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In Utero Smoke Exposure and Impaired Response to Inhaled Corticosteroids in Children with Asthma

Robyn T. Cohen, MD, MPH[1,2,*], **Benjamin A. Raby, MD.CM, MPH, MPH**[1,2,3], **Kristel Van Steen, PhD**[4], **Anne L. Fuhlbrigge, MD, MS**[1,2,3], **Juan C. Celedón, MD, DrPH**[1,2,3], **Bernard A. Rosner, PhD**[1], **Robert C. Strunk, MD**[5], **Robert S. Zeiger, MD, PhD**[6], and **Scott T. Weiss, MD, MS [on behalf of for the CAMP Research Group]**[1,3]

[1]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA

[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

[3]Harvard Medical School, Boston MA

[4]Montefiore Institute – Bioinformatics, University of Liège, Liège, Belgium

[5]Division of Allergy and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine and St Louis Children's Hospital, St. Louis, MO

[6]Department of Pediatrics, University of California-San Diego, and Allergy Department Kaiser Permanente, San Diego

Abstract

Background—Few studies have examined the effects of *in utero* smoke exposure (IUS) on lung function in children with asthma, and there are no published data on the impact of IUS on treatment outcomes in asthmatic children.

Objectives—To explore whether IUS exposure is associated with increased airway responsiveness among children with asthma, and whether IUS modifies the response to treatment with inhaled corticosteroids (ICS).

Methods—To assess the impact of parent-reported IUS exposure on airway responsiveness in childhood asthma we performed a repeated-measures analysis of methacholine PC_{20} data from the Childhood Asthma Management Program (CAMP), a four-year, multicenter, randomized double masked placebo controlled trial of 1041 children ages 5–12 comparing the long term efficacy of ICS with mast cell stabilizing agents or placebo.

Results—Although improvement was seen in both groups, asthmatic children with IUS exposure had on average 26% less of an improvement in airway responsiveness over time compared to unexposed children (p=.01). Moreover, while children who were not exposed to IUS who received budesonide experienced substantial improvement in PC_{20} compared to untreated children (1.25 fold-

[*]Corresponding Author's Current Affiliation: Department of Pediatrics, Drexel University College of Medicine and St. Christopher's Hospital for Children, Erie@ Front Street, Philadelphia, PA, USA. Telephone (215) 427-5183, Fax (215) 427-4621, robyn.cohen@drexelmed.edu.

increase, 95% CI 1.03, 1.50, p=.02) the beneficial effects of budesonide were attenuated among children with a history of IUS exposure (1.04 fold-increase, 95% CI 0.65, 1.68, p=.88).

Conclusions—IUS reduces age-related improvements in airway responsiveness among asthmatic children. Moreover, IUS appears to blunt the beneficial effects of ICS use on airways responsiveness. These results emphasize the importance of preventing this exposure through smoking cessation counseling efforts with pregnant women.

Keywords

asthma; *in utero* smoke exposure; airway responsiveness; inhaled corticosteroids

Introduction

Exposure to cigarette smoke during fetal development is harmful to children. *In utero* smoke exposure (IUS) increases risk of obstetric complications (e.g., abruptio placentae, premature birth, and intrauterine growth restriction); and sudden infant death syndrome (SIDS). Prenatal smoke exposure has also been shown to be associated with decreased cognitive development and school performance, and an increased risk of behavioral and psychiatric difficulties[1, 2].

There is compelling evidence that IUS results in significant respiratory sequelae as well, which can manifest early in life. Reductions in forced expiratory flows, tidal flow-volume ratios, and respiratory compliance have been observed in healthy newborns of mothers who smoked during pregnancy[3–5]. Similar reductions in peak expiratory flows[6] and small airway flows[6, 7] have been observed in school-aged children, suggesting a long-term impact of IUS on pulmonary function. An analysis of pooled data from several international studies demonstrated an increased risk of poor lung function among children exposed to IUS, even after adjustment for current exposure to environmental tobacco smoke (ETS)[7]. IUS has also been associated with an increased risk of recurrent wheeze[8] and incident asthma at school-age 9–11 and in adulthood.[12].

In contrast to numerous population-based studies about the effects of IUS on lung function in infants and children, only one study has specifically examined the effects of IUS on the lung function of children already diagnosed with asthma. Data from 5,933 participants in the California Children's Health Study showed that children and adolescents who were diagnosed with asthma before age 5 years and who had been exposed to IUS had greater deficits in FEV_1/FVC, $FEF_{25–75}$, and $FEF_{25–75}$/FVC than unexposed asthmatic children[13]. Importantly, there are no published data regarding the impact of IUS on airway responsiveness or treatment outcomes in asthmatic children.

Here we assess the relationship between IUS and subsequent airway responsiveness in a cohort of children aged 5–12 years with well-established mild to moderate persistent asthma who participated in a randomized, placebo controlled trial that evaluated the long term efficacy and safety of inhaled anti-inflammatory medications. This study design provides a unique opportunity to explore whether *in utero* tobacco smoke exposure attenuated the beneficial effect of inhaled steroids that was seen overall among study participants[14]. We demonstrate that IUS has a substantial detrimental impact on responsiveness to inhaled corticosteroid therapy.

Methods

Details of the Childhood Asthma Management Program (CAMP) trial have been described elsewhere[15, 16]. Briefly, CAMP is a multicenter, randomized, double-masked clinical trial to compare the long-term effectiveness and safety of three inhaled treatments for asthma:

budesonide, nedocromil, and placebo. CAMP enrolled 1041 children ages 5–12 years with mild-moderate asthma at eight clinical centers between December 1993 and September 1995. Asthma was defined by the presence of asthma symptoms or the use of an inhaled bronchodilator at least twice per week, or use of a daily asthma medication for the 6 months prior to the screening interview. All participants had increased airway responsiveness to methacholine (a provocation concentration causing a 20% reduction in FEV_1 [PC_{20}] ≤ 12.5mg/ml) at study entry. Children were excluded if they had severe asthma or other active sinopulmonary disease. Each parent or guardian signed a consent form, and each participant 7 years of age and older signed an assent form approved by each clinical center's institutional review board.

Information regarding *in utero* tobacco smoke exposure was obtained during the baseline medical interview, which was nearly always completed by the mothers of CAMP participants. Children were considered to have IUS exposure if respondents answered affirmatively to the question "Did this child's mother smoke while she was pregnant with this child?" Information about current environmental tobacco smoke exposure was obtained during follow-up interviews with the question "Do any caretakers of the child currently smoke cigarettes?"

Of the 1,041 participating children, 311 were assigned to receive budesonide (200 μg twice daily[Turbuhaler, AstraZeneca]), 312 were assigned to receive nedocromil sodium (8mg twice daily[Tilade, Rhone-Poulenc Rorer, Collegeville, PA]), and 418 were assigned to receive a matching placebo. Albuterol (two 90 μg actuations from a metered-dose inhaler [Ventolin, Glaxo Wellcome, Research Triangle Park, N.C]) was used as needed for symptoms of asthma and to prevent exercised-induced bronchospasm.

Spirometry, both before and after the administration of a bronchodilator, was performed twice per year. A methacholine challenge was performed at baseline (after a 28-day washout period during which no participants were taking inhaled steroids) and then annually during the treatment phase, using the Wright nebulizer-tidal breathing technique, at least 4 hours after the last use of a short-acting bronchodilator and at least 24 hours after the last use of a long-acting bronchodilator. After a control diluent challenge, nine doubling doses of methacholine were nebulized for 2 minutes each at 5-minute intervals. Spirometry was performed 90 seconds after each challenge until FEV1 had fallen by 20% or more. Methacholine challenge was not performed within 28 days of an upper respiratory tract infection or the use of prednisone for exacerbations of asthma. The child's height and weight were recorded at every visit.

The distribution of PC_{20} at each visit was skewed, with a long right tail. PC_{20} was therefore natural log (ln)-transformed for all regression analyses. Longitudinal regression was performed to test the association between IUS and PC_{20} before and after adjustment for potential confounders and to distinguish inter-individual changes in PC_{20} from within-subject change. We developed random-effects models using SAS PROC MIXED (SAS Institute, Cary, NC), related log-transformed PC_{20} to the aforementioned effects, and accounted for associated time observations within a patient. Components of variability were a random intercept supplemented with a serial correlation. Longitudinal analysis using PROC MIXED was also used to test the effect of treatment group assignment (budesonide vs. nedocromil or placebo) on PC_{20} after stratification by IUS status.

Results

All children with asthma in CAMP (n=1041) had baseline methacholine challenge tests. Methacholine challenge testing was completed for 92, 90, 85, and 82% of the cohort at 8, 20, 32, and 44 months after randomization, respectively. Baseline characteristics were generally similar between children with and without methacholine challenge data at 44 months. Children

who were missing PC_{20} measurements were more likely to have been recruited from three of the clinical sites (Albuquerque, Boston, and Seattle), to have come from families with lower household income, and to have mothers with a history of either asthma or smoking during pregnancy. Baseline median $\log_e PC_{20}$ was similar between groups (Wilcoxon rank sum p values >.30)[17].

Of the 1,041 participants, 5 subjects were missing IUS data and were therefore excluded from analyses. 150 (14%) had reported exposure to IUS (Table 1). 109 children (73% of those exposed) had IUS exposure during all three trimesters. Exposed children were more likely to have mothers without any college education (p<.001) and subsequent exposure to environmental tobacco smoke than children not exposed to IUS (p<.001). The characteristics of the two groups at baseline, including spirometry and PC_{20}, were otherwise similar.

A repeated-measures analysis of methacholine PC_{20} data collected over the 44 months of the CAMP clinical trial found, as previously reported,[17] that parental history of asthma, total serum IgE, and lung function were associated with increased airway responsiveness, both at baseline (prior to treatment randomization) and over the 44 months of observation. While current ETS exposure was associated with increased airway responsiveness at baseline, this relationship did not remain significant over time. Baseline PC_{20} (prior to the initiation of treatment) did not differ between children who were and were not exposed to IUS (p=.89), and there was improvement in the median PC_{20} in all treatment groups over time, regardless of IUS exposure. However, children in all treatment groups exposed to IUS demonstrated significantly less improvement in airways hyperresponsiveness than children who were not exposed, demonstrating a mean change in PC_{20} that was 26% lower than that of non-exposed children (95% CI 6% – 42%; p=0.01). Similar results were obtained after adjustment for environmental tobacco exposure, height, and lung function (both at baseline and over the course of the trial), suggesting an independent effect of IUS on airway responsiveness (Table 2). Although there were significant differences in household income and maternal education level between those exposed and unexposed to IUS, inclusion of these terms in multivariable models did not change the results; these terms were not included in final models.

As previously reported,[14,17] children randomized to budesonide (an inhaled corticosteroid) demonstrated a substantial improvement in airway hyperresponsiveness over the course of the CAMP clinical trial compared to children randomized to either inhaled nedocromil or placebo. The association between IUS and greater airway hyperresponsiveness following, but not prior to (at baseline), treatment randomization suggested that IUS may alter responsiveness to inhaled corticosteroids – the primary recommended treatment for persistent asthma[18]. To explore this possibility, we assessed the impact of inhaled corticosteroids on airway responsiveness in an analysis stratified by IUS status. Whereas children who had no history of IUS derived a substantial benefit from budesonide treatment on airway responsiveness over time compared to nedocrimil or placebo (25% increase [i.e. improvement] in PC_{20} from baseline, 95% CI 350%, p = .02, Table 3, Figure 1a), children exposed to IUS had a severely blunted response to inhaled budesonide, with no discernible difference in improvement in PC_{20} as compared to nedocromil or placebo (p = .88, Table 3, Figure 1b). This effect persisted after adjustment for height, current lung function and current environmental tobacco smoke exposure. We attempted to test the statistical significance of this differential effect of IUS on treatment response by repeating the original longitudinal analysis with the inclusion of an interaction term for treatment arm by IUS over time. The three-way interaction term of IUS*treatment group*time was significant (p-value test for interaction 0.02), though upon inclusion of second order terms (IUS*treatment, IUS*time, and treatment*time), this interaction term was no longer significant (p=.78), most likely due to the small number of subjects exposed to IUS that were randomized to the budesonide treatment arm (n=39).

Discussion

Inhaled corticosteroids are both commonly prescribed and efficacious for the treatment of asthma in children and adults. They have been shown to reduce airway responsiveness, asthma symptoms, need for breakthrough bronchodilator therapy, and exacerbation rates[14, 19]. However, there is considerable between-subject variability in clinical response to inhaled corticosteroids, including patients who manifest partial to substantial steroid resistance necessitating escalation of treatment dose[20]. Though there is evidence that a proportion of this variability has a genetic basis[21], other factors may be at play.

We here demonstrate for the first time that *in utero* tobacco smoke exposure may be an important determinant of responsiveness to inhaled corticosteroids. In our study, a history of IUS conferred near complete resistance to inhaled corticosteroid treatment, whereas children without such exposure demonstrated marked improvements. We also found a differential effect for paternal history of asthma between IUS exposed and unexposed groups (p=.005). The importance of a paternal history of asthma on airway responsiveness has been reported in a prior manuscript[17]. Our current findings may be indicative of additional gene by environment effects, however we are unable to examine this further in multivariable models because of sample size limitations.

Though the precise mechanisms underlying our findings are not yet known, the observation that airway responsiveness was similar between exposure groups prior to treatment but different thereafter suggests that the initiation of therapy with inhaled corticosteroids can differentiate clinical subgroups of asthmatic children with underlying differences in lung structure that result from IUS. Studies of animal and human lung morphology support the notion that IUS causes structural changes in the lung. Sekhon and colleagues have demonstrated that nicotine crosses the placenta and induces increased connective tissue expression within pulmonary vessels,22 resulting in notable impairment of lung function in newborn rhesus monkeys.23 This group also found decreased alveolar airspace complexity and increased expression of nicotinic cholinergic receptors in airway epithelial cells, smooth muscle cells, and blood vessels in rhesus monkeys exposed to IUS. Nicotinic receptor expression was strongly correlated with increased collagen deposition in cartilaginous airways of these monkeys24. Prenatal nicotine exposure stimulates branching morphogenesis in murine lung explants, potentially contributing to disynaptic lung growth[25]. Postmortem studies in infants provide further evidence of the adverse effects of IUS on airway morphology. In a study of airway morphology in 38 infants who died from SIDS (half of whom were exposed to IUS), IUS was associated with increased inner airway wall thickness[26]. Similar studies have demonstrated an association between IUS and increased alveolar attachments distance27, a finding previously associated with reduced elastic recoil28.

In addition to affecting lung structure, the effects of *in utero* tobacco smoke exposure on airway responsiveness may be due to changes in airway smooth muscle physiology. Singh and colleagues[29] demonstrated airway hyperresponsiveness in mice exposed to IUS that was not due to differences in airway inflammation. Lavage fluid from these mice contained decreased levels of cyclic adenosine monophosphate (cAMP) – a potent airway smooth muscle relaxant - compared to IUS-unexposed mice. IUS-induced reductions in cAMP could also influence response to inhaled corticosteroids in other ways, as cAMP is an inhibitor of T-cell chemotaxis and may inhibit airway remodeling. It is also possible that the impact of cigarette smoke exposure on subsequent glucocorticoid responsiveness is indirectly mediated through increased susceptibility to lower respiratory tract infections in early life, which in turn contribute to airway remodeling, as proposed by Piedimonte and others[30, 31]. Testing of this hypothesis in prospective birth cohorts with accurate assessments of early-life respiratory infections would help clarify this possibility.

The CAMP study was primarily designed to assess the primary effects of inhaled anti-inflammatory medication on lung function in asthmatic children, not to specifically evaluate the effects of *in utero* exposures on treatment response. Thus, it is important to consider whether our findings could be explained by design-related biases. Three major issues of concern are statistical power, exposure misclassification, and residual confounding by both current environmental tobacco smoke exposure and differences in adherence between IUS exposed and unexposed children. Of the 150 children with reported IUS, only 39 were randomized to budesonide. Therefore, we first assessed whether our inability to detect improvement in airway responsiveness among children exposed to IUS was due to low statistical power. This is unlikely because although low power may limit our ability to detect a statistical difference between treatment arms, the observed mean difference in response in the exposed group (as reflected in the fold changes in PC_{20} in Table 3) was a fraction of that observed in the unexposed group. Furthermore, there was a protocol in place for open-label rescue use of inhaled beclomethosone. By the end of the clinical trial, both the nedocromil and placebo groups had significantly more rescue use of beclomethasone than the budesonide groups[14]. This disproportionate use of supplemental ICS by the non-budesonide groups would be expected to reduce the likelihood that we would detect a difference between treatment arms. With regard to exposure misclassification, we recognize that IUS designation was based on self-report. Though several studies support the higher accuracy of self-reported smoking during pregnancy compared to other detection methods (i.e. serum cotinine32, urine cotinine33, 34, and exhaled carbon monoxide35), others suggest that self-report underestimates the true prevalence of smoking during pregnancy[36–38]. It is therefore possible that exposure misclassification was underestimated, particularly given that questionnaires were administered 5–12 years post-partum. If so, we may have underestimated the true effect of IUS on airway responsiveness.

Could our results be due to residual confounding by environmental tobacco smoke exposure rather than primary *in utero* effects? Because the majority of subjects with a history of IUS also report current exposure to cigarette smoke, it is not possible to fully exclude this possibility. However, in our study, models that do not adjust for IUS fail to demonstrate a significant association of current exposure with PC_{20} (p=.89 in multivariable models adjusted for IUS and .38 in multivariable models not adjusted for IUS). While this is somewhat reassuring, we recognize that confirmation of our findings in other populations with sufficient numbers of subjects with *in utero*, but not current, smoke exposure is required. We also note that we were unable to explore a possible dose-response relationship because for most IUS exposed subjects, the exposure was present for all three trimesters. An additional outstanding question is whether children exposed to IUS were also more likely to be non-compliant with daily inhaled corticosteroids. Unfortuntely, we do not have sufficient data available to us to compare adherence between the IUS exposed and unexposed groups. However, we note that we did not see significant differences between those subjects exposed to ETS and those without such exposure with regards to treatment effect on airway hyperresponsiveness. One might expect that adherence would similarly be a confounder among that subgroup as well.

In summary, this study demonstrates for the first time that IUS has the potential to attenuate the beneficial effect of inhaled corticosteroids on airways responsiveness in children with asthma. These results provide further reasons for physicians to emphasize the importance of preventing this exposure through smoking cessation counseling efforts with pregnant women. Further study is needed to define the mechanism of action of this exposure as well as to elucidate the effect of IUS on other measures of airway responsiveness including response to bronchodilators.

Key Messages

- In utero smoke exposure (IUS) has been associated with increased prevalence of asthma and reduced lung function in healthy children. There is little data about the impact of IUS on lung function of children diagnosed with asthma
- IUS is associated with less of an improvement in airway responsiveness over time among children with asthma
- IUS may attenuate the beneficial effect of inhaled corticosteroids among children with asthma

Abbreviations

IUS	*in utero* smoke
SIDS	sudden infant death syndrome
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
$FEF_{25–75}$	forced expiratory flow between the 25%–75% of the FVC maneuver
CAMP	Childhood Asthma Management Program
PC_{20}	provocation concentration of methacholine causing a 20% reduction in FEV_1
cAMP	cyclic adenosine monophosphate

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Members of the CAMP Research Group

Clinical centers

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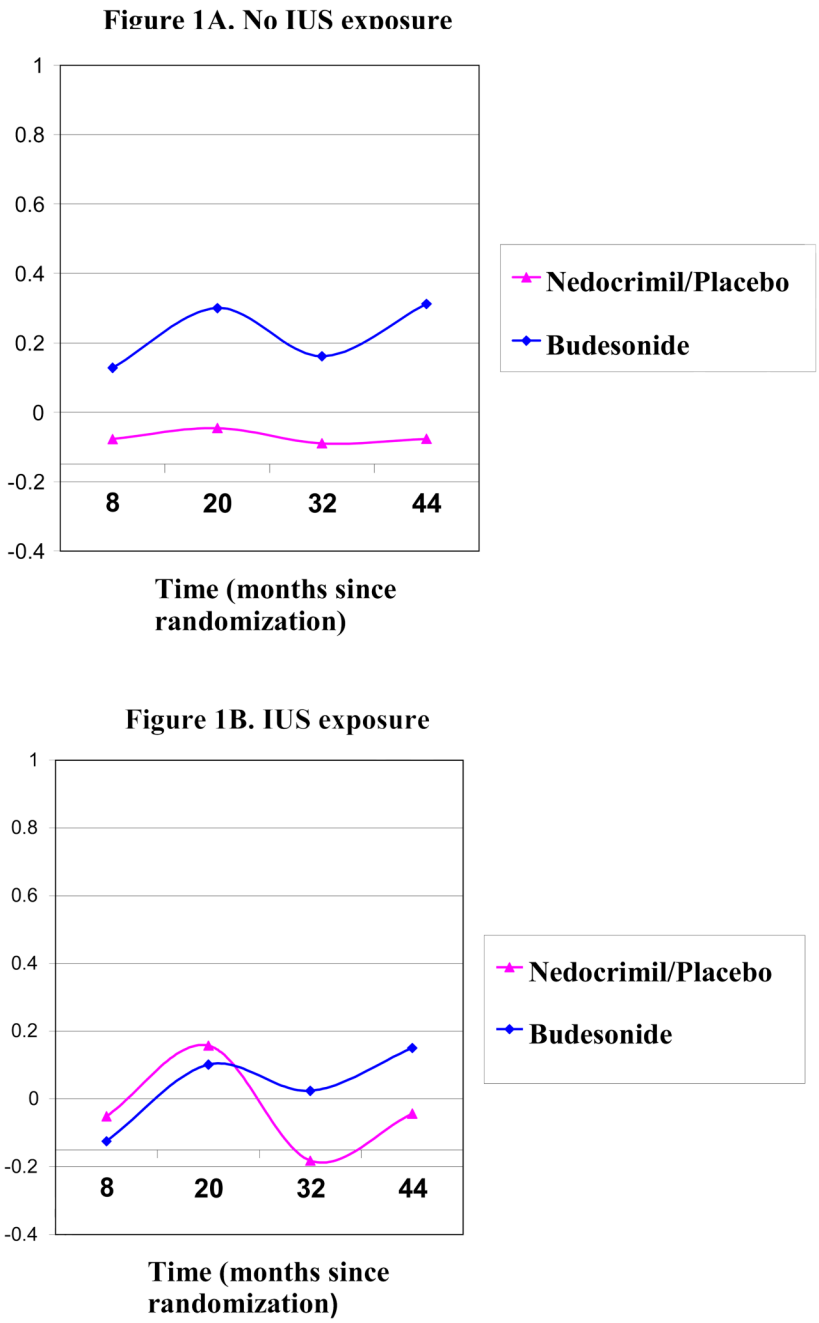

Figure 1.
Effects on longitudinal methacholine PC20 attributable to treatment with either budesonide or nedocrimil/placebo post-randomization.

Table I

Characteristics of the study population[a]

	Not exposed to *in utero* smoke (n=886) N (%)	Exposed to *in utero* smoke (n=150) N (%)	P Value[b]
Sex (female)	356 (40.2)	61 (40.7)	.91
"Current" ETS exposure			
8 months post-randomization	177 (20.6)	101 (69.7)	<.0001
20 months post-randomization	170 (20.1)	106 (73.6)	<.0001
32 months post-randomization	160 (19.1)	95 (68.8)	<.0001
44 months post-randomization	152 (18.2)	93 (69.9)	<.0001
Maternal history of asthma	232 (26.8)	30 (20.8)	.13
Paternal history of asthma	182 (21.6)	26 (20.0)	.67
Assigned to treatment group			.26
Budesonide	271 (30.6)	39/150 (26)	
Nedocrimil/Placebo	615 (69.4)	111/150 (74)	
Clinic Site			.41
Albequerque	103 (11.6)	17 (11.3)	
Baltimore	106 (12.0)	22 (14.7)	
Boston	105 (11.9)	19 (12.7)	
Denver	118 (13.3)	26 (17.3)	
San Diego	111 (12.5)	11 (7.3)	
Seattle	119 (13.4)	21 (14.0)	
St. Louis	119 (13.4)	14 (9.3)	
Toronto	105 (11.9)	20 (13.3)	
Income <$30,000	186 (21.9)	55 (37.9)	<.0001
Maternal Education: ≥ some college	756 (85.4)	95 (63.3)	<.0001
Median (IQR) Values at Baseline			
	No IUS	**IUS**	**P Value[c]**
Age at study entrance (years)	8.9 (3.4)	8.7 (3.4)	.39
FEV_1 (% predicted)	94 (18)	95 (16)	.52
FEV_1/FVC	81 (11)	81 (9)	.14
Serum total IgE (IU)	460 (1057)	368 (921)	.05
PC_{20} (mg/ml)	1.1 (2.3)	1.1(1.8)	.89
Height (cm)	132.8 (20.7)	131.2 (21.3)	.13

ETS=environmental tobacco smoke; FEV_1=forced expiratory volume in 1^{st} second; FVC=forced vital capacity; PC20= provocation concentration of methacholine causing a 20% reduction in FEV_1;

[a] Numbers and percentages may vary because of missing values for some variables.

[b] Chi square p value

[c] Kruskal Wallis p value

Table II

Effects of IUS on post-randomization repeated measures of methacholine PC_{20}[a]

	Fold-change in PC_{20} (95%CI)[b]	**P value**
IUS (yes)	**0.74 (0.58, 0.94)**	.01
Age (per year increase)	0.91 (0.86, 0.95)	.04
Female gender (yes)	0.94 (0.79, 1.10)	.40
Maternal history of asthma (yes)	0.83 (0.69, 0.99)	.04
Paternal history of asthma (yes)	0.80 (0.66, 0.97)	.02
Environmental tobacco smoke exposure (yes)[a]	0.99 (0.87, 1.13)	.89
Treatment with budesonide (yes)	1.26 (1.06, 1.50)	.01
FEV_1 (per Liter increase)[a]	2.90 (2.44, 3.46)	<.001
Height (per cm increase)[a]	0.98 (0.97, 0.99)	<.001
Total serum IgE at baseline (per log10 IU increase)	0.45 (0.40, 0.51)	<.001

[a] Measured at each study visit

[b] Fold-change in methacholine PC_{20} as determined from exponential of β-estimate derived from multivariate linear regression, adjusting for other covariates in table.

[c] Multivariable mixed models assumed an unstructured, autoregressive covariance and were also adjusted for study center.

Table III

The impact of IUS exposure on responsiveness of methacholine PC_{20} to treatment with inhaled budesonide[e].

	IUS =No (n=886)		IUS=Yes (n=150)	
	Fold-change in PC_{20} (95% CI)[c]	**P value**	**Fold-change in PC_{20} (95% CI)[c]**	**P value**
Treatment with budesonide (yes)	1.25 (1.03, 1.50)	.02	1.04 (0.65, 1.68)	.88
FEV_1 (per Liter increase)[a]	2.97 (2.46, 3.59)	<.001	3.16 (1.98, 5.02)	<.001
Height (per cm increase)[a]	0.97 (0.97, 0.98)	<.001	0.96 (0.94, 0.98)	<.001
Maternal history of asthma (yes)	0.82 (0.68, 1.00)	.05	0.82 (0.48, 1.4)	.64
Paternal history of asthma (yes)	0.72 (0.59, 0.89)	.003	1.72 (1.02, 2.92)	.07
Total serum IgE at baseline (per log10 IU increase)	0.43 (.030, 0.61)	<.001	0.44 (0.32, 0.61)	<.001
Clinic of origin		<.001 [b]		.05[b]
Current ETS exposure (yes)	0.96 (0.83, 1.11)	.65	0.96 (0.70, 1.32)	.81

[a] Assessed at each study visit

[b] F test p value

[c] Fold-change in methacholine PC_{20} as determined from exponential of β-estimate derived from multivariate linear regression, adjusting for other covariates in table.

[d] Multivariable mixed models assumed an unstructured, autoregressive covariance.

[e] P value for 3-way interaction IUS*Treatment with Budesonide*Time=.78. Model also includes interaction terms for IUS* Treatment with Budesonide, IUS* Time, Treatment with Budesonide*Time.