Effects of *In Utero* and Environmental Tobacco Smoke Exposure on Lung Function in Boys and Girls with and without Asthma

YU-FEN LI, FRANK D. GILLILAND, KIROS BERHANE, ROB McCONNELL, W. JAMES GAUDERMAN, EDWARD B. RAPPAPORT, and JOHN M. PETERS

Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California

To investigate whether the effects of *in utero* exposure to maternal smoking and environmental tobacco smoke (ETS) exposure on lung function vary by sex or asthma status, we examined medical history and tobacco smoke exposure data for 5,263 participants in the Children's Health Study. At study enrollment, parents or guardians of each subject completed a questionnaire, and lung function was measured spirometrically with maximum forced expiratory flow–volume maneuvers. To assess the *in utero* effects of maternal smoking and ETS exposure on lung function, we used regression splines that accounted for the nonlinear relationship between pulmonary function, height, and age. *In utero* exposure to maternal smoking was independently associated with deficits in lung function that were larger for children with asthma. Boys and girls with a history of *in utero* exposure to maternal smoking showed deficits in maximum midexpiratory flow (MMEF) and a decrease in the FEV_1/FVC ratio. As compared with children without asthma, boys with asthma had significantly larger deficits from *in utero* exposure in FVC, MMEF, and FEV_1/FVC, and girls with asthma had larger decreases in FEV_1/FVC. The effect of ETS exposure varied by children's gender and asthma status. Deficits in flows associated with current ETS exposure were present in children with and without asthma but were significant only among children without asthma. Past ETS exposure was associated with reduced FEV_1, MMEF, and FEV_1/FVC among boys with asthma. In contrast, past ETS exposure was associated with decreased flow rates in girls without asthma. In summary, both *in utero* exposure to maternal smoking and ETS exposure were associated with persistent deficits in lung function. The effects of *in utero* exposure were greatest among children with asthma.

A growing body of scientific evidence indicates that childhood environmental tobacco smoke (ETS) exposure adversely affects lung function, and especially measured indicators of flow, such as FEV_1 and maximum midexpiratory flow (MMEF) (1–7). Although studies consistently associate ETS exposure with deficits in lung function, interpretation of these findings requires consideration of *in utero* exposure to maternal smoking, which is associated with deficits in lung function at birth that may persist into young adulthood (4, 6, 8–15). However, remarkably few studies of the effect of ETS on lung function have investigated effects of *in utero* exposure to maternal smoking. The findings in studies that have investigated *in utero* effects on lung function are inconsistent, and the independent and joint effects of ETS and *in utero* exposure are uncertain. A clearer understanding of the effects of tobacco smoke exposures during the *in utero* and postnatal periods is needed.

The inconsistency in results for the independent and joint effects of ETS and *in utero* exposure on lung function may arise from variation in the proportion of sensitive children in the study population. Children with asthma are particularly sensitive to effects of ETS exposure during the postnatal period, and are more prone to the acute effects of ETS than are children without asthma (2). Children with asthma who are exposed *in utero* to maternal smoking may have large deficits because the effects of *in utero* exposure on lung function may add to chronic deficits from asthma (16). Although the combination of *in utero* and ETS exposures may be of particular importance for children with asthma, and may explain some of the inconsistencies among studies, the effects of *in utero* exposure on boys and girls with asthma have not been extensively investigated.

The University of Southern California Children's Health Study (CHS), an ongoing study in California, offers an opportunity to further investigate the modifying effects of asthma and sex on deficits in lung function associated with *in utero* exposure to maternal cigarette smoking and childhood ETS exposures. We examined cross-sectional data from the CHS to assess the relationships between lung function, asthma, *in utero* exposure to maternal smoking, and ETS exposures in boys and girls, using regression spline techniques.

METHODS

Study Design

The CHS is a 10-yr longitudinal study of schoolchildrens' respiratory health. Details of the study design, site selection, subject recruitment, and assessment of health effects in the study are reported elsewhere (17, 18). At study entry, in the spring of 1993, a parent or guardian of each participating child provided written informed consent and completed a self-administered questionnaire on demographics, medical and family health history, indoor air exposures, and household characteristics. In the spring of 1993 and in each subsequent year of the ongoing study, each child completed an update questionnaire, and pulmonary function testing (PFT) was conducted. In the fall of 1995, a second group of fourth grade students was recruited and completed the same baseline and follow-up questionnaires and PFT as the group enrolled in 1993. Of the 5,762 children participating in the study, both baseline questionnaire data and lung function measurements were available for 5,263 (91.3%) children (approximately 68% of whom were fourth-graders with an age range of 7 to 13 yr; 16% of whom were seventh-graders with an age range of 11 to 15 yr; and 16% of whom were tenth-graders with an age range of 14 to 19 yr) (Table 1). In the study reported here, we examined cross-sectional data collected at study entry.

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Correspondence and requests for reprints should be addressed to Frank Gilliland, Department of Preventive Medicine, USC Keck School of Medicine, 1540 Alcazar Street, CHP 236, Los Angeles, CA 90033. E-mail: gillilan@hsc.usc.edu

TABLE 1

PARTICIPANT CHARACTERISTICS BY ASTHMA STATUS AND SEX

	Boys		Girls	
	All Subjects n (%)	Asthmatics n (%)	All Subjects n (%)	Asthmatics n (%)
Total	2,586	442 (17.1)	2,677	307 (11.5)
Missing*	0	71	0	75
Grade				
4 (accrued in 1993)	842 (32.6)	148 (33.5)	816 (30.5)	75 (24.4)†
4 (accrued in 1995)	958 (37.0)	164 (37.1)	954 (35.6)	111 (36.2)
7	387 (15.0)	67 (15.2)	473 (17.7)	57 (18.6)
10	399 (15.4)	63 (14.2)	434 (16.2)	64 (20.8)
Race/ethnicity				
Non-Hispanic white	1,468 (57.9)	255 (58.1)†	1,458 (55.6)	179 (58.5)
Hispanic	661 (26.1)	97 (22.1)	726 (27.7)	78 (25.5)
Black	111 (4.4)	29 (6.6)	148 (5.6)	21 (6.9)
Asian	137 (5.4)	26 (5.9)	124 (4.7)	11 (3.6)
Other	158 (6.2)	32 (7.3)	166 (6.3)	17 (5.5)
Parental education				
Some graduate education	299 (12.0)	46 (10.5)†	276 (10.8)	33 (10.9)
College	264 (10.6)	48 (11.0)	276 (10.8)	31 (10.2)
Some college	1,100 (44.3)	222 (50.8)	1,067 (41.8)	135 (44.7)
12 grades	493 (19.9)	81 (18.5)	548 (21.5)	74 (24.5)
< 12 grades	326 (13.1)	40 (9.2)	387 (15.2)	29 (9.6)
Income				
> $100,000	153 (7.0)	24 (6.1)	133 (6.2)	15 (5.8)
$50,000 ~ $99,999	728 (33.4)	154 (39.0)	732 (34.0)	100 (38.9)
$30,000 ~ $49,999	593 (27.2)	109 (27.6)	545 (25.3)	60 (23.4)
$15,000 ~ $29,999	343 (15.7)	56 (14.2)	363 (16.9)	46 (17.9)
$7,500 ~ $14,999	230 (10.5)	29 (7.3)	248 (11.5)	22 (8.6)
< $7,500	134 (6.1)	23 (5.8)	130 (6.0)	14 (5.4)
Medical insurance				
No	351 (14.1)	36 (8.3)‡	443 (17.1)	31 (10.4)‡
Yes	2,147 (85.9)	400 (91.7)	2,145 (82.9)	267 (89.6)
Smoke exposure				
None	1,430 (60.1)	247 (59.5)	1,430 (57.3)	149 (51.0)†
Past ETS only	234 (9.8)	38 (9.2)	300 (12.0)	33 (11.3)
Past and current ETS only	277 (11.6)	49 (11.8)	295 (11.8)	34 (11.6)
In utero only	75 (3.2)	19 (4.6)	72 (2.9)	13 (4.5)
In utero and ETS	363 (15.3)	62 (14.9)	400 (16.0)	63 (21.6)
Personal smoking				
No	2,535 (98.0)	435 (98.4)	2,630 (98.2)	301 (98.1)
Yes	51 (2.0)	7 (1.6)	47 (1.8)	6 (1.9)

Definition of abbreviation: ETS = environmental tobacco smoke.

* Subjects with missing data were excluded from corresponding analyses.

† $p < 0.05$ for comparison of factor between boys or girls with and without asthma:

‡ $p < 0.001$ for comparison of factor between boys or girls with and without asthma.

Sociodemographic, Medical History, and Exposure Data

The CHS questionnaire provided information on sociodemographic factors, history of respiratory illness and its associated risk factors, exposure to ETS, and maternal smoking history. Current and past exposure to household ETS and prenatal exposure to maternal smoking were characterized from information on the current and past smoking status of each participant's mother, father, other adult household members, and regular household visitors. We defined past exposure only to household ETS as exposure to ETS in the past, but without current exposure to smokers in the household. Current ETS exposure was categorized as either the presence of only one or of two or more smokers in the household. To assess the joint effects of ETS and *in utero* smoking on lung function, we defined a new variable with five mutually exclusive categories: no ETS and no *in utero* smoking, past ETS only, past and current ETS only, *in utero* exposure to smoking only, and both *in utero* exposure to smoking and ETS.

Asthma was defined by a parent-reported history of physician-diagnosed asthma. Subject with current asthma included children with a history of physician-diagnosed asthma who had asthma symptoms or who had used medications for asthma in the 12 mo prior to completion of the study questionnaire.

Lung Function

The lung function testing and data management procedures used in the study have been reported previously (17, 18). Briefly, most PFT (92.5%) was completed during the morning hours of the spring months, in order to avoid daily and annual peak pollution periods. FVC, FEV_1, the FEV_1 to FVC ratio (FEV_1/FVC), and MMEF were determined from maximum forced expiratory flow–volume maneuvers that were recorded with rolling-seal spirometers (Spiroflow; P.K. Morgan Ltd., Gillingham, UK). Spirometer calibrations were made just before, during, and just after each testing session, using flow–volume syringes (Jones Medical Instrument Co., Oak Brook, IL), and variables for individual spirometers and technicians were included in the statistical models. Each subject was asked to perform at least three satisfactory maneuvers. No more than seven maneuvers were attempted during any test session. At the time of testing, subject's height and weight were measured according to standard protocols, and subjects were in-

terviewed privately about personal smoking habits, recent history of respiratory illness, and inhaler use, and whether they had performed vigorous exercise within half an hour before the test.

Statistical Analyses

The relationships between lung function and physiologic growth factors such as age and height have been found to be highly nonlinear from childhood through adolescence (19, 20). We used regression splines to capture the nonlinear relationship between pulmonary function, age, and height, and to assess the individual and joint effects of *in utero* exposure to maternal smoking and ETS on pulmonary function levels (11, 19, 20). The regression splines fit piecewise polynomials that are joined smoothly at the cutpoints between each regression, known as knots. This has the advantage of allowing appropriate statistical inference while capturing the nonlinear relationships in the data. Initially, a knot was placed at each integer age. The final models were fitted by using knots at ages 11, 13, 15, and 17 yr, leading to a more parsimonious model with essentially the same results.

All models were fitted separately for males and females, since the two sexes' smoothing shapes for the relationship between lung function and age are different. The sex-specific additive model was given as: $E\{\log(PFT)\} = \mu + S_1(AGE) + S_2(AGE) \times \log(HT) + X\beta$, where PFT is a pulmonary function test such as the FVC or FEV_1 test; μ is the overall mean; $S_1(AGE)$ is the smooth function of age at testing, depicting the age-dependent intercepts of height; $S_2(AGE) \times \log(HT)$ is the smooth function of the age-dependent slope of height on PFT, where HT is the residual of height at visit after smoothing of the height; and X is a vector of covariates including the smoking exposure of interest and a set of adjustment variables including school grade, community, technician, spirometer, race/ethnicity, barometric pressure, and other possible confounders. This model is an example of the varying-coefficient modeling strategy of Hastie and Tibshirani (21). We used natural cubic splines that impose the additional constraint of requiring the function described by each polynomial to be linear beyond the boundary knots. Because our models are additive on the logarithmic scale, we give model results in terms of percent change ($[e^{\beta} - 1] \cdot 100\%$) from the appropriate reference group. Using our model, we calculated mean PFT levels for the unexposed reference group among children with and without asthma (Table 2).

We performed univariate analyses and assessed each possible confounder of the relationship between tobacco smoke exposure and lung function. Subjects with missing data for a given covariate were excluded from the analyses involving that covariate. On the basis of previous analyses, parental education (< 12 grades, 12 grades, some college, college, and some graduate education), household income (< \$7,500, \$7,500 to \$14,999, \$15,000 to \$29,999, \$30,000 to \$49,999, \$50,000 to 99,999, and > \$100,000), body mass index (BMI; kg/m^2, by age- and sex-specific quintiles), low birth weight (< 5 lb., ≥ 5 lb.), early chest illness excluding asthma (any before 2 yr of age versus none), insurance status (yes/no), hay fever (any versus none), house water damage (yes/no), live plants in the house (yes/no), vigorous exercise within half an hour before PFT (yes/no), and respiratory illness at PFT (yes/no) were evaluated as potential confounders. Variables were included in models if the adjusted estimates differed by 10% or more from the unadjusted estimates. We assessed history of asthma as a potential effect modifier of the tobacco smoke effects by using stratified models and by testing the significance of an interaction term in the models. All analyses were done with the S-Plus statistical package (MathSoft Inc., Seattle, WA) (22).

TABLE 2

BASELINE† LUNG FUNCTION LEVEL IN CHILDREN WITH AND WITHOUT ASTHMA*

Lung Function	No Asthma			Asthma		
	n	ml	95% CI	n	ml	95% CI
Boys						
FVC	1,636	2,165	(2,015, 2,327)	347	2,272	(2,083, 2,478)
FEV_1	1,634	1,938	(1,804, 2,082)	347	1,868	(1,675, 2,083)
MMEF	1,623	2,268	(1,952, 2,637)	345	1,940	(1,517, 2,481)
Girls						
FVC	1,810	1,906	(1,782, 2,038)	220	1,944	(1,730, 2,183)
FEV_1	1,805	1,671	(1,562, 1,788)	218	1,696	(1,519, 1,895)
MMEF	1,790	2,060	(1,793, 2,368)	218	1,962	(1,534, 2,510)

Definition of abbreviations: CI = confidence interval; MMEF = median midexpiratory flow.

* Models are adjusted for community, grade, spirometer, pressure, technician, log (height), age, and race.

† Among participants without *in utero* exposure to maternal smoking.

RESULTS

Questionnaires and lung function tests were completed by 5,263 students (approximately 49% boys and 51% girls) in the 12 study communities (Table 1). Boys' ages ranged from 7 to 19 yr (fourth-grade students: mean age: 10.0 yr, age range: 7 to 13 yr; seventh-grade students: mean age: 13.1 yr, age range: 11 to 15 yr; tenth-grade students: mean age: 16.1 yr, age range: 14 to 19 yr); girls' ages ranged from 7 to 18 yr (fourth grade students: mean age: 9.9 yr, age range: 7 to 13 yr; seventh grade students: mean age: 13.0 yr, age range: 11 to 15 yr; tenth grade students: mean age: 16.0 yr, age range: 14 to 18 yr).

Among both boys and girls, the majority of participants were non-Hispanic white 4th grade students, from families with at least one parent who was a high school graduate, and had medical insurance. Participants' families were generally of middle class status on the basis of household incomes. Approximately 60% were never exposed to household ETS. About 3% of children were exposed only during the *in utero* period, and 12% had ETS exposure at the time of the study, but had not had *in utero* exposure. Few children were smokers themselves, reflecting the young ages of most participants. Overall, children with asthma came from families with a higher level of education, and had more insurance. The distribution of ethnicity, educational attainment, and insurance differed significantly between boys in whom asthma was ever diagnosed and those without asthma. There were fewer Hispanic and more black children than non-Hispanic white children with asthma. Girls in whom asthma was ever diagnosed were less likely to be in fourth grade and were more likely to have insurance and tobacco smoke exposure than were girls without asthma.

Past and current ETS exposures were approximately the same in boys with and without asthma and girls with and without asthma. The proportions of boys and girls exposed only to maternal smoking *in utero* were greater for those with asthma than for those without asthma. *In utero* and ETS exposure were lower for boys with than for those without asthma, but were higher for girls with asthma.

Table 2 shows mean baseline lung function in boys and girls with and without asthma who had no *in utero* exposure to maternal smoking. The levels were adjusted for community, grade, barometric pressure, height, age, and race/ethnicity. Estimates and 95% confidence intervals (CIs) are presented for non-Hispanic white children in Grade 4 who were 10 yr of age. Both boys and girls with asthma had higher FVC and lower MMEF values than did children without asthma. Girls with asthma had slightly larger FVC and FEV_1 values than did girls without asthma, but the CIs for the two groups were broad and overlapping. Girls with asthma had a FEV_1/FVC ratio of 0.88 (95% CI: 0.82 to 0.94) compared with 0.89 (95% CI 0.86 to 0.92) for girls without asthma. Among boys with and without asthma the FEV_1/FVC ratios were 0.82 (95% CI: 0.77 to 0.88) and 0.90 (95% CI: 0.86 to 0.93), respectively.

In utero exposure to maternal smoking was associated with deficits in lung function, especially among children with asthma (Table 3). Boys with a history of *in utero* exposure to maternal

TABLE 3

EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING ON LUNG FUNCTION LEVEL IN CHILDREN WITH AND WITHOUT ASTHMA*

Lung Function	All			No Asthma			Asthma		
	n **	% Change	95% CI	n	% Change	95% CI	n	% Change	95% CI
Boys									
FVC¶	444/2,005	0.3	(−0.8, 1.5)	351/1,636	1.4†	(0.1, 2.7)	82/347	−4.3‡	(−7.2, −1.3)
FEV_1¶	442/2,003	−1.6†	(−2.8, −0.3)	350/1,634	−0.2	(−1.5, 1.1)	82/347	−7.1§	(−10.7, −3.3)
FEV_1/FVC	442/2,003	−2.0§	(−2.7, −1.2)	350/1,634	−1.6§	(−2.4, −0.9)	82/347	−2.9†	(−5.2, −0.6)
MMEF¶	438/1,990	−5.9§	(−8.4, −3.4)	347/1,623	−4.2‡	(−6.7, −1.6)	82/345	−11.3‡	(−18.7, −3.2)
Girls									
FVC	480/2,061	1.5†	(0.3, 2.7)	397/1,810	1.0	(−0.3, 2.3)	78/220	3.3†	(0.2, 6.5)
FEV_1	479/2,054	−0.3	(−1.5, 0.9)	396/1,805	−0.3	(−1.6, 1.0)	78/218	−0.5	(−3.6, 2.8)
FEV_1/FVC¶	479/2,054	−1.7§	(−2.3, −1.0)	396/1,805	−1.2§	(−1.9, −0.5)	78/218	−3.6§	(−5.7, −1.6)
MMEF	473/2,039	−3.9‡	(−6.3, −1.5)	392/1,790	−3.0†	(−5.6, −0.3)	76/218	−8.7†	(−15.2, −1.7)

Definition of abbreviations: CI = confidence interval; FEV_1/FVC = ratio of FEV_1 to FVC; MMEF = median midexpiratory flow.

* Models are adjusted for community, grade, spirometer, pressure, technician, log (height), age, and race.

† $p < 0.05$, percent change from boys and girls without *in utero* exposure.

‡ $p < 0.01$, percent change from boys and girls without *in utero* exposure.

§ $p < 0.001$, percent change from boys and girls without *in utero* exposure.

¶ Significant difference in effect of *in utero* exposure by asthma status ($p < 0.05$).

** Exposed/unexposed.

smoking showed deficits in FEV_1 and MMEF, as well as decreases in the FEV_1/FVC ratio, as compared with those without *in utero* exposure. Girls with a history of *in utero* exposure showed deficits in MMEF as well as decreases in the FEV_1/FVC ratio as compared with those without *in utero* exposure. As compared with children without asthma, boys with asthma had significantly larger deficits from *in utero* exposure in FVC (1.4% versus −4.3%), FEV_1 (−0.2% versus −7.1%), and MMEF (−4.2% versus −11.3%). Girls with asthma had larger decreases in FEV_1/FVC (−1.2% versus −3.6%) and MMEF (−3.0% versus −8.7%), and had a larger increase in FVC (1.0% versus 3.3%) than did those without asthma. The decreases in FEV_1/FVC resulted from an increase in estimated FVC and a decrease in estimated FEV_1. The effects of *in utero* exposure on lung function did not vary by age (data not shown). Parental education, household income, insurance status, current or past ETS exposure, or personal smoking did not confound the relationship between *in utero* exposure and lung function.

Exposure to ETS was associated with deficits in lung flows and increases in lung volumes; however, the effects of past and current ETS exposure varied by children's asthma status (Table 4). Both boys and girls with past exposure or current exposure showed significantly decreased flow rates, as well as increases in FVC that reached statistical significance in girls. The effects of current exposure on lung flow rates were apparent for both boys and girls with and without asthma, but the deficits in flow rates were significant only for children without asthma. Exclusively past exposure was associated with different effects in boys and girls. Past ETS exposure was associated with reduced FEV_1 (−4.9%), MMEF (−9.2%), and FEV_1/FVC (−2.8%) among boys with asthma. No effect of past exposure was found among boys without asthma. In contrast, past ETS exposure was associated with reduced lung function in girls without asthma, but not in girls with asthma, for whom estimates were imprecise owing to the small size of this group. The effects followed the same pattern among children with current asthma, but were not as significant because of the smaller number of children with current asthma (data not shown). The effects of two or more current smokers in the household were generally larger than the effects associated with one current smoker, except for FEV_1 in both boys and girls. Parental education, household income, or insurance status did not confound the relationship between the number of smokers in the household and lung function.

On the basis of analyses done with mutually exclusive exposure categories, *in utero* exposure to maternal smoking was independently associated with deficits that were particularly apparent in boys and girls with asthma (Table 5). Although a limited number of participants had *in utero* exposure only, we found that children with a history of *in utero* exposure only or of both *in utero* exposure and postnatal ETS exposure had deficits of about 5% in MMEF, as well as decreases in the FEV_1/FVC ratio. The effect of *in utero* exposure alone was greatest for children with asthma. Boys with asthma who were exposed *in utero* had a 14% deficit in MMEF and a 5% decrease in the FEV_1/FVC ratio as compared with boys with asthma who were not exposed. Girls with asthma had a 17% deficit in MMEF and a 7% decrease in the FEV_1/FVC ratio as compared with girls who were not exposed. *In utero* exposure was also associated with a small but significant increase in FVC in girls, largely due to its effect among girls with asthma. In contrast, boys with asthma had a significant deficit in FVC associated with *in utero* exposure.

The effect of exclusive exposure to ETS was limited to girls with asthma, who had deficits of 4% for MMEF associated with past ETS exposure. Combined exposure to maternal smoking *in utero* and ETS was associated with deficits that varied by children's asthma status. Among children without asthma, the percent decreases in measures of lung function were larger for combined exposure than for *in utero* exposure alone. Restriction of the combined-exposure category to current ETS and *in utero* exposure resulted in larger deficits in flows than for the category that included both past and current ETS exposure and *in utero* exposure (data not shown). Among children with asthma, combined exposure was associated with smaller deficits than was *in utero* exposure alone, especially among girls; however, the CIs were wide and the effects of combined exposure as compared with those of *in utero* exposure alone are uncertain on the basis of these data. Parental education, household income, insurance status, or personal

TABLE 4

EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON LUNG FUNCTION LEVEL IN CHILDREN WITH AND WITHOUT ASTHMA*

Lung Function	Smoke Exposure	All			No Asthma			Asthma		
		n	% Change	95% CI	n	% Change	95% CI	n	% Change	95% CI
Boys										
FVC	None	1,450	ref		1,187	ref		251	ref	
	Past ETS only	432	−0.6	(−1.8, 0.6)	348	−0.3	(−1.6, 1.0)	76	−2.2	(−5.4, 1.1)
	One current smoker	352	−1.1	(−2.4, 0.2)	286	−0.6	(−2.0, 0.9)	59	−3.3	(−6.9, 0.4)
	Two or more current smokers	155	1.7	(−0.2, 3.7)	123	1.6	(−0.6, 3.8)	29	0.8	(−4.2, 6.0)
FEV_1	None	1,449	ref		1,186	ref		251	ref	
	Past ETS only¶	430	−1.3†	(−2.6, −0.1)	346	−0.5	(−1.8, 0.9)	76	−4.9†	(−8.9, −0.7)
	One current smoker	351	−1.5†	(−2.9, −0.1)	286	−1.1	(−2.5, 0.3)	59	−3.9	(−8.4, 0.9)
	Two or more current smokers	155	−0.3	(−2.4, 1.8)	123	0.1	(−2.0, 2.2)	29	−2.9	(−9.0, 3.7)
FEV_1/FVC	None	1,449	ref		1,186	ref		251	ref	
	Past ETS only¶	430	−0.8	(−1.5, 0.1)	346	−0.2	(−1.0, 0.6)	76	−2.8†	(−5.2, −0.3)
	One current smoker	351	−0.4	(−1.3, 0.4)	286	−0.6	(−1.4, 0.3)	59	−0.6	(−3.3, 2.3)
	Two or more current smokers	155	−2.0‡	(−3.2, −0.8)	123	−1.5†	(−2.8, −0.3)	29	−3.6	(−7.2, 0.1)
MMEF	None	1,440	ref		1,177	ref		251	ref	
	Past ETS only	425	−2.2	(−4.9, 0.6)	343	−0.5	(−3.2, 2.3)	75	−9.2†	(−17.2, −0.4)
	One current smoker	350	−2.7	(−5.6, 0.3)	285	−2.7	(−5.6, 0.3)	59	−4.0	(−13.4, 6.5)
	Two or more current smokers	153	−5.0†	(−9.1, −0.7)	122	−4.5†	(−8.6, −0.2)	28	−5.2	(−17.7, 9.5)
Girls										
FVC	None	1,443	ref		1,273	ref		151	ref	
	Past ETS only	512	0.8	(−0.4, 2.0)	437	0.5	(−0.8, 1.8)	70	2.5	(−0.8, 6.0)
	One current smoker	355	0.9	(−0.4, 2.3)	304	0.6	(−0.9, 2.1)	44	1.9	(−2.2, 6.1)
	Two or more current smokers	179	2.4†	(0.5, 4.3)	147	1.4	(−0.7, 3.5)	30	5.9†	(1.2, 10.9)
FEV_1	None	1,439	ref		1,271	ref		149	ref	
	Past ETS only	512	−0.1	(−1.3, 1.1)	437	−0.4	(−1.7, 0.9)	70	2.1	(−1.5, 5.7)
	One current smoker	351	0.4	(−1.0, 1.8)	300	0.2	(−1.3, 1.7)	44	1.1	(−3.2, 5.6)
	Two or more current smokers	179	0.2	(−1.6, 2.1)	147	−0.5	(−2.5, 1.6)	30	2.7	(−2.3, 7.8)
FEV_1/FVC	None	1,439	ref		1,271	ref		149	ref	
	Past ETS only	512	−0.8§	(−1.4, −0.1)	437	−0.9§	(−1.6, −0.2)	70	−0.2	(−2.5, 2.3)
	One current smoker	351	−0.8	(−1.6, 0.1)	300	−0.7	(−1.6, 0.1)	44	−0.8	(−3.7, 2.2)
	Two or more current smokers	179	−2.0§	(−3.0, −1.0)	147	−1.8‡	(−2.9, −0.7)	30	−2.7	(−6.0, 0.6)
MMEF	None	1,431	ref		1,263	ref		149	ref	
	Past ETS only	505	−2.6†	(−5.0, −0.2)	431	−3.2†	(−5.7, −0.6)	69	1.4	(−6.5, 10.0)
	One current smoker	346	−0.9	(−3.7, 2.1)	296	−2.2	(−5.2, 0.9)	43	7.0	(−3.3, 18.4)
	Two or more current smokers	178	−5.3‡	(−9.0, −1.5)	146	−5.9‡	(−9.8, −1.7)	30	−4.2	(−14.4, 7.2)

Definition of abbreviations: CI = confidence interval; ETS = environmental tobacco smoke; FEV_1/FVC = ratio of FEV_1 to FVC; MMEF = median midexpiratory flow.

* Models are adjusted for community, grade, spirometer, pressure, technician, log (height), age, and race.

† $p < 0.05$, percent change from boys and girls without *in utero* exposure.

‡ $p < 0.01$, percent change from boys and girls without *in utero* exposure.

§ $p < 0.001$, percent change from boys and girls without *in utero* exposure.

¶ $p < 0.05$ for comparison between children with and without asthma.

smoking did not confound the relationship between combined effects of ETS and *in utero* exposure with lung function.

DISCUSSION

A growing body of evidence supports the concept that *in utero* exposure to maternal smoking can produce persistent deficits in childhood lung function, and that the deficits may be greater in children predisposed to asthma (4–6, 9, 11, 13, 15, 23, 24). Recent studies of lung function in newborns and infants of mothers who smoked during pregnancy show that *in utero* exposure to maternal smoking is associated with reduced lung function in the perinatal period (6, 9, 12, 13, 24). Studies among newborns in East Boston, Massachusetts, and Perth, Australia, which excluded effects of ETS by measuring lung function near birth, reported an independent effect of *in utero* exposure on respiratory mechanics (9, 12).

The perinatal deficits from *in utero* exposure to maternal smoking may be larger in children who subsequently develop asthma. Stick and colleagues reported that newborns with a family history of asthma had greater deficits in lung function from *in utero* exposure than did newborns without a family history of asthma (12). Our findings suggest that the perinatal deficits in lung function are persistent and large during adolescence. The large deficits may be important, because maternal smoking is also associated with a higher incidence of asthma, more severe disease, an earlier onset of disease, and an increased likelihood of using asthma medications (25). Other reports of the relationship between *in utero* exposure and lung function in children have not examined the variation in the association among boys and girls with and without asthma (4, 8, 15).

The deficits observed at birth appear to persist into childhood and adolescence, especially in measures associated with airway flow rates (4, 5, 26). The relative contribution to persistent deficits in lung function of *in utero* exposure to maternal smoking and postnatal ETS exposure is less clear (4, 5). In analyses of white children from 24 cities, Cunningham and associates reported that the effect of maternal smoking during pregnancy on measures of airway flows was greater than that for current smoking, and was not reduced by adjustment for current smoking (4). The effects of current smoking were small and were not significant after adjustment for smoking

TABLE 5

EFFECTS OF *IN UTERO* AND ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON LUNG FUNCTION LEVEL IN CHILDREN WITH AND WITHOUT ASTHMA

Lung Function	Smoke Exposure	All			No Asthma			Asthma		
		n	% Change	95% CI	n	% Change	95% CI	n	% Change	95% CI
Boys										
FVC	None	1,415	ref		1,158	ref		245	ref	
	Past ETS only	233	−1.4	(−2.9, 0.2)	192	−1.3	(−2.9, 0.4)	38	−2.1	(−6.3, 2.3)
	Current ETS	274	−0.9	(−2.4, 0.6)	222	−1.4	(−2.9, 0.3)	49	1.3	(−2.7, 5.4)
	In utero only	74	−0.7	(−3.3, 1.9)	53	−0.5	(−3.4, 2.6)	19	−1.9	(−7.6, 4.1)
	In utero + ETS**	359	0.3	(−1.0, 1.7)	290	1.5†	(0.0, 2.9)	61	−4.6†	(−7.9, −1.1)
FEV_1	None	1,414	ref		1,157	ref		245	ref	
	Past ETS only	232	−1.1	(−2.7, 0.6)	191	−0.7	(−2.3, 1.0)	38	−2.7	(−8.1, 3.0)
	Current ETS	274	−1.0	(−2.5, 0.6)	222	−1.1	(−2.6, 0.5)	49	−0.4	(−5.5, 4.9)
	In utero only	74	−2.3	(−5.0, 0.4)	53	−0.4	(−3.3, 2.7)	19	−6.8	(−13.8, 0.7)
	In utero + ETS**	357	−1.6†	(−3.0, −0.2)	289	−0.3	(−1.7, 1.1)	61	−7.2‡	(−11.4, −2.8)
FEV_1/FVC	None	1,414	ref		1,157	ref		245	ref	
	Past ETS only	232	0.3	(−0.7, 1.3)	191	0.5	(−0.5, 1.5)	38	−0.6	(−3.8, 2.8)
	Current ETS	274	−0.1	(−1.0, 0.9)	222	0.3	(−0.7, 1.2)	49	−1.7	(−4.6, 1.4)
	In utero only¶	74	−1.6	(−3.3, 0.1)	53	0.1	(−1.7, 1.9)	19	−5.0†	(−9.2, −0.6)
	In utero + ETS	357	−2.0‡	(−2.8, −1.2)	289	−1.8§	(−2.7, −1.0)	61	−2.8†	(−5.4, −0.1)
MMEF	None	1,405	ref		1,148	ref		245	ref	
	Past ETS only	230	0.6	(−3.0, 4.3)	190	1.3	(−2.2, 4.9)	37	−2.8	(−14.2, 10.0)
	Current ETS	272	−1.1	(−4.4, 2.4)	221	−0.6	(−3.9, 2.8)	48	−2.9	(−13.3, 8.6)
	In utero only	72	−4.9	(−10.5, 1.1)	52	−0.3	(−6.4, 6.3)	19	−14.0	(−27.3, 1.7)
	In utero + ETS	355	−6.1§	(−8.9, −3.2)	287	−4.8§	(−7.6, −1.9)	61	−11.0†	(−19.5, −1.6)
Girls										
FVC	None	1,412	ref		1,247	ref		148	ref	
	Past ETS only	296	0.5	(−1.0, 2.0)	259	0.5	(−1.1, 2.1)	33	1.0	(−3.5, 5.6)
	Current ETS	291	0.6	(−0.9, 2.1)	248	0.2	(−1.4, 1.8)	34	2.4	(−2.1, 7.0)
	In utero only	72	2.3	(−0.5, 5.2)	58	0.9	(−2.1, 4.1)	13	8.5†	(1.3, 16.1)
	In utero + ETS	398	1.4†	(0.1, 2.8)	332	1.0	(−0.5, 2.5)	63	3.0	(−0.6, 6.7)
FEV_1	None	1,408	ref		1,245	ref		146	ref	
	Past ETS only	296	0.0	(−1.5, 1.5)	259	−0.4	(−2.0, 1.2)	33	2.7	(−2.1, 7.8)
	Current ETS	288	0.4	(−1.1, 1.9)	245	−0.2	(−1.8, 1.5)	31	3.3	(−1.5, 8.3)
	In utero only	72	−0.1	(−2.9, 2.7)	58	−0.3	(−3.4, 2.9)	13	1.3	(−5.7, 8.9)
	In utero + ETS	397	−0.3	(−1.7, 1.0)	331	−0.5	(−1.9, 1.0)	63	0.2	(−3.4, 4.0)
FEV_1/FVC	None	1,408	ref		1,245	ref		146	ref	
	Past ETS only	296	−0.4	(−1.2, 0.5)	259	−0.8	(−1.7, 0.1)	33	2.4	(−0.8, 5.7)
	Current ETS	288	−0.4	(−1.3, 0.5)	245	−0.7	(−1.6, 0.2)	31	0.9	(−2.2, 4.1)
	In utero only¶	72	−2.3‡	(−3.8, −0.7)	58	−1.1	(−2.8, 0.6)	13	−6.8‡	(−11.2, −2.3)
	In utero + ETS	397	−1.7§	(−2.4, −0.9)	331	−1.4§	(−2.2, −0.6)	63	−2.6†	(−4.9, −0.1)
MMEF	None	1,400	ref		1,237	ref		146	ref	
	Past ETS only¶	292	−2.1	(−5.1, 1.0)	255	−3.6†	(−6.7, −0.3)	33	10.3	(−0.9, 22.7)
	Current ETS¶	285	−0.5	(−3.7, 2.7)	242	−2.4	(−5.7, 1.0)	34	10.2	(−0.9, 22.5)
	In utero only	71	−6.2†	(−11.6, −0.5)	57	−3.2	(−9.3, 3.3)	13	−17.1†	(−29.5, −2.6)
	In utero + ETS	392	−4.1‡	(−6.8, −1.4)	328	−4.1‡	(−7.0, −1.3)	61	−3.5	(−11.3, 5.0)

Definition of abbreviations: CI = confidence interval; ETS = environmental tobacco smoke; FEV_1/FVC = ratio of FEV_1 to FVC; MMEF = median midexpiratory flow.

* Models are adjusted for community, grade, spirometer, pressure, technician, log (height), age, and race.

† $p < 0.05$, percent change from boys and girls without *in utero* exposure.

‡ $p < 0.01$, percent change from boys and girls without *in utero* exposure.

§ $p < 0.001$, percent change from boys and girls without *in utero* exposure.

¶ $p < 0.05$, for comparison between children with and without asthma.

** $p < 0.01$ for comparison between children with and without asthma.

during pregnancy. A second study of inner-city children by the same group of investigators also suggested an independent effect of *in utero* exposure to maternal smoking (5). In contrast, studies conducted in the Netherlands and New Zealand reported either no effect of *in utero* exposure to maternal smoking or that the effects of ETS were independent of *in utero* exposure (27, 28). Our findings support the hypothesis that *in utero* exposure to maternal smoking is independently associated with persistent deficits in lung function, and indicate that children with asthma may be a sensitive group. Longitudinal studies done to determine whether the deficits associated with *in utero* exposure increase with time or asthma activity are warranted.

Although current ETS exposure is known to trigger and aggravate asthma attacks and to produce acute reductions in lung function, it is less certain that ETS exposure is independently associated with chronic deficits in lung function (29, 30). After accounting for the effect of *in utero* exposure, we observed an effect of past ETS exposure alone that was significant in girls without asthma. However, the lack of an association between ETS exposure and deficits in lung function among children with asthma may also be due to changes in ETS exposure subsequent to the development of asthma. Although we did not include smoking that occurred outside the house in our ETS exposure estimates, changes in the behavior of household smokers or in the affected child may have reduced ETS exposure and led to smaller estimates of effect.

The biologic mechanisms that account for the deficits associated with *in utero* exposure to maternal smoking among children with asthma have not been clarified. Because the airways

are fully developed at birth, it may be that the small-airway deficits from *in utero* exposure reflect damage during critical periods of development that permanently alters the structure or function of the lung, such as its elastic recoil properties or immune function (15). Studies of rodents exposed to tobacco smoke during the *in utero* period show that newborns have increased bronchial reactivity (31). Increased bronchial reactivity may lead to both increased risk of asthma and deficits in small-airway flows. Because asthma is associated with deficits in flows, the effect of *in utero* exposure to maternal smoking may also be partly mediated by an increased occurrence of asthma. The effect may also be mediated by the increased occurrence of perinatal respiratory problems or early infections associated with *in utero* exposure (32).

Our study had some limitations. Asthma status was assigned on the basis of parental reports of a physician diagnosis of asthma. Parental reports have been shown to reflect physician diagnoses; however, the diagnosis of asthma by a physician depends on access to and utilization of medical care, and also on physician diagnostic practices (33, 34). Exposure to tobacco smoke was assessed retrospectively, using questionnaire responses, and was not validated by objective measurements. However, exposure estimates based on questionnaire responses have been validated (3, 35–38). We were unable to investigate any dose–response relationships for *in utero* exposure because we lacked information on the intensity or duration of exposure. We also lacked information on a number of potential confounders, such as maternal nutritional status and intake of alcohol or other potentially toxic substances during pregnancy. The pattern of ETS effects may have arisen from a differential measurement error for ETS as compared with *in utero* exposure. The measurement error for ETS is likely to be greater than that for *in utero* exposure, and may produce a larger bias toward the null for estimates of the effect of ETS.

Our findings have clinical and public health significance. The long-term effects of *in utero* exposure to maternal smoking on the growing lungs of children are of particular concern. If these deficits persist into adulthood, they may indicate increased risk for debilitating asthma and chronic obstructive pulmonary disease (32, 39–42). Reducing the long-term effects of tobacco smoke on children with asthma may require the reduction of smoking among women during their childbearing years.

In conclusion, we found that school-aged children with asthma show large deficits in lung function, especially airway flows, that are associated with *in utero* exposure to maternal smoking and that appear to be independent of ETS exposure. Because asthma itself is associated with chronic deficits in lung function, the additional deficits associated with *in utero* exposure to maternal smoking among children with asthma may indicate a group at high risk for adult chronic respiratory diseases. Further research is needed to clarify the roles of *in utero* exposure to maternal smoking and of asthma on lung growth and development.

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