Effects of Early Onset Asthma and *In Utero* Exposure to Maternal Smoking on Childhood Lung Function

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Both *in utero* exposures to maternal smoking and asthma are associated with chronic deficits in lung function. We hypothesized that *in utero* exposure affects lung function in children without asthma and synergistically affects children with early onset asthma. To investigate effects of *in utero* exposure and age at asthma diagnosis on lung function, we examined longitudinal medical history, tobacco smoke exposure, and lung function data from 5,933 participants in the Children's Health Study. We found that children exposed *in utero*, but without asthma, showed decreased FEV_1/FVC, $FEF_{25–75}$, and $FEF_{25–75}$/FVC ratio. Among children without *in utero* exposure, early asthma diagnosis was associated with larger decreases in FEV_1, $FEF_{25–75}$, and FEV_1/FVC ratio compared with later diagnosed asthma. Children with *in utero* exposure alone and early onset asthma showed deficits in FEV_1 (−13.6%; 95% confidence interval [CI], −18.9 to −8.2) and $FEF_{25–75}$ (−29.7%; 95% CI, −37.8 to −20.5) among boys; and $FEF_{25–75}$ (−26.6%; 95% CI, −36.4 to −15.1) and FEV_1/FVC (−9.3%; 95% CI, −12.9 to −5.4) among girls. The absolute differences in $FEF_{25–75}$ associated with *in utero* exposure increased with age in children with early onset asthma. We found little evidence for effects from environmental tobacco smoke exposure alone. In summary, deficits in lung function were largest among children with *in utero* exposure and early onset asthma.

Keywords: asthma; children; ETS; maternal smoking

Low adult lung function has been associated with elevated morbidity and mortality (1). The evidence that variation of lung function in the general population influences mortality suggests that the achievement of maximum attainable lung function may be an important determinant of population health. Achievement of maximum attainable lung function at maturity requires normal lung growth and development during childhood (2–4). A better understanding of the determinants of lung growth and development may provide useful insights for lung health promotion and disease prevention efforts.

A number of determinants of childhood lung function growth have been identified (5–9). Both *in utero* exposures to maternal smoking and asthma, especially early onset asthma, have been linked to chronic reductions in lung function during childhood and adolescence (6, 10). Because asthma and lung function are complex, interrelated traits that are both associated with *in utero* exposure, the interrelationships between *in utero* exposure, asthma occurrence, and lung function are yet to be established. On the basis of the existing evidence, we hypothesized that (*1*) *in utero* exposure is directly associated with lung function in children without asthma; (*2*) asthma is independently associated with lung function in children without *in utero* exposure; and (*3*) *in utero* exposure synergistically affects lung function in children with asthma, especially among children with early onset asthma. The Children's Health Study, a cohort study of schoolchildren's respiratory health, offered an opportunity to assess the effects of *in utero* exposure to maternal smoking and age at asthma diagnosis. To investigate the independent and joint effects of *in utero* exposure to maternal smoking and age at asthma diagnosis on lung function, we examined longitudinal medical history, tobacco smoke exposure, and lung function data collected over the first 8 years of the study from a cohort of 5,933 participants in the Children's Health Study. Some of the results of these studies have been previously reported in the form of an abstract (11).

METHODS

Children were recruited from public school classrooms in 12 southern California communities that were selected on the basis of historical measurements of air quality, demographic similarities, and a cooperative school district. The design, site selection, subject recruitment, and assessment of health effects have been previously reported (12, 13). Briefly, at study entry in 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 was conducted at schools. In 1996, a second group of 4th grade students was recruited and completed the same baseline and follow-up questionnaires and pulmonary function testing as the group enrolled in 1993. In this report, we examine longitudinal data collected during the first 8 years of the study.

Sociodemographic, Medical History, and Exposure Data

The Children's Health Study questionnaire provided information on sociodemographic factors, history of respiratory illness and its associated risk factors, exposure to environmental tobacco smoke (ETS), and maternal smoking history. Current and past exposure to household ETS and exposure to prenatal maternal smoking were characterized by questionnaire responses about the current and past smoking status of each participant's mother, father, other adult household members, and regular household visitors. Any ETS exposure was defined as having one or two or more smokers in the household. *In utero* exposure to maternal smoking was dichotomized as any exposure and no exposure. To assess the joint effects of lifetime ETS exposure and *in utero* exposure to maternal smoking on lung function, we defined four mutually exclusive categories: no ETS exposure and no *in utero* exposure to maternal smoking, ETS exposure alone, *in utero* exposure to maternal smoking alone, and both *in utero* exposure to maternal smoking and exposure to ETS. Personal smoking was ascertained during a private interview during lung function testing sessions. Asthma status and age

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at diagnosis were defined on the basis of a parent-reported history of physician-diagnosed asthma.

Statistical Analysis

The relation between pulmonary function (PF) in children and physiologic measures (e.g., age and height) is complex and linearity or any other simple parametric form may not adequately characterize the relationship. On the basis of preliminary analysis of the present study and the results of similar studies, the relation between log PF and log height (log HT) is linear within short age intervals; however, the slopes and intercepts of this relation vary by age (14, 15). To account for dependence from repeated lung function measurements on the same child and to capture the nonlinear relations between PF, age, and HT, we fitted sex-specific mixed-effects regression models with spline terms for the age-dependent intercepts and slopes for HT (i.e., f_1 and f_2 in the following varying coefficient model) of the form:

$$E[\log(PF_{cit})] = \mu + a_i + f_1(AGE_{cit}) + f_2(AGE_{cit}) \times \log(HT_{cit}) + X_{cit}\gamma + \alpha_g I_g, + \beta_g I_g \times AGE_{cit}$$

where c, i, t, and g are subscripts for community, child, year of visit, and asthma group of interest (e.g., early onset asthma and late onset asthma), respectively; and a_i denotes a child-specific random intercept assumed to be normally distributed, with zero mean and a finite variance. The age-specific intercepts (f_1) and slopes (f_2) of log height are smooth functions of age, which were estimated using regression splines (16–18). X_{cit} are covariates including community, school grade, race/ethnicity, technician, spirometer, room temperature, barometric pressure, respiratory infection at PF testing, and family history of allergy and asthma. Continuous covariates were centered at their mean values.

The primary parameter of interest is the coefficient α_g of I_g, an indicator for the g asthma group. Because the models were fitted on a log(PF) scale, α_g is the difference between the log(PF) curve for the asthma group and the log(PF) curve for the reference group. The term β_g reflects whether the parallel difference in the log(PF) curve of the asthma group deviates linearly with age from the log(PF) curve of the reference group. To facilitate interpretation, the effects of asthma groups are shown on an arithmetic scale in terms of parallel percent differences (e.g., $[\exp(\alpha_g) - 1] \times 100\%$) from the reference PF curve at the mean age. Initial flexible models were fitted using a knot at each integral age. The final models were fitted using knots at 11, 13, 15, and 17 years of age, leading to a more parsimonious model with essentially the same results.

We assessed potential confounders of the relationship between tobacco smoke exposure, asthma, 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 (less than 12 grades, 12 grades, some college, college, and some graduate), household income (less than $7,500; $7,500 to $14,999; $15,000 to $29,999; $30,000 to $49,999; $50,000 to $99,999; and more than $100,000), insurance status (yes/no), body mass index (BMI [kg/m^2], age- and sex-specific quintiles), low birth weight (less than 5 lb, 5 lb or more), early chest illness excluding asthma (any before 2 years of age versus none), hay fever (any versus none), house water damage (yes/no), live plants in the house (yes/no), vigorous exercise within half an hour of the lung function test (yes/no), and respiratory illness at lung function test (yes/no) were evaluated as potential confounders. Variables were included in models if the adjusted estimates changed by 10% or more compared with the unadjusted estimates. All analyses were done with the linear mixed-effects model function (LME) of the SPlus statistical software package (Mathsoft, Seattle, WA).

RESULTS

Participant characteristics at study entry are presented in Table 1. The 5,933 children ranged in age from 7 to 18 years at the beginning of follow-up. At study entry, 8.7% of participants had been diagnosed with asthma at age 5 years or younger and 8.6% were diagnosed after age 5 years. Almost 19% were exposed *in utero* to maternal smoking and 32% had any lifetime ETS exposure.

We found substantial deficits in lung function among children with *in utero* exposure to maternal smoking and early onset asthma (Tables 2 and 3). Boys and girls exposed *in utero* to maternal smoking, but without a history of asthma, showed deficits in $FEF_{25–75}$, and a decrease in the FEV_1/FVC and $FEF_{25–75}$/FVC ratios. Conversely, both boys and girls with early onset asthma who were unexposed *in utero* showed deficits in FEV_1 (liters per second) and $FEF_{25–75}$ (liters per second), and a decrease in the FEV_1/FVC and $FEF_{25–75}$/FVC ratios. Children with *in utero* exposure and early onset asthma had large percent deficits for FEV_1 (−8.8%; 95% confidence interval [CI], −11.5 to −5.9%), $FEF_{25–75}$ (−23.6%; 95% CI, −28.3 to −18.7%), and $FEF_{25–75}$/FVC (−22.4%; 95% CI, −27.1 to −17.4%) among boys; and in FEV_1/FVC (−5.4%; 95% CI, −7.1 to −3.7%), $FEF_{25–75}$ (−14.9%; 95% CI, −20.1 to –9.4%), and $FEF_{25–75}$/FVC (−19.0%; 95% CI, −23.9 to −13.7%) among girls. The effects of *in utero* exposure to maternal smoking were significantly larger ($p < 0.05$) for both boys (FEV_1, $FEF_{25–75}$, and the FEV_1/FVC and $FEF_{25–75}$/FVC ratios) and girls ($FEF_{25–75}$ and the FEV_1/FVC and $FEF_{25–75}$/FVC ratios) with early onset asthma (5 years old or less at diagnosis) than asthma onset at an older age. The deficits in lung function associated with early and later onset asthma, and *in utero* exposure to maternal smoking, were essentially unchanged after adjustment for lifetime ETS exposure and personal smoking.

To further investigate the effects of *in utero* exposure to maternal smoking with and without ETS exposure, we assessed lung function levels using mutually exclusive exposure categories (Tables 4 and 5). Compared with nonasthmatic children unexposed to ETS and maternal smoking *in utero*, children with *in utero* exposure alone and early onset asthma showed deficits in FEV_1 (−13.6%; 95% CI, −18.9 to –8.2%), FEV_1/FVC (−9.1%; 95% CI, −12.2 to −5.8%), $FEF_{25–75}$ (−29.7%; 95% CI, −37.8 to −20.5%), and $FEF_{25–75}$/FVC (−25.9%; 95% CI, −34.5 to −16.2%) among boys; and in FEV_1/FVC (−9.3%; 95% CI, −12.9 to −5.4%), $FEF_{25–75}$ (−26.6%; 95% CI, −36.4 to −15.1%), and $FEF_{25–75}$/FVC

TABLE 1. SELECTED CHARACTERISTICS OF CHILDREN'S HEALTH STUDY PARTICIPANTS AT THE FIRST LUNG FUNCTION MEASUREMENT

	Number*	%
All	5,933	
Sex		
Girls	3,064	51.6
Boys	2,869	48.4
Age, yr		
7–10	1,863	31.4
10–12	2,133	36.0
12–14	948	16.0
14–18	989	16.6
Race/ethnicity		
White/Hispanic	4,945	83.3
Black	320	5.4
Others	668	11.3
Diagnosed asthma		
None	4,809	82.8
Early onset (≤ 5 yr)	503	8.7
Late onset (> 5 yr)	498	8.6
In utero exposure to maternal smoking		
No	4,645	81.3
Yes	1,071	18.7
ETS exposure		
Never	3,880	67.6
Past only	604	10.5
Current	1,254	21.9

Definition of abbreviations: ETS = environmental tobacco smoke; PFT = pulmonary function testing.

* Numbers may not add up because of missing values.

TABLE 2. INDEPENDENT AND JOINT EFFECT OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND ASTHMA STATUS ON LUNG FUNCTION AMONG BOYS PARTICIPATING IN THE CHILDREN'S HEALTH STUDY

Lung Function	Asthma Status	No *in Utero* Exposure (*% Difference*)	95% CI	*In Utero* Exposure (*% Difference*)	95% CI
FEV_1	No asthma	Reference	—	−1.0	−2.3 to 0.2
	Late onset	−0.2	−1.1 to 0.6	−0.2	−2.3 to 1.9
	Early onset	−3.3†	−4.8 to −1.8	−8.8†	−11.5 to −5.9
FVC	No asthma	Reference	—	0.3	−0.9 to 1.5
	Late onset	0.6	−0.2 to 1.3	1.4	−0.4 to 3.3
	Early onset	0.3	−1.2 to 1.8	−1.6	−4.4 to 1.4
FEV_1/FVC	No asthma	Reference	—	−1.3†	−2.1 to −0.6
	Late onset	−0.9†	−1.5 to −0.4	−1.8†	−3.0 to −0.5
	Early onset	−3.6†	−4.4 to −2.7	−7.3†	−9.0 to −5.6
$FEF_{25–75}$	No asthma	Reference	—	−4.8†	−7.3 to −2.3
	Late onset	−3.1†	−4.8 to −1.3	−4.3*	−8.4 to −0.1
	Early onset	−12.4†	−15.1 to −9.6	−23.6†	−28.3 to −18.7
$FEF_{25–75}$/FVC	No asthma	Reference	—	−5.1†	−7.5 to −2.6
	Late onset	−3.4†	−5.0 to −1.7	−5.5†	−9.5 to −1.4
	Early onset	−12.6†	−15.3 to −9.8	−22.4†	−27.1 to −17.4

Definition of abbreviation: CI = confidence interval.

Models are adjusted for age, log (height), race, community, spirometer, technician, barometric pressure, temperature, respiratory illness, family history of atopy and asthma, and ETS exposure.

* $p < 0.05$.

† $p < 0.01$.

(−29.9%; 95% CI, −39.5 to −18.9%) among girls. We found that ETS exposure alone was not significantly associated with persistent deficits in lung function in any subgroup after considering the effects of early and later onset asthma. Among children without asthma, joint exposure to ETS and maternal smoking *in utero* was associated with significant deficits in flows; however, the joint effect of ETS and *in utero* exposure was of similar magnitude as for *in utero* exposure alone and was not significantly different from the effect of *in utero* exposure alone. Among children with asthma, the deficits in FEV_1 in boys and $FEF_{25–75}$/FVC and $FEF_{25–75}$ were smaller in girls with early onset asthma and who were exposed to both *in utero* and ETS exposures than girls exposed to *in utero* maternal smoking alone. The associations between lung function, early and later onset asthma, and *in utero* exposure to maternal smoking were essentially unchanged after adjustment for personal smoking.

We found that the deficits in lung function associated with *in utero* exposure and early onset asthma persisted into adolescence (Tables 6 and 7). Among girls, the percent deficits in lung function associated with *in utero* exposure and asthma status did not change with age except among unexposed girls with early onset asthma, who showed increasing deficits in $FEF_{25–75}$ with age. The magnitude of the percent deficits in $FEF_{25–75}$ and the FEV_1/FVC ratio associated with *in utero* exposure in boys without asthma did not change with age. The percent deficits among unexposed boys with early onset asthma increased by 0.2%/year of age for

TABLE 3. INDEPENDENT AND JOINT EFFECT OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND ASTHMA STATUS ON LUNG FUNCTION AMONG GIRLS PARTICIPATING IN THE CHILDREN'S HEALTH STUDY

Lung Function	Asthma Status	No *in Utero* Exposure (*% Difference*)	95% CI	*In Utero* Exposure (*% Difference*)	95% CI
FEV_1	No asthma	Reference	—	−0.4	−1.7 to 0.9
	Late onset	−0.1	−0.8 to 0.8	1.0	−0.8 to 3.1
	Early onset	−2.2*	−4.2 to −0.1	−0.8	−3.9 to 2.5
FVC	No asthma	Reference	—	1.0	−0.2 to 2.3
	Late onset	0.7*	0.0 to 1.4	2.8†	1.0 to 4.6
	Early onset	0.8	−1.3 to 2.8	4.9†	1.6 to 8.4
FEV_1/FVC	No asthma	Reference	—	−1.3†	−2.0 to −0.6
	Late onset	−0.7†	−1.2 to −0.2	−1.9†	−3.0 to −0.7
	Early onset	−2.9†	−4.0 to −1.8	−5.4†	−7.1 to −3.7
$FEF_{25–75}$	No asthma	Reference	—	−4.6†	−6.9 to −2.3
	Late onset	−2.3†	−4.0 to −0.7	−1.7	−5.6 to 2.2
	Early onset	−10.7†	−14.1 to −7.1	−14.9†	−20.1 to −9.4
$FEF_{25–75}$/FVC	No asthma	Reference	—	−5.5†	−7.8 to −3.1
	Late onset	−2.9†	−4.5 to −1.2	−4.3*	−8.0 to −0.5
	Early onset	−11.3†	−14.8 to −7.7	−19.0†	−23.9 to −13.7

For definition of abbreviation, *see* Table 2.

Models are adjusted for age, log (height), race, community, spirometer, technician, barometric pressure, temperature, respiratory illness, family history of atopy and asthma, and ETS exposure.

* $p < 0.05$.

† $p < 0.01$.

TABLE 4. INDEPENDENT AND JOINT EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING, ENVIRONMENTAL TOBACCO SMOKE EXPOSURE, AND ASTHMA STATUS ON LUNG FUNCTION AMONG BOYS PARTICIPATING IN THE CHILDREN'S HEALTH STUDY

		Smoke Exposure							
		None		ETS only		*In Utero* Only		Both	
Lung Function	Asthma Status	(*% Difference*)	95% CI	(*% Difference*)	95% CI	(*% Difference*)	95% CI	(*% Difference*)	95% CI
FEV_1	No asthma	Reference	—	−0.7	−2.0 to 0.5	−1.0	−3.8 to 1.9	−1.0	−2.4 to 0.5
	Late onset	−0.8	−1.8 to 0.2	0.6	−1.2 to 2.5	2.5	−2.2 to 7.3	−0.7	−3.0 to 1.7
	Early onset	−3.3†	−5.0 to −1.5	−3.6*	−6.4 to −0.7	−13.6†	−18.9 to −8.2	−7.4†	−10.7 to −4.0
FVC	No asthma	Reference	—	−0.5	−1.6 to 0.7	−0.6	−3.3 to 2.1	0.7	−0.7 to 2.1
	Late onset	0.0	−0.8 to 0.9	1.4	−0.2 to 3.1	1.3	−2.7 to 5.5	1.5	−0.6 to 3.7
	Early onset	0.3	−1.4 to 2.1	−0.2	−3.0 to 2.7	−5.0	−10.4 to 0.7	−0.7	−4.1 to 2.8
FEV_1/FVC	No asthma	Reference	—	−0.2	−1.0 to 0.5	−0.3	−2.0 to 1.4	−1.6†	−2.5 to −0.8
	Late onset	−1.0†	−1.6 to −0.4	−0.9	−2.0 to 0.2	0.9	−1.9 to 3.8	−2.3†	−3.7 to −0.9
	Early onset	−3.6†	−4.6 to −2.6	−3.4†	−5.1 to −1.7	−9.1†	−12.2 to −5.8	−6.8†	−8.7 to −4.8
$FEF_{25–75}$	No asthma	Reference	—	−0.9	−3.7 to 1.6	−2.5	−8.0 to 3.3	−5.4†	−8.1 to −2.6
	Late onset	−4.3†	−6.4 to −2.2	−0.9	−4.6 to 2.9	3.3	−6.2 to 13.7	−5.8*	−10.3 to −1.0
	Early onset	−12.1†	−15.3 to −8.9	−12.0†	−17.1 to −6.5	−29.7†	−37.8 to −20.5	−21.9†	−27.3 to −15.9
$FEF_{25–75}$/FVC	No asthma	Reference	—	−0.6	−3.0 to 1.9	−1.9	−7.5 to 3.9	−6.0†	−8.7 to −3.3
	Late onset	−4.2†	−6.1 to −2.1	−1.9	−5.5 to 1.8	2.0	−7.1 to 12.1	−7.2†	−11.5 to −2.6
	Early onset	−12.7†	−15.5 to −9.1	−11.9†	−17.0 to −6.4	−25.9†	−34.5 to −16.2	−21.3†	−26.9 to −15.4

Definition of abbreviations: CI = confidence interval; ETS = environmental tobacco smoke.

Models are adjusted for age, log (height), race, community, spirometer, technician, barometric pressure, temperature, respiratory illness, family history of atopy and asthma. Columns headed "% Difference" and "95% CI" indicate the percent difference in lung function level and 95% confidence interval, respectively.

* $p < 0.05$.

† $p < 0.01$.

FEV_1. Late onset asthma in unexposed boys showed a larger percent deficit with age for FEV_1 (−0.6%/year), FVC (−0.2%/year), FEV_1/FVC ratio (−0.3%/year), $FEF_{25–75}$ (−0.8%/year), and $FEF_{25–75}$/FVC ratio (−0.6%/year).

The percent deficits in FEV_1, FVC, $FEF_{25–75}$, and the FEV_1/FVC and $FEF_{25–75}$/FVC ratios decreased significantly with increasing age among the boys with early onset asthma who were exposed *in utero*. For example, the 27.7% deficit in $FEF_{25–75}$ among boys decreased by 1.9% between ages 10 and 11 years. This age trend was not observed among girls. To illustrate the effects of the changes in deficits with age on predicted lung function level, we calculated the predicted lung function level at ages 10 and 15 years, using the covariates for non-Hispanic white children with average height at their age and with different asthma status and *in utero* exposure combinations (Tables 8 and 9). We found that the effects of *in utero* exposure to maternal smoking on FEV_1 and $FEF_{25–75}$ increased with age among children without asthma and among those with early onset asthma. Although the percent deficits in lung function decreased significantly as age increased among the boys with early onset asthma

TABLE 5. INDEPENDENT AND JOINT EFFECT OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING, ENVIRONMENTAL TOBACCO SMOKE EXPOSURE, AND ASTHMA STATUS ON LUNG FUNCTION AMONG GIRLS PARTICIPATING IN THE CHILDREN'S HEALTH STUDY

		Smoke Exposure							
		None		ETS only		*In Utero* Only		Both	
Lung Function	Asthma Status	(*% Difference*)	95% CI	(*% Difference*)	95% CI	(*% Difference*)	95% CI	(*% Difference*)	95% CI
FEV_1	No asthma	Reference	—	0.8	−0.4 to 1.9	−0.5	−3.5 to 2.6	−0.3	−1.6 to 1.1
	Late onset	−0.2	−1.2 to 0.7	1.4	−0.4 to 3.2	0.0	−4.7 to 5.0	1.6	−0.5 to 3.8
	Early onset	−3.0*	−5.3 to −0.6	0.5	−3.3 to 4.4	−5.3	−12.2 to 2.1	−0.2	−3.4 to 3.8
FVC	No asthma	Reference	—	1.1	−0.0 to 2.3	1.2	−1.8 to 4.2	1.2	−0.2 to 2.6
	Late onset	0.7	−0.1 to 1.4	1.5	−0.2 to 3.1	1.0	−3.3 to 5.4	3.4†	1.4 to 5.3
	Early onset	0.6	−1.8 to 3.0	2.2	−1.6 to 6.1	4.5	−3.0 to 12.6	5.2*	1.5 to 9.0
FEV_1/FVC	No asthma	Reference	—	−0.4	−1.0 to 0.3	−1.5	3.1 to 0.2	−1.3†	−2.1 to −0.6
	Late onset	−1.0†	−1.5 to −0.4	0.0	−1.1 to 1.1	−1.6	−4.4 to 1.4	−1.8†	−3.7 to −0.6
	Early onset	−3.5†	−4.8 to −2.2	−1.8	−3.8 to 0.2	−9.3†	−12.9 to −5.4	−4.7†	−6.6 to −2.8
$FEF_{25–75}$	No asthma	Reference	—	−0.3	−2.5 to 2.0	−5.2	−10.6 to 0.6	−4.1†	−6.7 to −1.5
	Late onset	−2.9†	−4.8 to −1.0	−0.3	−4.0 to 3.5	−6.0	−14.9 to 3.9	−0.1	−4.4 to 4.3
	Early onset	−12.7†	−16.7 to −8.5	−5.9	−12.6 to 1.3	−26.6†	−36.4 to −15.1	−12.3†	−18.2 to −6.1
$FEF_{25–75}$/FVC	No asthma	Reference	—	−1.4	−3.6 to 0.9	−6.1*	−11.5 to −0.4	−5.2†	−7.7 to −2.5
	Late onset	−3.5†	−5.3 to −1.6	−1.3	−4.9 to 2.5	−7.2	−16.0 to 2.4	−3.2	−7.3 to 1.1
	Early onset	−13.1†	−17.2 to −8.9	−8.0*	−14.6 to −1.0	−29.9†	−39.5 to −18.9	−16.7†	−22.3 to −10.6

For definition of abbreviation, *see* Table 4.

Models are adjusted for age, log (height), race, community, spirometer, technician, barometric pressure, temperature, respiratory illness, family history of atopy and asthma. Columns headed "% Difference" indicate the percent difference in lung function level.

* $p < 0.05$.

† $p < 0.01$.

TABLE 6. AGE TRENDS IN THE EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND ASTHMA STATUS ON LUNG FUNCTION LEVEL AMONG BOYS PARTICIPATING IN THE CHILDREN'S HEALTH STUDY

			Percent Difference in Lung Function Level		Age Trend in Lung Function Level	
Lung Function	*In Utero* Exposure	Asthma Status	(*% Difference*)	95% CI	(*% Difference*)	95% CI
FEV_1	No	No	Reference	—	Reference	—
	Yes	No	−0.5	−1.9 to 0.9	−0.2	−0.4 to 0.1
	No	Late onset	2.0†	0.8 to 3.2	−0.6†	−0.8 to −0.3
	Yes	Late onset	−1.4	−4.1 to 1.4	0.3	−0.1 to 0.8
	No	Early onset	−2.6†	−4.2 to −1.0	−0.2*	−0.4 to −0.0
	Yes	Early onset	−11.1†	−14.1 to −8.1	0.9†	0.5 to 1.4
FVC	No	No	Reference	—	Reference	—
	Yes	No	0.3	−1.0 to 1.7	0.0	−0.2 to 0.2
	No	Late onset	1.5†	0.5 to 2.5	−0.2†	−0.4 to −0.1
	Yes	Late onset	0.4	−1.9 to 2.8	0.3	−0.1 to 0.6
	No	Early onset	0.9	−0.7 to 2.4	−0.2*	−0.4 to −0.0
	Yes	Early onset	−3.1*	−6.1 to −0.0	0.5†	0.2 to 0.9
FEV_1/FVC	No	No	Reference	—	Reference	—
	Yes	No	−0.9†	−1.7 to −0.0	−0.1*	−0.3 to −0.0
	No	Late onset	0.3	−0.5 to 1.1	−0.3†	−0.5 to −0.2
	Yes	Late onset	−1.9*	−3.6 to −0.2	0.1	−0.2 to 0.4
	No	Early onset	−3.4†	−4.4 to −2.5	0.0	−0.2 to 0.1
	Yes	Early onset	−8.4†	−10.2 to −6.5	0.4†	0.1 to 0.7
$FEF_{25–75}$	No	No	Reference	—	Reference	—
	Yes	No	−4.2†	−6.9 to −1.3	−0.2	−0.6 to 0.2
	No	Late onset	0.2	−2.3 to 2.8	−0.8†	−1.3 to −0.4
	Yes	Late onset	−6.6*	−11.9 to −0.9	0.7	−0.3 to 1.7
	No	Early onset	−12.2†	−15.1 to −9.1	−0.1	−0.5 to 0.4
	Yes	Early onset	−27.7†	−32.5 to −22.6	1.9†	1.0 to 2.9
$FEF_{25–75}$/FVC	No	No	Reference	—	Reference	—
	Yes	No	−4.4†	−7.1 to −1.6	−0.2	−0.6 to 0.2
	No	Late onset	−1.0	−3.4 to 1.5	−0.6†	−1.0 to −0.2
	Yes	Late onset	−6.8*	−11.9 to −1.4	0.4	−0.5 to 1.4
	No	Early onset	−12.9†	−15.8 to −10.0	0.2	−0.3 to 0.6
	Yes	Early onset	−25.4†	−30.3 to −20.2	1.4†	0.5 to 2.3

For definition of abbreviation, *see* Table 2.

Models are adjusted for age, log(height), race, community, spirometer, technician, barometric pressure, temperature, respiratory illness, family history of atopy and asthma, and ETS exposure.

* $p < 0.05$.

† $p < 0.01$.

who were exposed *in utero*, the absolute deficit increased with age. Children exposed *in utero* who had late onset asthma presented a different pattern than did children with early onset asthma, and the absolute deficits were smaller at age 10 years and decreased by age 15 years.

DISCUSSION

We found that early onset asthma and *in utero* exposure to maternal smoking were associated with large persistent deficits in measures of airflow and that the deficits were largest among exposed children who developed early onset asthma. Previous studies of the relationship between *in utero* exposure and lung function in children have not reported the independent and joint associations of early onset asthma and *in utero* exposure among boys and girls (7, 19, 20). Our findings support the hypothesis that *in utero* exposure and early onset asthma are synergistically associated with persistent deficits in lung function and indicate that children with early onset asthma may be a high-risk group for subsequent adverse respiratory health outcomes during their life course. We did not observe an independent effect of ETS exposure on lung function.

A growing body of evidence supports the plausibility that *in utero* exposure to maternal smoking can produce persistent deficits in childhood lung function and that the deficits may be larger in children with asthma (7, 19, 21–28). Studies of lung function in newborns and infants of mothers who smoked during pregnancy show that *in utero* exposure is associated with reduced lung function in the perinatal period (22, 23, 26, 27, 29). Studies among newborns in eastern 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 (22, 29). The perinatal deficits from *in utero* exposure may be larger in children who subsequently develop asthma. Stick and coworkers reported that newborns with a family history of asthma had larger deficits in lung function from *in utero* exposure compared with newborns without a family history of asthma (29). Our findings suggest that the perinatal deficits in lung function from *in utero* exposure to maternal smoking are persistent and increasingly large during adolescence, especially among children who were diagnosed with asthma at an early age. Martinez and coworkers showed that prewheezing lung function persisted into later childhood, even in those children who stopped wheezing. These data support the hypothesis that there is a persistent underlying airflow abnormality independent of wheezing status (30). The large and increasing deficits may be important because *in utero* exposure to maternal smoking has been associated with higher incidence of asthma, more severe disease, an earlier onset of the disease, and an increased likelihood of using asthma medications (10, 31).

The biological mechanisms that account for the deficits associated with *in utero* exposure among children with early onset

TABLE 7. AGE TRENDS IN THE EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND ASTHMA STATUS ON LUNG FUNCTION LEVEL AMONG GIRLS PARTICIPATING IN THE CHILDREN'S HEALTH STUDY

			Percent Difference in Lung Function Level		Age Trend in Lung Function Level	
Lung Function	*In Utero* Exposure	Asthma Status	(*% Difference*)	95% CI	(*% Difference*)	95% CI
FEV_1	No	No	Reference	—	Reference	—
	Yes	No	−0.4	−1.8 to 1.0	0.0	−0.2 to 0.2
	No	Late onset	−0.4	−1.6 to 0.9	0.1	−0.2 to 0.3
	Yes	Late onset	0.9	−2.2 to 4.0	0.0	−0.5 to 0.6
	No	Early onset	−1.3	−3.5 to 0.9	−0.3	−0.6 to 0.0
	Yes	Early onset	−0.7	−4.2 to 3.0	−0.0	−0.6 to 0.5
FVC	No	No	Reference	—	Reference	—
	Yes	No	0.8	−0.6 to 2.1	0.1	−0.1 to 0.3
	No	Late onset	0.3	−0.7 to 1.4	0.1	−0.1 to 0.3
	Yes	Late onset	3.4*	0.8 to 6.2	−0.1	−0.5 to 0.3
	No	Early onset	1.1	−1.1 to 3.3	−0.1	−0.3 to 0.1
	Yes	Early onset	4.5*	1.0 to 8.2	0.1	−0.3 to 0.6
FEV_1/FVC	No	No	Reference	—	Reference	—
	Yes	No	−1.1*	−1.9 to −0.3	−0.1	−0.2 to 0.1
	No	Late onset	−0.7	−1.5 to 0.1	−0.0	−0.2 to 0.1
	Yes	Late onset	−2.3	−4.2 to −0.4	0.1	−0.2 to 0.4
	No	Early onset	−2.4†	−3.6 to −1.1	−0.2	−0.4 to 0.0
	Yes	Early onset	−4.9†	−6.8 to −2.9	0.2	−0.5 to 0.2
$FEF_{25–75}$	No	No	Reference	—	Reference	—
	Yes	No	−4.1†	−6.8 to −1.4	−0.2	−0.6 to 0.3
	No	Late onset	−1.5	−4.1 to 1.2	−0.2	−0.7 to 0.3
	Yes	Late onset	−4.3	−10.3 to 2.2	0.6	−0.6 to 1.7
	No	Early onset	−8.8†	−12.8 to −4.7	−0.7*	−1.3 to −0.0
	Yes	Early onset	−15.3†	−21.1 to −9.0	0.1	−1.0 to 1.3
$FEF_{25–75}$/FVC	No	No	Reference	—	Reference	—
	Yes	No	−4.7†	−7.3 to −2.0	−0.3	−0.7 to 0.2
	No	Late onset	−1.6	−4.2 to 1.0	−0.3	−0.8 to 0.2
	Yes	Late onset	−6.9*	−12.7 to −0.8	0.6	−0.5 to 1.7
	No	Early onset	−9.7†	−13.6 to −5.6	−0.6	−1.2 to 0.1
	Yes	Early onset	−18.9†	−24.5 to −12.8	−0.0	−1.1 to 1.1

For definition of abbreviation, *see* Table 2.

Models are adjusted for age, log (height), race, community, spirometer, technician, barometric pressure, temperature, respiratory illness, family history of atopy and asthma, and ETS exposure.

* $p < 0.05$.

† $p < 0.01$.

asthma have yet to be established. Airway structures are present at birth but continue developing and growing in the postnatal period. Because the effects of *in utero* exposure appear to be independent from the effects of postnatal ETS exposure, the deficits from *in utero* exposure may reflect damage during critical periods of fetal development that permanently alters the structure or function of the lung, such as its elastic recoil properties, smooth muscle, epithelial organization, neural function, or immune function (7). Studies of rodents exposed to tobacco smoke during the *in utero* period show that newborns have increased bronchial reactivity (32). Increased bronchial reactivity may lead to increased risk of wheezing illnesses during infancy, asthma, and deficits in lung function growth during childhood. Any direct effects of *in utero* exposure on lung development may be amplified by asthma, which is associated with both *in utero* exposure and chronic deficits in lung function. The effects may also be mediated through the increased occurrence of perinatal respiratory problems or infections associated with *in utero* exposure (33). Mechanistic studies are needed to better understand these physiologic and anatomic changes that account for our findings.

Our study had some limitations that need to be considered when interpreting the results. Asthma is a complex clinical syn-

TABLE 8. EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND ASTHMA ON ESTIMATED LEVEL AND ABSOLUTE DIFFERENCES IN LUNG FUNCTION AT AGE 10 AND 15 YEARS AMONG BOYS

		No *in Utero* Exposure		*In Utero* Exposure	
Lung Function	Asthma Status	Age 10 yr	Age 15 yr	Age 10 yr	Age 15 yr
FEV_1, ml	No asthma	**(2,252.96)**	**(4,064.31)**	−11.94	−51.77
	Late onset	44.38	−32.66	−30.87	8.87
	Early onset	−58.35	−150.59	−250.98	−283.55
$FEF_{25–75}$, ml/s	No asthma	**(2,565.73)**	**(4,536.90)**	−106.48	−231.59
	Late onset	4.87	−174.71	−168.06	−155.40
	Early onset	−311.74	−565.16	−709.94	−931.54

Boldface numbers in parentheses represent lung function for the reference groups at ages 10 and 15 years, respectively.

TABLE 9. EFFECTS OF *IN UTERO* EXPOSURE TO MATERNAL SMOKING AND ASTHMA ON ESTIMATED LEVEL AND ABSOLUTE DIFFERENCES IN LUNG FUNCTION AT AGE 10 AND 15 YEARS AMONG GIRLS

		No *in Utero* Exposure		*In Utero* Exposure	
Lung Function	Asthma Status	Age 10 yr	Age 15 yr	Age 10 yr	Age 15 yr
FEV_1, ml	No asthma	**(2,059.05)**	**(3,165.29)**	−8.85	−13.61
	Late onset	−7.41	−1.92	18.33	34.56
	Early onset	−27.59	−84.35	−14.00	−26.24
	No asthma	**(2,440.60)**	**(3,751.83)**	−100.31	−182.89
$FEF_{25–75}$, ml/s	Late onset	−36.85	−97.12	−104.95	−59.66
	Early onset	−214.77	−439.93	−372.44	−550.21

Boldface numbers in parentheses represent lung function for the reference groups at ages 10 and 15 years, respectively.

drome. In this study, asthma status was assigned on the basis of parental reports of age at physician diagnosis of asthma. Parent reports have been widely used in epidemiologic studies and shown to reflect physician diagnoses; however, the diagnosis of asthma by a physician may depend on access and utilization of medical care as well as physician diagnostic practices (34, 35). We considered factors associated with access and utilization of medical care such as insurance, education, and income and found no substantial change in the associations between *in utero* exposure, asthma, and lung function. This suggests that differences in access and utilization of medical care are unlikely to account for our results. To further investigate the effects of undiagnosed asthma in our study population, we examined the effects of wheezing in the 12 months before study entry in children without asthma (56 boys and 57 girls). We found that children with wheezing but without diagnosed asthma showed no reductions in lung function compared with children without asthma or wheeze. *In utero* exposure was associated with lung function deficits in undiagnosed children with and without wheezing. The magnitude of the deficits from *in utero* exposure were smaller in undiagnosed children with wheezing than in children with early onset asthma. Because the number of undiagnosed children with wheezing was small in our population and the effects of *in utero* exposure were smaller than in children with early onset asthma, bias from undiagnosed asthma cannot explain our results as the presence of undiagnosed asthma in the reference group would produce a small bias toward no effect.

Errors in measurement of *in utero* and chronic levels of postnatal ETS exposure are another potential source of bias. Exposure to tobacco smoke was assessed retrospectively, using questionnaire responses, and was not validated by objective measurements such as cotinine or nicotine levels. However, exposure estimates based on questionnaire responses have been validated by other investigators (36–40). The pattern of stronger effects from *in utero* than ETS exposure may have arisen from differential measurement error for ETS compared with *in utero* exposure. The measurement error for ETS is likely to be larger than for *in utero* exposure and may produce a larger bias toward the null for ETS estimates. *In utero* exposure was reported at study entry and errors in reporting are unlikely to bias the associations with lung function measured prospectively. We were unable to investigate any dose–response relationships for *in utero* exposure in the entire cohort because we lacked information about the intensity or duration of exposure. In an ongoing case-control study nested in the cohort, we have observed that 15% of women who smoked at conception quit smoking during the first trimester and 84% continued to smoke during the pregnancy. In this study, women smoked an average of half a pack per day while pregnant. These data indicate that most women in the study were light smokers, but the majority continued to smoke throughout pregnancy. We also lacked information about a number of potential confounders such as maternal nutritional status and intake of alcohol or other potentially toxic substances during pregnancy.

Our findings may have clinical and public health significance. The long-term effects of *in utero* exposure on the growing lungs of children with early onset asthma are of particular concern. If the growing deficits continue and persist into adulthood, children with early onset asthma may be at increased risk for debilitating symptoms from asthma and chronic obstructive pulmonary disease (2–4, 33, 41). Reducing the long-term effects of tobacco smoke on children with asthma may require the reduction of smoking among women during their childbearing years. Furthermore, clinicians need to be aware of this high-risk group in treatment decision-making.

In conclusion, school-aged children with early onset asthma and *in utero* exposure to maternal smoking show large deficits in lung function, especially airflows that are not explained by postnatal ETS exposure. Because early onset asthma itself is associated with substantial chronic deficits in lung function, the additional deficits associated with *in utero* exposure may produce 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 phenotypes on lung growth and development.

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