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Biologic Mechanisms of Environmental Tobacco Smoke in Children with Poorly Controlled Asthma: Results from a Multicenter Clinical Trial

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Abstract

Background—Environmental tobacco smoke (ETS) negatively affects children with asthma. The prevalence of ETS exposure among children with poor asthma control may be changing. Importantly, the mechanisms by which ETS worsens asthma control are poorly understood.

Objective—We describe how ETS affects gastroesophageal reflux (GER), respiratory infections, and leukotriene production among children with poor asthma control.

Methods—We analyzed data from 306 children between 6 and 17 years of age with poorly controlled asthma enrolled in a 6-month clinical trial. We evaluated prevalence and determinants of ETS exposure by interview, questionnaire, and urinary cotinine and the association of ETS

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exposure on leukotriene production, respiratory infections, GER, lung function, and asthma control. We used multivariable linear, logistic, and Poisson regressions to assess outcomes.

Results—ETS prevalence estimates ranged from 6% to 30%. Children with domestic indoor exposure had worse asthma control (c-Asthma Control Test, 17.8 vs 21.5; $P = .04$), worse FEV₁ % predicted (84.1 vs 90.7; $P = .02$), and a trend for increased mean urinary leukotriene E₄. ETS from any setting was associated with increased symptomatic respiratory infections (adjusted incidence rate ratio: 1.30; $P = .02$). However, children exposed to ETS did not have symptoms or pH probe results, suggestive of heightened GER.

Conclusions—Domestic smoking exposure was associated with both higher rates of symptomatic respiratory infection and poorer asthma control despite generally intensive controller therapy. ETS exposure is common among asthmatic children with poor control and may worsen asthma control by promoting respiratory infections. Further investigation is required to elucidate ETS mechanisms in poor asthma control.

Keywords

Asthma; Children; Environmental tobacco smoke; Spirometry; Leukotriene; Gastroesophageal reflux; respiratory infection

Asthma is a significant public health problem in the United States, and its prevalence is increasing.¹ Of the estimated 8 million US children with asthma, roughly 50% each year have an asthma attack.² Uncontrolled asthma symptoms are a leading cause of missed school days, emergency department visits, and hospitalizations for children. Environmental tobacco smoke (ETS) is a public health burden in the United States,³ leading to impaired lung growth, reduced quality of life, greater incident asthma, and reduced asthma control.³ The mechanisms by which ETS worsens asthma remain unclear and may involve more than one mechanism. Because smoking increases the production of cysteinyl leukotrienes,^{4,5} potent mediators in the pathogenesis of asthma,⁶ ETS similarly may upregulate leukotriene production and exacerbate asthma. In addition, because nicotine appears to affect lower esophageal sphincter tone,^{7,8} ETS may contribute to asthma severity via gastroesophageal reflux (GER)-related mechanisms. Measurement of ETS exposure can be confounded by reporting bias and the technical limitations of current biomarker assays. Cotinine is a direct metabolite of nicotine, and urinary cotinine has been shown to be a specific and reasonably sensitive marker of recent ETS exposure.⁹

Smoking prevalence in the United States has diminished in recent decades, and public health awareness of the risks of smoking and ETS has improved. However, the extent to which asthma symptoms among children with poorly controlled asthma are currently attributable to ETS is incompletely defined. We sought to evaluate the prevalence of ETS among children with poor asthma control. We quantified ETS and the likely attributable risk of ETS on poor asthma control in a diverse cohort of children. Through the simultaneous measurement of urinary cotinine, urinary leukotriene E₄ (uLTE₄), GER measures, including pH probes, and a comprehensive assessment of respiratory and asthma-related outcomes, we sought to better understand the mechanisms by which ETS affects asthma. We tested the hypothesis that

children exposed to ETS would display increased inflammation (measured by uLTE₄ and expired nitric oxide), respiratory infections, and pH probe-diagnosed GER.

Methods

Details of the main study design have been published.¹⁰ The legal guardian for each participant signed a written informed consent. The clinical trial titled Study of Acid-Reflux in Childhood Asthma (SARCA) was approved by the Nemours Florida Institutional Review Board (82404-31) and by all other American Lung Association–Asthma Clinical Research Centers network institutional review boards, and was registered at www.ClinicalTrials.gov (NCT00604851). We included data from >900 study visits that involved 306 participants age 6 to 17 years with poor asthma control^{10,11} despite daily treatment with an inhaled corticosteroid. Participants were randomly assigned into the 24-week multicenter clinical trial to assess the efficacy of daily oral lansoprazole versus placebo in the control of asthma. We collected demographics, baseline asthma characteristics, exhaled breath condensate, exhaled nitric oxide, spirometry, provocation methacholine concentration to cause 20% reduction in FEV₁ (PC₂₀), asthma control measures, and GER measures at baseline and periodically during the 24-week follow-up period.

Details on inclusion criteria

Poor asthma control for the purposes of study inclusion was defined at any one of the following: use of short-acting β -agonist for asthma symptoms ≥ 2 times per week, nocturnal awakening because of asthma more than once per week in the prior month, ≥ 2 emergency department visits, unscheduled physician visits, prednisone courses or hospitalization for asthma in the prior year, or a score of 1.25 or higher on the Asthma Control Questionnaire (ACQ).

ETS assessment

At visit 1, we inquired about active smoking status and ETS exposure in varied settings with the use of a structured caregiver and child interview. At visit 9, we assessed domestic indoor smoking (IS) exposure with the use of a validated Home Smoking Activity Questionnaire at visit 9.¹² More details on the wording of the questionnaires are available (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

At visit 9, all children were asked to submit urine for analysis of cotinine, LTE₄, and creatinine levels (Figure 1). Urinary creatinine was measured by the colorimetric method to normalize uLTE₄ concentrations. Cotinine was measured with gas chromatography-mass spectrometry as described previously⁴ and was expressed in ng/mL. The lower limit of detection for urinary cotinine was 0.5 ng/mL.

At study completion, participants and caregivers were asked to complete the Home Smoking Questionnaire (HSQ). A participant was considered to have positive exposure if the caregiver reported “occasional” or more frequent smoke exposure in the previous 2 weeks or if there were 1 or more days that anyone smoked in the living room in the past 2 weeks. More details on the timing of ETS assessments are available (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Asthma outcomes

Asthma symptoms and quality of life were assessed with patient reporting from the Asthma Control Test (ACT),¹³ Juniper ACQ,¹¹ and both patient and caregiver pediatric asthma quality-of-life questionnaires. Children age 6 to 11 years completed the Childhood ACT (cACT),¹⁴ and children 12 and older completed the ACT questionnaire.^{15,16}

Participants and caregivers were instructed to record their morning peak flows, asthma symptoms, and medications on a daily diary card. An episode of poor asthma control (EPAC) was defined by an increase in rescue medication over baseline, unscheduled contact with an asthma provider, use of systemic corticosteroids for asthma, or a reduction in morning peak expiratory flow rate on 2 consecutive days.

Lung function was assessed by spirometry measurements that were obtained by adhering to procedures defined by the American Thoracic Society/European Respiratory Society.¹⁷ Exhaled nitric oxide and breath condensate pH were collected as airway biomarkers with the use of standardized procedures.¹⁸ We estimated exacerbation risk by counting EPACs during the intervention and divided by the person-time to get episodes per year.¹⁹

Urinary LTE₄ concentrations were determined by liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis (Kronos Science, Phoenix, Ariz) on an API 4000 LC/MS/MS System (Applied Biosystems/MDS SCIEX) in conjunction with an Agilent 1100 Series HPLC system (Agilent, Santa Clara, Calif). The method's accuracy ranges from 100% to 114%. The method's relative error was between 0.4% and 2.2% for low-to-medium concentrations and 1.6% to 1.8% for high concentrations. The intraprecision and interprecision ranges are from 4% to 6% daily and 13% to 19% over a 3-year period. The method has a limit of quantitation of 91 fmole/mL (0.04 ng/mL).

For EPACs, 2 separate scores derived from participant daily diaries (EPAC score 1 and 2) estimated the risk of exacerbation. EPAC1 constituted a decrease of >30% in the morning peak flow rate from personal best (assessed during run-in) for 2 consecutive days, addition of an oral steroid treatment for asthma symptoms, or unscheduled contact with a health care provider for asthma. EPAC2 was similar to EPAC1 but also included an increased use of short-acting bronchodilators from baseline (4 additional puffs of rescue medication or additional nebulizer treatments in 1 day).

The ACQ integrates markers of asthma control, including cough, bronchodilator use, nocturnal symptoms, activity level, and lung function. ACQ ranges from 0 to 6 with a higher score corresponding to worse asthma control. A 0.5-point change or greater in ACQ score equates to a meaningful clinically important difference. The ACT for adolescents¹⁵ (age 12-17 years) and cACT for children¹⁴ (age 6-11 years) have score ranges of 5 to 25 and 0 to 27, respectively. The meaningful clinically important difference is 3 for ACT¹⁶ and undefined for cACT.

Gastroesophageal reflux

GER symptoms were measured on all participants at baseline and periodically during the study with the use of the Pediatric Patient GERD (gastroesophageal reflux disease)

Symptom Assessment questionnaire.²⁰ A subset of participants also completed a 24-hour pH probe at baseline to determine the total number of reflux episodes (defined as a pH < 4), the reflux index (percentage of time that esophageal pH was <4), the longest reflux episode, and the number of reflux episodes that lasted >5 minutes. Pathologic GER by pH probe was defined as an esophageal pH of 4 or lower for at least 6% of the time for 6- to 11-year-olds and at least 4% of the time for 12- to 17-year-olds.²¹

Respiratory infection reporting

At each of 8 scheduled clinic visits during the 24-week trial period, participants were interviewed to document recent respiratory infections symptoms. Research staff asked, “Since the last visit, did you have any of the following? (check any that apply): upper respiratory infection (cold); sore throat; strep throat; bronchitis; pneumonia; ear infection; acute sinusitis (sinus infection); N/A, none since last visit.”

Data analysis

Data were collected and stratified by domestic IS exposure status. We used χ^2 , Wilcoxon, or Kruskal-Wallis tests as appropriate for comparing variables between groups. We determined incidence rate ratios for upper respiratory infections, sinusitis, pneumonia, strep throat, sore throat, bronchitis, and ear infections among ETS-exposed versus nonexposed children. We used the k statistic to determine the correlation between significant ETS exposure by interview at visit 1 and the HSQ at visit 9. We used simple and multiple linear regressions to determine the effect of ETS on continuous asthma measures and simple and multiple Poisson regressions to determine the effect of ETS on incidence rate ratios for respiratory infection. Linear regression models were adjusted for race. All GER-related outcomes were evaluated with and without adjustment for lansoprazole treatment.

No differences were noted, and the data adjusted solely for race are presented. Spirometry results were assessed as percentage of predicted values and accounted for race, sex, and age. The multiple Poisson regression models were adjusted for treatment assignment and race.

SAS 9.2 (SAS Institute, Inc, Cary NC) and STATA 11 (StataCorp, College Station, Tex) statistical packages were used. All tests were 2-tailed at a level of significance of 0.05.

Results

Baseline characteristics by home smoking behavior

Baseline characteristics of the SARCA study sample have been published.¹⁰ The present study population, stratified by IS status, is presented in Table I. None of the participants reported being active smokers, whereas 17 of 265 participants (6%) reported to have IS defined as smoking occurring recently in the home living room. We found no significant association between IS and age, sex, body mass index percentile, or study treatment assignment (Table I). IS was associated with race ($P < .01$) and recent prednisone bursts. When prednisone bursts were adjusted for race, the IS-related difference disappeared ($P = .17$).

Prevalence of ETS exposure and cotinine detection

Just >6% of participants reported recent indoor smoking in the home living room (Table II). Because only 265 of the 306 participants completed the HSQ, we also evaluated ETS-related responses from the baseline interview. Participants who reported some exposure at home or “places other than home” totaled approximately 30%. Weak concordance was observed between the HSQ and baseline interview ($k = 0.21$; 95% CI, 0.06-0.36) and weak concordance between HSQ and cotinine detection (defined as ≥ 0.5 ng/mL; $k = 0.17$; 95% CI, -0.08 to 0.42). Race was associated with ETS exposure both in ($P < .01$) and outside ($P = .02$) the home, according to interview and HSQ. We noted significantly increased odds for blacks to report ETS exposure within or outside the home (odds ratio, 2.8; 95% CI, 1.6-5.0) and a trend to report recent smoking in the main living room of the child's home (odds ratio, 4.2; 95% CI, 0.91-19.3), compared with white participants (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Domestic IS and asthma control

In-home exposure was associated with worse control and more asthma symptoms on all 5 of the validated patient-centered measures of asthma control (Table III). Children with domestic indoor exposure completing the cACT had significantly worse control (17.8 vs 21.5; adjusted $P = .04$), whereas older children with IS completing the standard ACT showed similarly worse symptoms (17.8 vs 20.3; adjusted $P < .01$). Participants with IS also showed significantly worse asthma-related quality of life (5.3 vs 6.0; adjusted $P = .05$).

Children with IS had significantly reduced forced expiratory volume in 1 second (FEV₁) percent predicted (84.1 vs 91.0; $P = .02$). We saw a nonsignificant reduced mean methacholine PC₂₀ among those with IS. No association was observed between IS and either fractional expired nitric oxide or exhaled breath condensate pH. Asthma outcomes were generally worse among the indoor smoke exposed even after adjustment by race (Table III; see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Biologic mechanisms of ETS

Asthmatic children exposed to domestic IS showed a trend for increased respiratory infections (incidence rate ratio, 1.51; $P = .11$) compared with children unexposed (Table IV). However, children reporting frequent ETS exposure at visit 1 had a 30% higher incidence rate than unexposed children (incidence rate ratio, 1.30; adjusted $P = .02$).

We did not find any evidence for ETS-induced asthma worsening via the mechanism of heightened GER either by symptom scoring or pH probe. No difference was observed in prevalence of GER (13% vs 47%; $P = .14$), number of reflux episodes measured by pH probe (55.3 vs 75.7; $P = .60$), or percentage of time with pH <4 (4.2 vs 6.8; $P = .48$), based on IS exposure (Table III). Similar results were seen when defining ETS by baseline questionnaire or by cotinine detection (data not shown).

Participants reporting ETS exposure had consistently higher mean uLTE₄ than participants without exposure, but these differences did not reach statistical significance (Table V).

Discussion

Our study took place from 2007 through 2011 and showed that US children with asthma continue to be exposed to environmental tobacco smoke. Depending on the method of assessment, ETS prevalence ranged from 6% to 30%. Domestic indoor exposure, in particular, contributed to poor asthma control in many children. Children with regular smoking in the primary living area of their home consistently displayed worse asthma control, a difference which met the ACT minimal clinically important difference.¹⁶ Children exposed in home indoor ETS had more respiratory infections and significantly worse asthma-related quality of life. We also found that ETS exposure was disproportionately prevalent among African American children which may constitute a contributing factor to disparities in asthma control. These data strongly suggest that continued antitobacco counseling remains vitally important to the care of children with asthma.

Both public health efforts and regulations that prohibit indoor smoking appear to have been successful at reducing ETS,²² especially among nonsmoking adults.³ However, children are relatively less empowered to avoid ETS than adults, and our results should be alarming to pediatricians and policy makers. We used a well-characterized cohort of children with poorly controlled persistent asthma to evaluate the epidemiology and mechanisms of ETS exposure. As much as 30% of children with difficult-to-control asthma had significant ETS exposure. The primary source of ETS exposure associated with worse asthma control was from domestic indoor exposure. Children with asthma might be expected to have a lower ETS exposure rate than children without respiratory disease because of caregiver efforts to reduce known asthma triggers. Overall, we would conclude that, because asthmatic children are a vulnerable population to the effects of secondhand smoke and because nearly one-third of families report frequent smoke exposure, ETS is likely to still be an epidemiologically important trigger for poor asthma control.

Accurately measuring ETS exposure remains a challenge, in part because of the limitations of current biomarkers. In addition, little is known about what constitutes a threshold level of ETS for children with asthma. We used 3 assessments to evaluate ETS exposure and found poor concordance among the measures. The limited concordance may be related to the fact that many children have ETS exposure that is intermittent, and because a significant study limitation [the fact that the interview (visit 1) and HSQ (visit 9)] were taken at different times during the study. We cannot explain the poor concordance between the HSQ and urinary cotinine, both measured at visit 9. Only 8.1% of the 160 children submitting urine for analysis had detectable cotinine (> 0.5 ng/mL). Although cotinine is the primary metabolite of nicotine, it has a half-life of 16 to 30 hours^{23,24} and likely has limited sensitivity in the setting of intermittent exposure.

Home indoor exposure displayed the strongest association with worse asthma. Perhaps importantly, IS status may also reflect the effects of thirdhand smoke exposure. Thirdhand smoke (known as smoke residue re-emitted from fabrics and surfaces)²⁵ would likely play a smaller role among children exposed to smokers outside and may explain why we did not see a ETS effect on asthma outcomes determined through the baseline interview.

The biologic mechanisms of ETS in asthma remain unclear. It is rational to expect that ETS might worsen asthma through the mediating mechanisms of esophageal reflux,²⁶ heightened viral infection risk, or cysteinyl leukotriene production⁵ or a combination. ETS has been associated in the past with greater upper respiratory infections, including otitis.³ In the present study that involved children with poorly controlled asthma, we found that ETS was associated with increased symptomatic respiratory infections. It is possible that ETS reduces viral clearance and promotes the progression from minor colonization to transepithelial invasion, leading to host immune responses and asthma triggering.

We also tested the hypothesis that ETS would lead to reduced esophageal pH, greater reflux symptoms, and greater asthma severity. However, we found that ETS was in no way associated with any of the GER measures, including several pH probe indices even after adjusting for antireflux treatment. In the parent study by Holbrook et al,¹⁰ we found no association between asthma severity and GER or between GER treatment and asthma control, so it is not unexpected that GER does not play a role in ETS-related asthma.

Finally, we tested whether ETS increases systemic cysteinyl leukotrienes. Mean uLTE₄ levels were consistently elevated among children reporting ETS exposure, but in none of the comparisons was the difference statistically significant. Urinary leukotrienes are elevated among active smokers.⁵ Rabinovitch et al^{27,28} found that uLTE₄ levels among ETS-exposed children was associated with albuterol use and asthma exacerbations. Although our cohort may have been underpowered to show a significant increase in urinary leukotrienes with ETS exposure, our data are consistent with the presence of ETS-induced leukotriene upregulation. We were surprised that the mean uLTE₄ level among children having detectable cotinine was not higher than children with detectable cotinine.

African American children constituted 50% of the entire cohort and were nearly 3 times as likely as white children to report frequent ETS exposure. Nonwhite participants, made up primarily of participants reporting a race of African American, Asian or “other,” were 5 times more likely to live in a home with regular indoor smoking. Although smoking rates are similar between white and African American adults,²⁹ African American adults were more likely to report in-home smoking activity in a recent report that used data from the National Health and Nutrition Examination Survey.²² Our data suggest that it is possible that poorer asthma control described among African American children may stem from greater exposure to environmental tobacco smoke. Future studies assessing race and asthma control should adjust for environmental tobacco smoke exposure.

Our study shows that domestic indoor smoking is associated with poorer asthma control, reduced quality of life, and reduced lung function, even after accounting for race. Vulnerability to viral infections and leukotriene upregulation are the most probable mechanisms in ETS-induced asthma. Smoking cessation counseling is likely to improve asthma control, especially when targeted to high-risk groups. Continued counseling and efforts to reduce secondhand smoke exposure must continue to be a point of emphasis in both anticipatory guidance and asthma action plans for children with asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
cACT	Childhood Asthma Control Test
EPAC	Episode of poor asthma control
ETS	Environmental tobacco smoke
FEV₁	Forced expiratory volume in 1 second
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
HSQ	Home smoking questionnaire
IS	Indoor smoke exposure
LTE₄	Leukotriene E ₄
SARCA	Study of Acid Reflux in Childhood Asthma

What is already known about this topic?

Environmental tobacco smoke (ETS) worsens asthma symptoms and airway responsiveness in children. More data on the precise mechanisms that mediate ETS-related asthma symptoms are needed.

What does this article add to our knowledge?

Despite nicotine's effect on esophageal sphincter tone, gastroesophageal reflux does not appear to mediate ETS-induced asthma. Vulnerability to viral infections and leukotriene upregulation are the most probable mechanisms in ETS-induced asthma.

How does this study impact current management guidelines?

Clinicians are reminded that intermittent ETS exposure remains common among children with poor asthma control. Continued antitobacco counseling to caregivers of children with asthma is important, particularly to avoid enhanced vulnerability to viral respiratory infections.

Figure 1.

Assessing environmental tobacco smoke exposure. The screening interview asked about smoke exposure at home or in workplace (BA25) and other places (BA26). The Home Smoking Questionnaire at visit 9 asked about smoking in child's home living room in the past 2 weeks and asked parent to quantify recent smoke exposure for child.

Table 1
Baseline participant characteristics by domestic indoor smoking exposure

Variables	Home indoor smoking	No home indoor smoking	Total no. of patients	P value
Demographics				
No. (%)	17 (6)	248 (94)	265	
Age, y, mean $\pm$ SD	12.8 $\pm$ 2.7	11.3 $\pm$ 3.0	265	.05
BMI percentile, mean $\pm$ SD	67.0 $\pm$ 33.3	73.4 $\pm$ 27.3	265	.35
Sex, no. (%)				.30 [*]
Male	13 (76)	153 (62)	166	
Female	4 (24)	94 (39)	99	
Ethnicity, n (%)				.48 [*]
Hispanic	1 (6)	39 (16)	40	
Not Hispanic	16 (94)	209 (84)	225	
Race, n (%)				
White	2 (12)	101 (41)	103	.01 [*]
African American	11 (65)	125 (50)	136	
Other	4 (24)	22 (9)	26	
Asthma characteristics				
Allergies make asthma worse, no. (%)	16 (94)	197 (79)	265	.21 [*]
Did you ever or now smoke, no. (%)	0 (0)	2 (1)	265	>.99 [*]
Frequently go places with ETS, no. (%)	5 (29)	41 (17)	265	.19 [*]
β -Agonist use 2/wk last month, no. (%)	15 (88)	191 (77)	265	.38 [*]
Nocturnal awakening 1/wk, no. (%)	7 (41)	107 (44)	265	.87
2 Urgent interventions in 12 mo, no. (%) [†]	11 (65)	158 (64)	265	.93
No. of prednisone bursts, mean $\pm$ SD	1.2 $\pm$ 1.2	1.7 $\pm$ 2.0	265	.04
Treatment, n (%)				
Intervention				
Lansoprazole	6 (35)	128 (52)	134	.19
Placebo	11 (65)	120 (48)	131	
Controller therapy				
ICS-LABA	12 (71)	143 (58)	155	.30
LTRA	12 (71)	140 (56)	152	.25
ICS-LABA + LTRA	9 (53)	90 (36)	99	.17

BMI, Body mass index; ICS, inhaled corticosteroids; LABA, long-acting β -agonists; LTRA, leukotriene receptor antagonist.

Participants were considered to have home indoor smoking by the HSQ if there was a response to at least "occasional" to any of the HSQ questions, or if there were 1 or more days that anyone smoked in the living room in the past 2 weeks.

^{*} Value from Fisher exact test.

[†] Urgent intervention represents emergency department visit, prednisone (or equivalent) burst, unscheduled acute visit or hospitalization.

Table II
Prevalence of ETS exposure

Method of ETS assessment	No.	Frequency, no. (%)
Smoking in home living room (SQ1, SQ4)	265	17 (6)
Exposed at home (BA25)	306	54 (18)
Exposed outside home (BA26)	306	54 (18)
Any frequent exposure (BA25/26)	306	91 (30)
Detectable cotinine (≥ 0.5 ng/mL)	160	13 (8)

SQ1, Did anyone smoke in your living room in the past 2 weeks? ("living room" refers to the main area in the house where your child spends a lot of time with other family members. For example, the family room, den, or TV room); *SQ4*, Please estimate how often and how much tobacco smoke exposure your child has had in the past 2 weeks? (occasional or more); *BA25*, Exposed to second hand smoke at home or in work place?; *BA26*, Do you frequently go places other than home or work where you are exposed to second hand smoke?

Table III
Asthma characteristics by smoking status within child's home living area

	Indoor home smoking	No indoor home smoking	Total no. of patients	P value	P value *
No. (%)	17 (6)	248 (94)	265		
Asthma Questionnaire Scores, mean $\pm$ SD					
Childhood Asthma Control Test [†]	17.8 $\pm$ 6.7	21.5 $\pm$ 3.9	130	.17	.04
Asthma Control Test [†]	17.8 $\pm$ 4.4	20.3 $\pm$ 3.6	133	.05	<.01
ACT/cACT (combined) [†]	17.8 $\pm$ 5.0	20.9 $\pm$ 3.8	263	<.01	<.001
Asthma Symptom Utility Index	0.8 $\pm$ 0.2	0.9 $\pm$ 0.1	259	.03	.02
Asthma Control Questionnaire [‡]	1.4 $\pm$ 0.8	1.0 $\pm$ 0.7	257	.03	.05
Asthma Control Questionnaire [§]	1.3 $\pm$ 0.8	0.9 $\pm$ 0.8	257	.05	.08
Pediatric Asthma Quality of Life Questionnaire [‡]	5.6 $\pm$ 1.3	5.9 $\pm$ 1.0	255	.51	.27
Pediatric Asthma Caregiver Quality of Life Questionnaire [‡]	5.3 $\pm$ 1.5	6.0 $\pm$ 1.0	253	.08	.05
Lung function, mean $\pm$ SD					
Pre-FEV ₁ % predicted	84.1 $\pm$ 10.7	90.7 $\pm$ 15.3	259	.02	__
Pre-FEV ₁ /FVC	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1	259	.35	.28
Post-FEV ₁ % predicted	91.6 $\pm$ 8.0	96.4 $\pm$ 14.8	161	.17	__
Post-FEV ₁ /FVC	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1	161	.52	.67
PC ₂₀ (mg/mL)	0.8 $\pm$ 1.0	2.5 $\pm$ 3.2	115	.37	.52
Biomarkers, mean $\pm$ SD					
Nitric oxide first reading	51.7 $\pm$ 42.9	41.4 $\pm$ 37.7	123	.46	.74
Nitric oxide second reading	53.5 $\pm$ 44.7	40.9 $\pm$ 38.8	119	.38	.63
Nitric oxide third reading	45.0 $\pm$ 40.2	39.3 $\pm$ 39.5	102	.60	.77
Mean for 3 readings	52.6 $\pm$ 43.9	40.8 $\pm$ 38.1	124	.39	.67
EBC pH	6.0 $\pm$ 0.8	6.1 $\pm$ 1.0	197	.43	.87
GER status, mean $\pm$ SD [¶]					
GERD symptom score	1.0 $\pm$ 1.9	1.2 $\pm$ 1.6	262	.14	.80

	Indoor home smoking	No indoor home smoking	Total no. of patients	P value	P value*
GER, n (%)**	1(13)	43(47)	99	.08 ^{††}	.14
No. of reflux episodes	55.3 ± 52.6	75.7 ± 71.8	99	.28	.60
No. of reflux episodes > 5 minutes	1.0 ± 1.4	2.6 ± 3.9	99	.38	.33
Longest reflux episode in minutes	5.6 ± 4.7	19.3 ± 49.4	99	.34	.39
Percentage of time pH < 4.0	4.2 ± 5.1	6.8 ± 8.7	99	.32	.47
Exacerbation risk, mean ± SD					
EPAC1 rate	3.7 ± 6.3	3.1 ± 4.3	255	.94	.63
EPAC2 rate	5.3 ± 6.9	4.5 ± 4.9	255	.87	.49

FVC, Forced vital capacity; EBC, exhaled breath condensate.

HSQ was completed at visit 9 and assessed the presence of smoking in child's home living room. For the purposes of this study, GERD is used only to specify the Pediatric Patient GERD Symptom Assessment questionnaire. P values were determined by Wilcoxon test for continuous variables and by χ^2 test for discrete variables.

* Adjusted by race.

[†]Permission obtained from GlaxoSmithKline.

[‡]Permission obtained from Professor Elizabeth Juniper.

[§]ACQ with FEV₁ component.

^{||}Percentage predicted spirometry results accounted for race using race-adjusted normative values.

[¶]All GER outcomes were evaluated with and without adjustment for lansoprazole treatment. No differences were noted, and the data adjusted solely for race are presented.

** For those undergoing pH probe, pathologic GER was defined as those with esophageal pH of 4 or lower for at least 6% of the time for 6- to 11-year-olds and at least 4% of the time for 12- to 17-year-olds.

^{††}Determined by Fisher test.

Table IV

Incidence of respiratory infections by exposure status

	No. exposed	Crude incidence rate ratio	P value	Model 1 incidence rate ratio	P value	Model 2 incidence rate ratio	P value
In-home exposure (n =265)	17	1.46	.13	1.51	.11	1.51	.11
Baseline interview (n = 306)	91	1.26	.03	1.28	.02	1.30	.02

Incidence rates ratios involve rates expressed events per person-visits. Children unexposed to ETS serve as the referent group. In model 1, the rate ratio was adjusted for treatment assignment (lansoprazole versus placebo). In model 2, the rate ratio was adjusted for treatment assignment and race. Incident respiratory infections were determined during the trial at interim clinic visits and included report of recent upper respiratory infection, ear infection, acute sinusitis, sore throat, strep throat, bronchitis, and pneumonia.

Table V
Urinary LTE4 levels according to exposure using different methods of exposure assessment

ETS assessment method	No secondhand smoke		Yes to secondhand smoke		P value
	No.	uLTE ₄ , mean ± SD	No.	uLTE ₄ , mean ± SD	
Does smoking occur in child's main living room? (IS status) *	183	34.8 ± 22.5	8	49.7 ± 39.2	.32
Child exposed at home or in workplace †	158	33.7 ± 18.0	33	43.3 ± 40.2	.19
Child exposed frequently in other places ‡	160	35.4 ± 23.9	31	35.6 ± 22.0	.96
Combined († and ‡) §	136	33.7 ± 18.5	55	39.6 ± 32.7	.12
Detectable urinary cotinine ¶	180	35.6 ± 24	11	32.1 ± 12.1	.63

* Did anyone smoke in your living room? ("Living room" refers to the main area in the house where your child spends a lot of time with other family members. For example, the family room, den, or TV room.)

† Current smoking exposure: Exposed to secondhand smoke at home or in work place (if applicable)?

‡ Current smoking exposure: Do you frequently go places other than home or work, if applicable, where you are exposed to secondhand smoke?

§ Union of yes respondents from questions 2 and 3.

¶ Cotinine detectable in urine at visit 9 (>.5 ng/mL).