Effects of Maternal Smoking during Pregnancy and Environmental Tobacco Smoke on Asthma and Wheezing in Children

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The effects of maternal smoking during pregnancy and childhood environmental tobacco smoke (ETS) exposure on asthma and wheezing were investigated in 5,762 school-aged children residing in 12 Southern California communities. Responses to a self-administered questionnaire completed by parents of 4th, 7th, and 10th grade students were used to ascertain children with wheezing or physician-diagnosed asthma. Lifetime household exposures to tobacco smoke were assessed using responses about past and current smoking histories of household members and any history of maternal smoking during pregnancy. Logistic regression models were fitted to cross-sectional data to estimate the effects of *in utero* exposure to maternal smoking and previous and current ETS exposure on the prevalence of wheezing and physician-diagnosed asthma. *In utero* exposure to maternal smoking without subsequent postnatal ETS exposure was associated with increased prevalence of physician-diagnosed asthma (OR, 1.8; 95% CI, 1.1 to 2.9), asthma with current symptoms (OR, 2.3; 95% CI, 1.3 to 4.0), asthma requiring medication use in the previous 12 mo (OR, 2.1; 95% CI, 1.2 to 3.6), lifetime history of wheezing (OR, 1.8; 95% CI, 1.2 to 2.6), current wheezing with colds (OR, 2.1; 95% CI, 1.3 to 3.4) and without colds (OR, 2.5; 95% CI, 1.4 to 4.4), persistent wheezing (OR, 3.1; 95% CI, 1.6 to 6.1), wheezing with exercise (OR, 2.4; 95% CI; 1.3 to 4.3), attacks of wheezing causing shortness of breath (OR, 2.4; 95% CI, 1.3 to 4.4) or awakening at night in the previous 12 mo (OR, 3.2; 95% CI, 1.7 to 5.8), and wheezing requiring medication (OR, 2.1; 95% CI, 1.2 to 3.7) or emergency room visits during the previous year (OR, 3.4; 95% CI, 1.4 to 7.8). In contrast, current and previous ETS exposure was not associated with asthma prevalence, but was consistently associated with subcategories of wheezing. Current ETS exposure was associated with lifetime wheezing (OR, 1.3; 95% CI, 1.1 to 1.5), current wheezing with colds (OR, 1.6; 95% CI, 1.3 to 2.0) and without colds (OR, 1.5; 95% CI, 1.1 to 1.9), wheezing with exercise (OR, 1.7; 95% CI, 1.3 to 2.2), attacks of wheezing causing shortness of breath (OR, 1.6; 95% CI, 1.2 to 2.1) or awakening at night (OR, 1.5; 95% CI, 1.1 to 2.0), and wheezing requiring medication (OR, 1.4; 95% CI, 1.1 to 1.8) or emergency room visits within the previous year (OR, 1.9; 95% CI, 1.2 to 3.0). The effects of current ETS exposure on subcategories of wheezing were most pronounced among children exposed to two or more smokers and remained significant after adjusting for maternal smoking during pregnancy. We conclude that maternal smoking during pregnancy increases the occurrence of physician-diagnosed asthma and wheezing during childhood. In contrast, current ETS exposure is associated with wheezing, but not physician-diagnosed asthma. Taken together, our findings support the hypothesis that ETS operates as a cofactor with other insults such as intercurrent infections as a trigger of wheezing attacks, rather than as a factor that induces asthma, whereas *in utero* exposure acts to increase physician-diagnosed asthma

Asthma is an important worldwide public health problem. Prevalence of asthma is high and increasing in industrialized regions of the world (1–3). The rapid rise in childhood asthma suggests a role for environmental exposures in the etiology of this evolving epidemic (4). Although a number of hypotheses are being actively investigated, the exposures underlying the increasing prevalence have yet to be firmly established (4, 5).

The effect of involuntary tobacco smoke exposure on childhood asthma has been one focus of investigation (6–11). In the United States, an estimated 15 million children, accounting for more than 25% of the population in this age group, are currently exposed to household environmental tobacco smoke (ETS) and are at risk for adverse health effects from this exposure (12). An extensive body of evidence indicates that involuntary tobacco smoke exposure increases the prevalence of wheezing, cough, and phlegm and that childhood household ETS exposures cause exacerbations in asthma (6–11).

Evidence supporting a causal relationship between involuntary tobacco smoke exposure and asthma induction is inconsistent (4, 6–11). Although an effect of paternal smoking has been reported, exposure to maternal smoking has consistently had the strongest association with adverse respiratory health effects, including asthma and wheezing. Studies using cotinine as a biomarker of ETS exposure show that the strength of the association between maternal smoking and asthma and wheeze is in part due to larger ETS doses from maternal smoking than from other sources (4). Although fetal exposure to maternal smoking during pregnancy may contribute to the consistently larger effects of maternal smoking, the effects of *in utero* exposure on the occurrence of asthma and wheeze have not been as extensively studied as the effects of ETS, and the evidence for independent effects of *in utero* exposure on the occurrence of asthma and wheezing have yet to be established (4, 6–11).

The Children's Health Study (CHS) offers an opportunity to further investigate the effects of involuntary tobacco smoke on the occurrence of asthma and wheezing during childhood. The CHS, which began in 1993, is a 10-yr longitudinal study of the effects of air pollution on children's respiratory health (13). A total of 5,762 children from grades 4, 7, and 10 who attended public schools in 12 communities in Southern California participated in the study. We used lifetime tobacco smoke exposure histories and parental reports of wheezing and physician-diagnosed asthma collected at cohort entry to examine

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the relationships of maternal smoking during pregnancy and childhood exposure to ETS with wheezing or asthma.

METHODS

The elements of the Southern California Children's Health Study have been described previously (13). A total of 5,762 children were recruited from public school classrooms from grades 4, 7, and 10 in 12 communities. Questionnaire responses by parents or guardians were used to categorize children's asthma status, age at asthma diagnosis, and wheezing history. Children were classified as having asthma if a doctor had ever diagnosed the child as having asthma. Persistent asthma was defined as wheezing or asthma medication use during the school years. Active asthma was defined as physician-diagnosed asthma with any asthma-related symptoms or illness in the previous 12 mo. Wheezing was defined as the child's chest ever sounding wheezy or whistling. Persistent wheezing was defined as wheezing for 3 or more days out of the week for a month or longer in the previous year.

Information was collected about the current and past household smoking status of each participant's adult household members and regular household visitors. The current number of household smokers and the current number of cigarettes smoked inside the house per day were recorded. *In utero* exposure to maternal smoking was defined as any smoking while pregnant. Mutually exclusive categories of tobacco smoke exposure were defined as none, any current or past household ETS only, *in utero* exposure to maternal smoking only, or both *in utero* and household ETS exposure. Personal smoking by participants was defined as a history of ever smoking more than 100 cigarettes ascertained by a private interview during spirometry.

Health insurance coverage was defined as having any health plan or health coverage. Occurrence of any severe chest illness, including pneumonia, bronchitis, bronchiolitis, croup, and other illnesses, before age 2 or after age 2 were dichotomized. Personal history of atopy included any history of hay fever, allergies to food or medicine, inhaled dusts, pollen, molds, animal fur or dander, or skin allergies not including poison ivy and oak. Family history of atopy was defined as any biologic parent or full siblings in whom hay fever or allergies had been diagnosed. Family history of asthma was defined as any biologic parent or full siblings in whom asthma had been diagnosed. Categories of children's time/activity patterns were defined using the number of hours each child spent outdoors over a 2-wk period.

Logistic regression models were used to assess the individual and joint effects of *in utero* and ETS exposures on the occurrence of asthma and wheezing. On the basis of the study design and a priori consideration of potential confounders, all models included terms for grade, age, sex, ethnicity cohort, and community. If estimates of the tobacco smoke effects changed by at least 10% when a covariate was included in the base model, the covariate was included in the final model. Although the number of ever smokers was small (1.7%), the effect of personal smoking was considered by excluding ever smokers from analyses and by modeling personal smoking as a potential confounder or effect modifier. All analyses were conducted using SAS software (14).

RESULTS

Questionnaires were collected from parents of 5,762 students in the 12 study communities. The majority of students were 10 yr of age or younger, white, and from households with health insurance and high educational attainment (*see* online data supplement at www.atsjournals.org). Twenty-three percent of participants had no siblings at the time of interview, 19.5% had a family history of asthma, 47.7% had a family history of atopy, and 35.3% had a personal history of atopy. Premature birth occurred for 10.8% of children and 9.6% required neonatal special care. A severe chest illness before 2 yr of age occurred in 10.6% of participants.

Only 1.7% of children were active smokers (Table 1). *In utero* exposure to maternal smoking occurred for 18.8% of children and 39.5% had any lifetime exposure to ETS. Children were classified into four mutually exclusive exposure categories: no household tobacco smoke exposure (57.7%); ETS exposure only (23.3%); *in utero* exposure only (3.0%); and both ETS and *in utero* exposure (16.0%). Both ETS and *in utero* exposure varied by age and grade, reflecting decreases in the prevalence of parental smoking (*see* online data supplement at www.atsjournals.org). ETS exposure was highest among African American children, children with a parent who had less than a college education, children from low-income families, families with one child, and for those whose questionnaires were not completed by a parent. *In utero* exposure was lower among Asian and Hispanic children than non-Hispanic white children and among children whose parent had a college degree than those whose parent had a lower educational attainment. The number of siblings was inversely associated with *in utero* exposure. Twenty-two percent of children were exposed to household ETS at the time of questionnaire completion.

The lifetime prevalence of wheezing was 33.7% and a physician-diagnosis of asthma was reported for 14.6% of children. Most cases were diagnosed by 5 yr of age and the majority of children who were ever diagnosed with asthma continued to require medication or had persistent symptoms since entry into 1st grade. The prevalence of asthma was higher in the children exposed *in utero* to maternal smoking than unexposed children, and was higher in those exposed to ETS than unexposed children (Table 2). The proportion of children with active asthma or medication use was higher in the *in utero* exposure group than in the unexposed group, but it was slightly lower in the group with any lifetime ETS exposure than those unexposed to ETS. In contrast, the prevalence of lifetime wheezing was higher in the ETS-exposed than the unexposed group.

Of the potential determinants of physician-diagnosed asthma considered, tobacco smoke exposure, race/ethnicity, education, hay fever, family histories of asthma or allergy, gestational age, pets, and use of a humidifier were univariately associated with asthma (Table 3). The odds of physician-diag-

TABLE 1

TOBACCO SMOKE EXPOSURE AND INDOOR EXPOSURE AMONG CHS PARTICIPANTS

	n	% of Total
Tobacco smoke exposure		
Active smoking by child	98	1.7%
In utero smoking exposure	1,035	18.8%
Any lifetime ETS exposure	2,156	39.5%
Current ETS exposure	1,243	22.4%
Mom only	359	6.5%
Dad only	350	6.3%
Both parents	273	4.9%
Others	261	4.7%
Number of current smokers		
0	4,326	77.7%
1	804	14.5%
2+	439	7.9%
In utero smoking and ETS exposure*		
None	3,071	57.7%
ETS only	1,243	23.3%
In utero only	161	3.0%
Both *in utero* and ETS	849	16.0%
Indoor exposures		
Any pets	4,425	76.8%
Any pests	4,132	79.1%
Air conditioning use	3,385	60.5%
Gas stove use	4,393	79.0%
House water damage	961	17.3%
Humidifier use	1,525	28.1%

Definition of abbreviations: CHS = Children's Health Study; ETS = household environmental tobacco smoke.

* Any lifetime ETS.

TABLE 2

PERCENTAGE OF PARTICIPANTS WITH PHYSICIAN-DIAGNOSED ASTHMA AND WHEEZING WITHIN TOBACCO SMOKE EXPOSURE CATEGORIES

	In Utero		Lifetime ETS		Current ETS	
	Yes	No	Yes	No	Yes	No
Total	1,035	4,466	2,156	3,306	1,243	4,316
Asthma	17.8%	14.0%	15.2%	14.3%	15.7%	14.3%
Age at diagnosis*						
Younger†	11.2%	8.2%	9.0%	8.6%	9.1%	8.6%
Older‡	6.6%	5.5%	6.1%	5.3%	6.6%	5.4%
In the past 12 mo						
Active asthma	10.4%	8.4%	8.7%	9.0%	8.3%	8.9%
Medication for asthma	11.7%	9.6%	9.7%	10.0%	10.8%	8.4%
Lifetime history of wheezing	44.7%	31.2%	38.3%	30.7%	38.1%	32.5%
In the past 12 mo						
Wheeze with cold	29.5%	19.0%	24.5%	18.9%	25.5%	19.8%
Wheeze without cold	19.3%	12.5%	15.0%	12.9%	14.9%	13.2%
Persistent wheeze	11.8%	7.3%	8.6%	7.9%	8.8%	7.9%
Shortness of breath	18.0%	11.0%	14.2%	11.0%	14.1%	11.7%
Awakened at night	13.8%	9.3%	11.2%	9.3%	11.3%	9.7%
Wheeze with exercise	20.6%	12.5%	15.7%	12.7%	16.9%	13.0%
Medication for wheeze	19.4%	13.2%	15.8%	13.5%	15.6%	13.9%
Emergency room for wheeze	7.3%	4.0%	5.7%	4.0%	5.7%	4.3%

* Percentages may not sum up because of missing values.
† Younger: asthma diagnosed by 5 yr of age.
‡ Older: asthma diagnosed after 5 yr of age.

TABLE 3

DETERMINANTS OF PHYSICIAN-DIAGNOSED ASTHMA* AMONG CHS PARTICIPANTS, ODDS RATIOS (OR), AND 95% CONFIDENCE INTERVALS (95% CI) FOR ASTHMA

	Boys†			Girls†			All‡	
	n	OR	95% CI	n	OR	95% CI	OR	95% CI
Smoking								
None	1,521	1.0	—	1,550	1.0	—	1.0	—
ETS only	569	1.0	(0.8–1.3)	674	1.1	(0.8–1.4)	1.0	(0.9–1.3)
In utero only	82	1.7	(1.1–2.9)	79	1.9	(1.1–3.5)	1.8	(1.2–2.7)
Both	401	1.1	(0.8–1.4)	448	1.6	(1.2–2.2)	1.3	(1.1–1.6)
Race								
Not-Hispanic white	1,576	1.0	—	1,598	1.0	—	1.0	—
Hispanic	723	0.9	(0.7–1.1)	803	0.9	(0.7–1.2)	0.9	(0.7–1.1)
African American	125	2.0	(1.3–3.1)	169	1.3	(0.8–2.2)	1.6	(1.2–2.2)
Asian	143	1.1	(0.7–1.8)	136	0.8	(0.4–1.5)	1.0	(0.7–1.4)
Others	170	1.2	(0.8–1.8)	187	0.9	(0.6–1.5)	1.1	(0.8–1.5)
Education								
Some graduate	319	1.0	—	292	1.0	—	1.0	—
College	274	1.3	(0.8–2.0)	293	0.9	(0.5–1.5)	1.1	(0.8–1.5)
Some college	1,183	1.5	(1.1–2.1)	1,196	1.1	(0.8–1.7)	1.3	(0.9–1.7)
12 grades	532	1.1	(0.8–1.7)	600	1.1	(0.7–1.7)	1.1	(0.8–1.5)
< 12 grades	371	0.8	(0.5–1.3)	434	0.6	(0.3–0.9)	0.7	(0.5–0.9)
Income								
> $100,000	161	1.0	—	141	1.0	—	1.0	—
$50,000–$99,999	768	1.5	(0.9–2.3)	785	1.3	(0.7–2.2)	1.4	(0.9–1.9)
$30,000–$49,999	628	1.2	(0.7–2.0)	609	1.1	(0.6–1.9)	1.1	(0.8–1.7)
$15,000–$29,999	371	1.0	(0.6–1.8)	403	1.1	(0.6–2.0)	1.1	(0.7–1.6)
$7,500–$14,999	256	0.9	(0.5–1.5)	285	0.9	(0.4–1.7)	0.9	(0.6–1.3)
< $7,500	157	1.2	(0.6–2.1)	151	0.9	(0.4–2.0)	1.0	(0.6–1.7)
Hay fever	487	2.9	(2.3–3.7)	437	2.5	(1.9–3.3)	2.7	(2.3–3.2)
Family history of asthma	498	3.9	(3.1–4.9)	521	3.6	(2.8–4.6)	3.7	(3.1–4.4)
Family history of atopy	1,203	2.9	(2.3–3.7)	1,259	2.6	(2.0–3.4)	2.8	(2.4–3.3)
Gestational age								
Not born prematurely	2,406	1.0	—	2,541	1.0	—	1.0	—
< 4 wk early	182	1.4	(1.0–2.1)	197	1.8	(1.2–2.6)	1.6	(1.2–2.1)
⩾ 4 wk early	103	2.4	(1.5–3.7)	119	2.9	(1.9–4.5)	2.6	(1.9–3.6)
Any pets	2,135	1.5	(1.1–1.9)	2,290	1.7	(1.2–2.3)	1.6	(1.3–1.9)
Humidifier use	754	1.6	(1.3–1.9)	771	2.1	(1.6–2.6)	1.8	(1.5–2.1)

* Asthma as parent-reported of any lifetime physician diagnosis of asthma.
† Models are adjusted for towns, grade, cohort, and age.
‡ Models are adjusted for towns, grade, cohort, age, and sex.

nosed asthma were higher, especially among boys, for African Americans compared with non-Hispanic whites, and lower for children with a parent who had less than a high school education. However, household income was not strongly associated with physician-diagnosed asthma. Asthma was more likely to be diagnosed in children who were born prematurely than in children born at full-term.

We found that *in utero* exposure to maternal smoking without subsequent postnatal ETS exposure was associated with physician-diagnosed asthma and wheezing (Table 4). The odds of physician-diagnosed asthma for *in utero* exposure alone was 1.8-fold higher (95% CI, 1.1 to 2.9) than for no involuntary tobacco smoke exposure. Postnatal exposure to ETS in the absence of *in utero* exposure to maternal smoking was not associated with physician-diagnosed asthma (OR, 1.1; 95% CI, 0.9 to 1.4). Exposure to postnatal ETS in addition to maternal smoking *in utero* did not further increase the effect estimates beyond that for *in utero* exposure alone. In fact, the point estimates for joint exposures were generally lower than estimates for *in utero* exposure alone; however, the confidence intervals were wide and overlapping. The effects of *in utero* exposure did not vary substantially between sexes.

In contrast to the findings for physician-diagnosed asthma, both *in utero* exposure to maternal smoking alone and ETS exposure alone were independently associated with lifetime history of wheezing (Table 4). In general, joint exposure appeared to increase the individual effects of ETS, but not *in utero* exposure on wheezing; however, the point estimates were imprecise. Indoor exposure variables including pets, pests, air conditioning, gas stove, water damage, and humidifier use did not confound the relationship between ETS and asthma or wheezing. The effects of ETS and *in utero* exposure on wheezing did not vary substantially between sexes.

We found limited support for the hypothesis that the effects of involuntary tobacco smoke exposure on wheezing are largest in children without a family history of asthma or a family history of atopy; however, in contrast to other studies, the effects of *in utero* exposure rather than ETS exposure appeared to differ by family history (Table 4). The point estimates for the effects of *in utero* exposure on wheezing were larger in the negative family history subgroups. ETS exposure was associated with increased prevalence of wheezing, independent of family history. For asthma, only *in utero* exposure appeared to be independently associated with increased prevalence and the variation by family history of asthma or atopy was not as consistent.

The effect of involuntary tobacco smoke exposure appeared to vary by age at asthma diagnosis (*see* online data supplement at www.atsjournals.org). Among children in whom a diagnosis was made by 5 yr of age, *in utero* exposure to maternal smoking alone had an adjusted OR of 2.1 (95% CI, 1.2 to 3.7) compared with no tobacco smoke exposure. In contrast, among children in whom a diagnosis was made after 5 yr of age, *in utero* exposure to maternal smoking had an adjusted OR of 1.2 (95% CI, 0.5 to 2.8). Although estimates were imprecise, the effect of ETS exposure appeared to be larger in the older age at diagnosis group, especially among girls (OR, 1.4; 95% CI, 0.9 to 2.1). We found little evidence that the magnitude of the effects of involuntary tobacco smoke exposure on asthma occurrence varied by income, parental education, insurance status, or personal smoking status. Indoor exposure variables, including pets, pests, air conditioning, gas stove, water damage, and humidifier use did not confound the relationship between *in utero* exposure to maternal smoking or ETS and asthma or wheezing.

To further investigate the different patterns of effects of ETS and *in utero* exposure to maternal smoking on wheezing and asthma, we examined their relationships with subcategories of asthma (active and requiring medication in previous 12 mo), and wheezing within the previous 12 mo, including wheezing with and without colds, attacks of wheezing with shortness of breath or nighttime awakening, wheezing with exercise, and wheeze requiring medication or emergency care (Table 5). In models for the effects of ETS that did not include *in utero* exposure, we found that previous ETS exposure was associated with increased prevalence of wheezing with colds, wheezing with exercise, attacks of wheezing with shortness of breath or nighttime awakening, and wheezing requiring medication or emergency care. Current ETS exposure was associated with increased prevalence of a wider range of wheezing subcategories, including wheezing with and without colds, attacks of wheezing with shortness of breath or nighttime awakening, wheezing with exercise, and wheezing requiring medication or emergency care. Neither previous nor current ETS exposure was significantly associated with active asthma, asthma requiring medication, or persistent wheezing, but the presence of two or more household smokers was associated with all the subcategories of wheezing. Paternal smoking was not associated with any of the outcomes. When *in utero* exposure was included in the models for ETS and prevalence of subcategories of asthma and wheezing, the effects of exposure to two or more current smokers were reduced, but they remained statistically significant for use of medication for asthma and wheez-

TABLE 4

EFFECTS OF TOBACCO SMOKE ON WHEEZING AND PHYSICIAN-DIAGNOSED ASTHMA AMONG CHS PARTICIPANTS, ODDS RATIOS (OR), AND 95% CONFIDENCE INTERVALS (95% CI) BY FAMILY HISTORY OF ASTHMA AND ATOPY

	Wheeze		Asthma	
	OR	95% CI	OR	95% CI
All subjects*				
None	1.0	—	1.0	—
ETS only	1.3	(1.5–1.5)	1.1	(0.9–1.4)
In utero only	1.8	(1.2–2.6)	1.8	(1.1–2.9)
In utero and ETS	1.8	(1.5–2.2)	1.3	(1.0–1.7)
Family history of asthma†				
Without family history				
None	1.0	—	1.0	—
ETS only	1.3	(1.1–1.6)	1.1	(0.8–1.4)
In utero only	2.0	(1.2–3.2)	1.9	(1.0–3.7)
In utero and ETS	2.0	(1.6–2.5)	1.4	(1.0–1.9)
With family history				
None	1.0	—	1.0	—
ETS only	1.3	(0.9–1.9)	1.1	(0.7–1.6)
In utero only	1.5	(0.7–3.2)	1.8	(0.8–3.8)
In utero and ETS	1.3	(0.9–2.0)	1.2	(0.8–1.8)
Family history of atopy‡				
Without family history				
None	1.0	—	1.0	—
ETS only	1.2	(0.9–1.6)	1.1	(0.7–1.5)
In utero only	1.9	(1.1–3.3)	1.6	(0.8–3.4)
In utero and ETS	1.9	(1.5–2.5)	1.4	(0.9–2.1)
With family history				
None	1.0	—	1.0	—
ETS only	1.3	(1.1–1.7)	1.1	(0.8–1.5)
In utero only	1.5	(0.8–2.8)	1.9	(0.9–3.6)
In utero and ETS	1.6	(1.3–2.1)	1.3	(0.9–1.7)

* Models are adjusted for sex, towns, grade, cohort, age, race, hay fever, family history of asthma, family history of atopy, and gestational age.

† Models are adjusted for sex, towns, grade, cohort, age, race, hay fever, family history of atopy, and gestational age.

‡ Models are adjusted for sex, towns, grade, cohort, age, race, hay fever, family history of asthma, and gestational age.

TABLE 5

EFFECTS OF TOBACCO SMOKE EXPOSURE ON SUBCATEGORIES OF PHYSICIAN-DIAGNOSED ASTHMA AND WHEEZING IN THE PAST 12 mo AMONG CHS PARTICIPANTS, ADJUSTED ODDS RATIOS, AND 95% CONFIDENCE INTERVALS (95% CI)*

	Asthma		Wheezing		
	Active Asthma	Medication for Asthma	Wheeze with Cold	Wheeze without Cold	Persistent Wheeze
Exposure sources					
None	1.0	1.0	1.0	1.0	1.0
ETS only	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.3 (1.0–1.6)	1.2 (0.9–1.5)	1.0 (0.7–1.5)
In utero only	2.3 (1.3–4.0)	2.1 (1.2–3.6)	2.1 (1.3–3.4)	2.5 (1.4–4.4)	3.1 (1.6–6.1)
In utero and ETS	1.3 (0.9–1.8)	1.2 (0.9–1.7)	1.8 (1.4–2.3)	1.6 (1.2–2.1)	1.5 (1.0–2.3)
ETS status					
None	1.0	1.0	1.0	1.0	1.0
Previously	1.2 (0.9–1.7)	1.1 (0.9–1.5)	1.4 (1.1–1.7)	1.3 (0.9–1.8)	1.3 (0.9–1.8)
Currently	1.3 (0.9–1.7)	1.3 (0.9–1.7)	1.6 (1.3–2.0)	1.5 (1.1–1.9)	1.4 (0.9–2.0)
Current ETS sources					
None	1.0	1.0	1.0	1.0	1.0
Mom only	0.9 (0.5–1.5)	1.0 (0.6–1.6)	1.5 (1.1–2.2)	1.5 (0.9–2.3)	1.2 (0.7–2.3)
Dad only	1.1 (0.7–1.8)	1.2 (0.8–1.9)	1.1 (0.8–1.6)	1.1 (0.7–1.8)	1.1 (0.6–1.9)
Both parents	1.4 (0.9–2.3)	1.4 (0.9–2.3)	2.1 (1.5–3.1)	1.6 (1.0–2.6)	1.6 (0.9–3.0)
Others	1.0 (0.6–1.9)	1.0 (0.6–1.8)	1.3 (0.8–2.0)	1.3 (0.7–2.2)	1.3 (0.7–2.7)
Number of current smokers					
0	1.0	1.0	1.0	1.0	1.0
1	0.9 (0.6–1.3)	1.0 (0.7–1.4)	1.2 (0.9–1.5)	1.2 (0.9–1.6)	1.1 (0.7–1.7)
2+	1.7 (1.1–2.5)	1.7 (1.1–2.4)	2.2 (1.6–3.0)	1.9 (1.2–1.8)	1.8 (1.0–3.1)
p Value for trend	$p = 0.073$	$p = 0.109$	$p < 0.001$	$p = 0.006$	$p = 0.067$
	Attacks of Wheezing			Treatments for Wheezing	
	Shortness of Breath	Awakened at Night	Wheeze with Exercise	Medication for Wheeze	Emergency Room for Wheeze
Exposure sources					
None	1.0	1.0	1.0	1.0	1.0
ETS only	1.3 (0.9–1.7)	1.4 (1.0–1.9)	1.2 (0.9–1.6)	1.3 (0.9–1.6)	1.4 (0.9–2.2)
In utero only	2.4 (1.3–4.4)	3.2 (1.7–5.8)	2.4 (1.3–4.3)	2.1 (1.2–3.7)	3.4 (1.4–7.8)
In utero and ETS	2.0 (1.4–2.7)	1.5 (1.0–2.2)	1.8 (1.3–2.4)	1.6 (1.2–2.1)	2.3 (1.4–3.8)
ETS status					
None	1.0	1.0	1.0	1.0	1.0
Previously	1.6 (1.2–2.1)	1.6 (1.2–2.2)	1.3 (0.9–1.7)	1.4 (1.1–1.9)	1.7 (1.0–2.7)
Currently	1.6 (1.2–2.1)	1.5 (1.1–2.0)	1.7 (1.3–2.2)	1.4 (1.1–1.8)	1.9 (1.2–3.0)
Current ETS sources					
None	1.0	1.0	1.0	1.0	1.0
Mom only	1.1 (0.7–1.8)	1.0 (0.6–1.7)	1.7 (1.1–2.6)	1.2 (0.7–1.8)	1.4 (0.7–3.0)
Dad only	1.1 (0.7–1.8)	1.0 (0.6–1.7)	1.1 (0.7–1.7)	1.2 (0.8–1.8)	1.5 (0.7–2.9)
Both parents	2.0 (1.2–3.2)	1.9 (1.1–3.1)	2.1 (1.3–2.4)	1.7 (1.1–2.6)	1.8 (0.8–4.1)
Others	1.7 (1.0–2.9)	1.4 (0.8–2.6)	1.6 (1.6–2.6)	1.4 (0.8–2.3)	2.0 (0.9–4.4)
Number of current smokers					
0	1.0	1.0	1.0	1.0	1.0
1	1.0 (0.7–1.4)	0.9 (0.6–1.4)	1.3 (0.9–1.8)	1.0 (0.8–1.4)	1.3 (0.8–2.1)
2+	2.1 (1.4–3.2)	1.9 (1.2–3.0)	2.2 (1.5–3.3)	1.9 (1.3–2.8)	2.0 (1.0–4.0)
p Value for trend	$p < 0.001$	$p = 0.026$	$p < 0.001$	$p = 0.007$	$p = 0.031$

* Models are adjusted for towns, grade, cohort, age, race, sex, hay fever, family history of asthma, family history of atopy, and gestational age.

ing, wheezing with colds, attacks of wheezing with shortness of breath, and wheezing with exercise (data not shown). Consistent with the adjusted estimates, we found independent effects for ETS exposure when we examined mutually exclusive exposure categories only for wheezing with colds and being awakened at night by wheezing. In contrast, *in utero* exposure was independently associated with all of the subcategories of asthma and wheezing examined.

DISCUSSION

A substantial body of evidence indicates that involuntary exposure to tobacco smoke adversely affects children's respiratory health by decreasing lung growth and increasing the risk of respiratory infections, respiratory symptoms, including wheezing, and exacerbation of asthma (4, 6–11). Maternal smoking has been most strongly associated with the adverse respiratory effects in children, suggesting that fetal exposure to maternal smoking may have important long-term effects on children's respiratory health (4, 6–11). Because women who smoke during pregnancy are likely to continue smoking after delivery, it has been difficult to study the independent effects of *in utero* exposure to maternal smoking and postnatal ETS exposure and the evidence for an independent effect of *in utero* exposure on asthma and wheezing are inconsistent (4, 6–11). In our study, 161 (3%) women reported successful long-term smoking cessation before the child's birth and no subsequent postnatal household ETS exposure for the participating child, a

percentage that is consistent with that expected based on recent studies of tobacco use among pregnant women in the United States (15, 16). On the basis of the reports of these participants, we found that *in utero* exposure to maternal smoking was independently associated with physician-diagnosed asthma, current asthma, and asthma requiring current medications. Moreover, *in utero* exposure to maternal smoking, with or without subsequent ETS exposure, was associated with increased lifetime history of wheezing, current wheezing with and without colds, persistent wheezing, attacks of wheezing causing shortness of breath or awakening at night in the previous 12 mo, and wheezing requiring medication or emergency room visits in the previous year. The body of evidence for an independent effect of maternal smoking during pregnancy on wheezing and asthma is growing, but it remains mixed (6, 7, 9, 10, 17–19). Although many studies have assessed maternal smoking during pregnancy, few have been able to separate out the independent effect for *in utero* exposure to active maternal smoking versus post-natal ETS exposure. In a study of 750 5th grade students, the association of physician-diagnosed asthma was stronger with maternal smoking during pregnancy than current maternal smoking (17). A second study of 16,000 school-aged Scandinavian children found that maternal smoking during pregnancy was associated with increases in asthma attacks, dry cough, and asthma treatments. In contrast, current ETS exposure was inversely associated with these end points (20). Cunningham and colleagues (21) also reported that among 11,500 8- to 11-yr-old children in 24 U.S. and Canadian cities the effect of *in utero* exposure on asthma and wheezing symptoms was stronger for *in utero* exposure to maternal smoking than for measures of ETS exposure. Several prospective studies of wheezing illnesses have also shown that maternal smoking during pregnancy is a stronger predictor of wheezing and asthma than postnatal ETS exposure (10, 18, 19).

Among children with both *in utero* exposure to maternal smoking and subsequent household ETS, ETS exposure did not appear to increase the occurrence of asthma or wheezing beyond that associated with *in utero* exposure. As suggested by studies of Scandinavian children, the lower effect estimates may reflect differences in parental smoking behavior in children with a predisposition to wheezing from *in utero* exposure (20). However, the precision of the estimates for individual effects was too imprecise to draw a firm conclusion about the effects of joint exposures.

Among children who were exposed to ETS alone, the majority of whom were exposed to two or more household smokers, ETS exposure was associated with wheezing, but was, at most, weakly associated with physician-diagnosed asthma. Postnatal ETS exposure increased lifetime wheezing and persistent wheezing as well as current wheezing with and without colds, attacks of wheezing causing shortness of breath or awakening at night in the previous 12 mo, and wheezing requiring medication or emergency room visits within the previous year. Furthermore, the prevalence of current wheezing was highest in children exposed to two or more household smokers, even after accounting for the effects of maternal smoking during pregnancy. In a recent series of meta-analyses of the effects of parental smoking on asthma, wheezing, and respiratory symptoms, Cook and Strachan (6) reported a summary odds ratio for ETS and wheezing of 1.2 (95% CI, 1.2 to 1.3) that is consistent with our estimate of 1.3 (95% CI, 1.1 to 1.5). Our estimate for the association between ETS and asthma (1.1; 95% CI, 0.9 to 1.4) is slightly lower than that from the meta-analysis (1.2; 95% CI, 1.1 to 1.3), but the confidence intervals show considerable overlap. In contrast to the meta-analysis by Cook and Strachan, which concluded that prevalence of respiratory symptoms was not raised in children previously exposed to ETS, we found that previous exposure increased the prevalence of wheezing with colds, attacks of wheezing, and treatments for wheezing. Our paradoxical finding that current and previous ETS exposure is associated with wheezing, but not with asthma, is consistent with the hypothesis recently proposed by Cook and Strachan that ETS operates as a cofactor with other insults such as intercurrent infections as a trigger of reversible bronchial hyperactivity (BHR) and wheezing attack, rather than as a factor that induces asthma (10).

Smoking during pregnancy clearly exposes the fetus to carcinogens and other toxins in tobacco that are metabolized into more potent active compounds (22). Our findings of associations of *in utero* exposure with both wheezing and asthma are consistent with the evolving evidence that *in utero* exposure adversely affects postnatal lung function and increases the occurrence of asthma (23). Because the human lung's airway structures are largely complete at birth, it may be that *in utero* exposure increases asthma occurrence by altering critical developmental pathways leading to lower lung function, increased BHR, and a permanent predisposition to asthma and wheezing. A growing number of reports suggest that *in utero* exposure is associated with deficits in lung function at birth that may persist into young adulthood (24–29). The resultant persistent deficits in small airways function associated with *in utero* exposure may predispose children to wheezing during respiratory infections or other insults that produce inflammation, subsequent BHR, and airflow obstruction (30). Studies of human neonates show that maternal tobacco smoke exposure during the *in utero* period is associated with increased BHR, especially in those with a family history of asthma (31). Animal studies also suggest that exposure during the period of lung development leads to BHR (32). Chronically increased BHR from *in utero* exposure in addition to other postnatal insults may contribute to persistent wheezing and increased asthma predisposition and diagnosis (4, 31). Furthermore, *in utero* exposure may affect the development and maturation of the pulmonary immune system (33). Inappropriate persistence of a TH2-dominant response pattern appears to increase likelihood of allergic sensitization upon sufficient exposure to a variety of common antigens (34). Because increased and early sensitization to common antigens, in conjunction with decreased lung function and increased BHR, appear to underlie the pathogenesis of asthma, it is biologically plausible that *in utero* exposure to maternal smoking increases the occurrence of wheezing and asthma, especially during the first 5 yr of life. Although genetics may contribute to the effects of *in utero* exposure on wheezing and asthma, a family predisposition for asthma or atopy was not clearly apparent among exposed children, suggesting that *in utero* exposure more generally affects normal development consistent with its effects on birth weight (33).

Our study has some limitations that influence the interpretation of our results. The findings are based upon cross-sectional data collected at cohort entry and are subject to the selection bias, information bias, and problems with temporality inherent to cross-sectional studies. Parents or children may change their time-activity patterns to avoid ETS exposure. As noted previously, such changes may account for the lower effect estimates in participants with both ETS and *in utero* exposure than with *in utero* exposure alone. We lack data to directly assess changes in time activity patterns after the diagnosis of asthma. We note that the proportion of children with asthma who were exposed to ETS in the past but not currently (40%) was approximately the same as for children without asthma (43%), suggesting that adult smoking patterns did not differ-

entially change over time. Differential participation by children with asthma who had different tobacco smoke exposure histories is unlikely to have been large enough to produce substantial bias because participation rates in each classroom were high. Asthma was ascertained by parental report of physician-diagnosed asthma. Misclassification of asthma status or age at diagnosis may have arisen from imperfect parental recall of events, variation in access to medical care, differences in medical practice, or delay in diagnosis. More than 84% of participants had medical insurance suggesting that any bias from differential access to care is likely to be small. We lack data to assess the magnitude of misclassification of asthma status from parental recall or medical practice; however, it is unlikely that our findings are the result of a spurious association that arose from consistent variations in medical practice across the 12 communities or from parents who smoked overreporting asthma in their children. Retrospective recall of tobacco smoking is likely to have produced some misclassification of exposure. Exposure to tobacco smoke was assessed using questionnaire responses about household sources and was not validated by objective measurements such as cotinine levels. However, the validity of exposure estimates based on questionnaire responses have been investigated and found to provide reasonably valid estimates of exposure (4, 7, 9). Some studies using cotinine for exposure assessment suggest that the dose of ETS from household sources decreases with age, but the metabolism of nicotine and the excretion of its metabolites relative to creatinine change with age, making interpretation of the studies using cotinine for exposure assessment difficult (4). If this change in dose does occur, it would introduce more misclassification into our study than in studies of younger children, and result in a larger bias toward no effect for ETS exposure. Although smoking is associated with an increasing social stigma, it seems unlikely that mothers would admit to smoking during pregnancy, but falsely deny smoking in the postnatal period. However, parents of children with asthma may have underreported tobacco smoke exposure and biased our results toward the null. We were unable to investigate any dose-response relationships for *in utero* exposure because we lacked information on the intensity or duration of exposure. However, pregnant women do not generally smoke as heavily as nonpregnant women, averaging 10 cigarettes per day (15). We also lack information on a number of potential confounders such as maternal nutritional status and intake of alcohol or other potentially toxic substances during pregnancy.

As to the public health significance of our findings, we estimate that elimination of *in utero* exposure to maternal smoking would prevent 5 to 15% of asthma cases in children (35). Reducing the burden of chronic respiratory diseases may require a stronger focus on the reduction of smoking among women during their childbearing years.

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