the prevalence nor the magnitude of the differences related to these items was sufficient to explain the overall differences in PC₂₀ between sexes over time.

The fact that the sex-specific difference emerges at about 11 years of age, the average age of transition from Tanner stage 1 to Tanner stage 2 (Figure 2), may speak directly to potential mechanisms. Several other longitudinal cohorts have evaluated

airway responsiveness in subjects at pre- and postpubertal time points, noting in each case that females demonstrated significantly greater responsiveness than males after puberty, but not before (5, 16, 24). Mechanistically, these differences may be potentially explained either by dysanapsis or hormonal changes. Dysanapsis refers to the differential growth between airway size and lung size; adult females are known to have relatively

Figure 2. Adjusted geometric mean FEV₁ PC₂₀ (mg/ml) by Tanner stage. Males are represented by squares and females by circles. Geometric means were adjusted for clinic, race, duration and severity of asthma at baseline, positive skin test at baseline, and recent inhaled corticosteroid usage using multiple linear regression. Within-patient repeated measures were accounted for using generalized estimating equations. *P* value for the Tanner stage course of FEV₁ PC₂₀ by sex was determined by conducting a Wald *F* test on a Tanner stage-by-sex linear spline term. Tanner genital stage was used for males and breast stage was used for females. Tanner stage was recorded annually at nonmethacholine visits and carried forward. Stage is allowed to fluctuate in this analysis. Tanner staging in males and females shown on same axes for illustrative purposes. Error bars are 95% confidence limits.

TABLE 2. CHARACTERISTICS OF CHILDREN WITH MILD TO MODERATE ASTHMA THAT AFFECT LOG FEV₁ PC₂₀ IN EITHER SEX

	Male		Female		Sex Interaction <i>P</i> [†]
	(599 patients, 4,504 measures)		(396 patients, 2,859 measures)		
	Difference in log FEV ₁ PC ₂₀ , b*	<i>P</i>	Difference in log FEV ₁ PC ₂₀ , b*	<i>P</i>	
Baseline characteristics					
Diagnosis age	0.15	0.01	0.16	0.02	0.54
Smoking passive <i>in utero</i> (yes vs. no)	−0.13	0.28	−0.24	0.05	0.95
History of hay fever (yes vs. no)	−0.12	0.16	−0.30	0.005	0.02
Respiratory allergy (yes vs. no)	0.06	0.49	−0.32	0.006	0.002
Any positive skin test (yes vs. no)	−0.53	<0.001	−0.20	0.11	0.53
IgE ≥ median (yes vs. no)	−0.55	<0.001	−0.59	<0.001	0.55
Eosinophils ≥ median (yes vs. no)	−0.44	<0.001	−0.31	0.006	0.69
BD response, %	−0.02	<0.001	−0.02	0.002	0.91
Time-varying characteristics					
BMI, kg/m ²	0.03	0.01	0.02	0.04	0.21
Duration of asthma, yr	0.16	0.005	0.18	0.01	0.07
Pre-BD FEV ₁ , % predicted	0.01	<0.001	0.02	<0.001	0.89
Pre-BD FEV ₁ /FVC ratio	0.04	<0.001	0.05	<0.001	0.41
Recent ICS usage (yes vs. no)	0.07	0.23	−0.18	0.02	0.01

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; ICS = inhaled corticosteroid; PC₂₀ = provocative concentration producing 20% decrease in FEV₁.

* Regression coefficients (b) were determined from separate multiple linear regression models used to relate log FEV₁ PC₂₀ in males and females to the characteristics. Within-patient repeated measures were accounted for using generalized estimating equations. Linear spline terms for age at challenge (5–18 yr), clinic, race (white/other, black, Hispanic), and height were included. Education, income, weight, Tanner stage, asthma severity, family history of asthma, food allergy, eczema, sensitive and exposed to perennial allergen, furry/feathered pet in home, passive smoking, and maternal smoking were analyzed but were not related to FEV₁ PC₂₀ at *P* = 0.05 level of significance, using backward stepwise selection (*P* = 0.05 for removal). FVC was dropped due to collinearity.

[†] Differential effects of characteristics by sex were tested by adding sex-by-effect interaction terms to the multiple linear regression models. *Note:* A total of 181 challenges among males and 204 challenges among females were dropped due to missing values for one or more characteristics in the model.

smaller airways in proportion to a given lung volume (25) compared with adult males (26). In turn, small airway size relative to lung size is associated with higher airway sensitivity and responsiveness to Mch (27). Therefore, the transition period between childhood and adulthood may indicate a time in which females become more susceptible to airway responsiveness. However, the calculated peak difference in dysanapsis between sexes is at around age 18 years (26), making dysanapsis an unlikely explanation for our findings.

Hormonal regulation of airway responsiveness must be considered as a potential mechanism for our findings, because the mean PC₂₀ diverged after progression to Tanner stage 2. Moreover, although we did not directly measure hormone levels, further increases in the PC₂₀ difference between sexes occurred with increasing sexual maturation, consistent with a possible effect of increasing hormonal levels over time. In females with asthma, studies have demonstrated an impaired ability to increase β₂-adrenergic receptor numbers despite a significant increase in airway responsiveness accompanying the luteal phase of the menstrual cycle (28). This increase in airway responsiveness may be related to relative reductions in serum estrogen or relative excesses in progesterone. Exogenous administration of estrogen may inhibit airway responsiveness (29), whereas exogenous progesterone may decrease β₂-adrenergic receptor response (30). These data are further supported in recent animal models, which demonstrate that both estrogen receptor knock-out mice (31) as well as mice with increased progesterone (32) levels have markedly increased allergic airway responsiveness. Although the major increases in progesterone accompany ovulation, which generally is seen late in puberty, there are clear-cut increases in serum progesterone in females as early as Tanner stage 2 (33, 34).

It was the postpubertal boys in our study that increased their PC₂₀, whereas the PC₂₀ of the girls plateaued. Thus, it is interesting that animal models have demonstrated that testosterone can relax previously contracted airway smooth muscle in what appears to be a nitric oxide-mediated mechanism (35).

Therefore, it is possible that the postpubertal decreases in airway responsiveness among males may be mediated through increases in testosterone levels. Although a previous cohort study failed to note any association between level of androstenediolglucuronide (a marker of peripheral testosterone metabolism) and bronchial reactivity to cold air challenge (36), the sample size of the study may not have been sufficiently powered to detect this association.

The change in airway responsiveness over time in both sexes was influenced by several factors measured on entry into the study. Those factors included duration of asthma, indicators of atopy, increased lability as measured by reactivity to bronchodilator, and abnormalities in spirometry. The importance of atopy in long-term determination of airway responsiveness is indicated by three separate variables—skin test reactivity, IgE, and peripheral blood eosinophil count—all being retained in the multivariable model. The measures of atopy, as well as those of lung function, are consistent with multiple cross-sectional studies that have evaluated factors associated with airway responsiveness (37–43). Indeed, aside from bronchodilator response, each of the factors associated with PC₂₀ longitudinally in both sexes was also noted to be associated with PC₂₀ in prior cross-sectional CAMP studies (37, 44). Moreover, the relationship between increased bronchodilator reactivity and persistence of increased airway responsiveness is expected from the known highly significant correlations that we previously reported (7).

Although the data are consistent with cross-sectional results, the persistence of these associations over 8 years has not been previously demonstrated. Overall, there have been few longitudinal studies of airway responsiveness. These studies have noted associations between baseline atopy (16, 22, 24) and/or lung function (16, 22, 45, 46) and subsequent airway responsiveness. Measures of atopy and lung function were strongly associated with degree of PC₂₀ in our cohort. However, together with extensive phenotyping, a large sample size and annual follow-up visits provided our study with the statistical power to identify new factors previously not attributed to the persistent

airway responsiveness over time, including duration of asthma, age at diagnosis, body mass index, and bronchodilator response, as well as sex-specific factors, including history of hay fever or respiratory allergy and recent ICS usage.

There are several potential limitations to our study. As mentioned above, no direct hormonal measures were obtained, limiting our ability to formally test some hypotheses related to sex-specific effects. Our study also involved a cohort that followed a clinical trial period, making treatment assignment during the trial a potential confounder. However, by the end of the washout period after the clinical trial, there was no significant difference in airway responsiveness between subjects who had been randomized to the budesonide and placebo groups (18), making confounding by residual treatment effects as an explanation for any observed differences highly unlikely. Finally, we assigned a value of 37.5 mg/ml to subjects who did not respond to Mch at the highest doses administered. Therefore, some predictors of log PC₂₀ may not have been identified due to the imposed upper limit bounds. However, relatively few "marginal" predictors were identified (Table 2), suggesting that this was not a major study problem.

In conclusion, the natural history of airway responsiveness in childhood through early adulthood in asthma has now been comprehensively described. The fact that there is a sex-specific association of postpubertal females with increased airway responsiveness in asthma provides a rationale for, and mechanistic insights into, the prevalence and pathogenesis of the disease in early adulthood. Moreover, careful attention to several factors, including duration of asthma, indicators of atopy, increased bronchodilator response, and lower pulmonary function, even from a young age may have prognostic implications in the determination of those patients with asthma in whom airway responsiveness is most likely to persist.

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