Maternal and Grandmaternal Smoking Patterns Are Associated With Early Childhood Asthma

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Maternal and Grandmaternal Smoking Patterns Are Associated With Early Childhood Asthma*

Yu-Fen Li, PhD, MPH; Bryan Langholz, PhD; Muhammad T. Salam, MBBS, MS; and Frank D. Gilliland, MD, PhD

Objective: **To investigate the associations of maternal and grandmaternal smoking before, during, and after pregnancy with childhood asthma.**
Design, setting, and participants: **We conducted a case-control study nested within the Children's Health Study in southern California. The case patients consisted of 338 children with asthma that had been diagnosed in the first 5 years of life, and 570 control subjects were countermatched on *in utero* exposure to maternal smoking within grade, sex, and community of residence.**
Measurements: **Detailed maternal and household smoking histories and other asthma risk factor information was obtained by telephone interview.**
Results: **The participation rates were 72.3% and 82.5%, respectively, for control subjects and case patients. *In utero* exposure to maternal smoking was associated with increased risk for asthma diagnosed in the first 5 years of life (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.0 to 2.3), and for persistent asthma (OR, 1.5; 95% CI, 1.0 to 2.3). The associations did not differ in children with early transient asthma compared to those with early persistent asthma. Relative to never-smokers, children whose mothers smoked throughout the pregnancy had an elevated risk of asthma in the first 5 years of life (OR, 1.6; 95% CI, 1.0 to 2.6). Children of mothers who quit smoking prior to the pregnancy showed no increased risk (OR, 0.9; 95% CI, 0.5 to 1.5). We were unable to assess the association of smoking cessation during pregnancy because very few mothers were reported to have done so (15%). Asthma risk did not increase in a monotonic pattern with smoking intensity during pregnancy. Postnatal secondhand smoke exposure was not independently associated with asthma. Grandmaternal smoking during the mother's fetal period was associated with increased asthma risk in her grandchildren (OR, 2.1; 95% CI, 1.4 to 3.2).**
Conclusions: **Maternal and grandmaternal smoking during pregnancy may increase the risk of childhood asthma.** ***(CHEST 2005; 127:1232–1241)***

Key words: asthma; *in utero* exposure to maternal smoking; smoking cessation; transgenerational association

Abbreviations: CHS = Children's Health Study; CI = confidence interval; EARS = Early Asthma Risk Factor Study; OR = odds ratio; SHS = secondhand smoke

Asthma has emerged as a major worldwide public health problem.[1–6] The number of people with asthma in the United States has more than doubled in the last 20 years, with most notable increases occurring among preschool children.[6] Based on the 2001 National Health Interview Survey,[7] it was estimated that 113.4 per 1,000 Americans had been diagnosed with asthma by a physician in their lifetime and that, among children ages 5 to 17 years, the lifetime prevalence was 144.2 per 1,000 individuals. The economic costs associated with asthma were estimated to be $12.7 billion in the United States during 1998.[6] The asthma burden poses a serious public health challenge that is difficult to address because modifiable targets for intervention have yet to be firmly established.

Tobacco smoke exposure is an important determinant of childhood asthma occurrence.[8–18] Second-

*From the University of Southern California, Keck School of Medicine, Department of Preventive Medicine, Los Angeles, CA.
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Correspondence to: Frank Gilliland, MD, PhD, Department of Preventive Medicine, USC Keck School of Medicine, 1540 Alcazar St, CHP 236, Los Angeles, CA 90033; e-mail: gillilan@usc.edu

hand smoke (SHS) is causally related to exacerbations of asthma and increased school absenteeism.[9] Accumulating evidence[8,10–18] indicates that maternal smoking is associated with new-onset asthma, which may be mediated, in part, by *in utero* exposure to maternal smoking. In previous publications from the Children's Health Study (CHS),[14,17,18] we reported that *in utero* exposure to maternal smoking was independently associated with an increased risk for childhood asthma.

In our previous reports on the CHS,[14,17,18] we were unable to investigate the associations of smoking before pregnancy, smoking cessation, or smoking intensity during pregnancy because we lacked detailed information on smoking habits. To further investigate the associations of *in utero* tobacco exposure, we conducted a case-control study nested within the CHS cohort to collect more detailed smoking histories. The central question to be addressed in this study was whether *in utero* tobacco exposure affects asthma occurrence, and, if so, to assess the role of smoking patterns, cessation, and intensity on asthma occurrence.

In the nested case-control study, we collected more detailed information about the maternal prepregnancy tobacco smoke exposure for each child as well as about the timing, intensity, and cessation of smoking during the index pregnancy. We also examined the role of SHS exposure in the first year of life and the transgenerational associations of smoking by the maternal grandmother during the mother's fetal period with asthma risk for children.

Materials and Methods

Cohort

The Southern California CHS has been described in detail previously.[19,20] The relevant cohort for this nested case-control study (Early Asthma Risk Factor Study [EARS]) was a subset of 4,082 children who were recruited from public school classrooms (grades 4, 7, and 10) in 12 southern California communities in 1993. At study entry, the parents or guardians of each participating student provided written informed consent and completed a self-administered questionnaire, which included detailed information about demographic and household characteristics as well as information regarding the child's respiratory health and factors potentially related to respiratory health. In particular, we collected information about the diagnosis of asthma by a physician and its activity during childhood as well as maternal smoking during pregnancy (*in utero* exposure) was assessed as a yes/no question.

Case Definition

In this nested case-control study, we defined case patients as children in whom asthma was diagnosed by a physician in the first 5 years of life (n = 338) based on the answer in the CHS questionnaire that was administered at cohort entry. We also categorized asthma cases into the following three subtypes based on the child's age at asthma onset and the persistency of the disease: early-onset persistent asthma; early-onset transient asthma; and late-onset asthma. We classified the age of onset into early (in the first 3 years of life) and late (after age 3 years). An asthma case patient was assigned as having persistent asthma if the child had the following: (1) one or more episodes of asthma in the 12 months prior to study entry; (2) any wheezing in the 12 months prior to study entry or since starting the first grade; or (3) medication use for asthma in the 12 months prior to study entry or since starting first grade. Thus, the basic cohort data consisted of CHS enrollees with the outcome of asthma diagnosis during the first 5 years of life.

EARS: Countermatched Control Subjects

We conducted this nested study to collect additional detailed information on *in utero* exposure to maternal smoking. The basic idea behind countermatching is to maximize the efficiency of the nested case-control study by using the crude exposure information that is available for the entire cohort in the sampling of control subjects.[21] In this study, sampling for the nested case-control study was based on *in utero* exposure status (exposed vs unexposed) of case patients and control subjects that was available for the entire cohort.

This novel sampling design can best be understood in relationship to the standard random sampling used in most nested case-control studies. Consider a 1:1 matched, nested case-control study in which control subjects are randomly sampled within each risk set. Case patients and control subjects who are concordant on the exposure collected in the new study contribute no information to the odds ratio (OR) estimation. In a 1:1 countermatched, nested case-control study, the less detailed exposure information (a surrogate) available for the entire cohort is used to select control subjects, with one control subject selected from the risk set that has the "opposite" exposure status as the case based on the surrogate exposure data. Although sampling using exposure information may appear to be a biased approach, unbiased estimates for ORs are calculated by incorporating the sampling weights into the conditional logistic regression likelihood.[22]

Figure 1 illustrates a general form of countermatching, where x is an exposure surrogate that is available for the entire cohort of N subjects with N_1 exposed (including D_1 exposed case patients) and N_0 unexposed (including D_0 unexposed case patients). After defining the number of subjects (m_1D exposed and m_0D unexposed subjects in the sample) to be sampled from the exposed and unexposed cohort members, the sampling probability (weight) of countermatching is $m_1D - D_1$ exposed and $m_0D - D_0$ unexposed control subjects sampled from the cohort consisting of $N_1 - D_1$ exposed and $N_0 - D_0$ unexposed control subjects.

Countermatching on an exposure correlate has been shown to be more efficient than the random sampling of control subjects for assessing exposure-related relative risks.[21] In a 1:1 case-control study, countermatching can be at most twice more efficient than a simple random-sampling method performed under the null hypothesis (Fig 2), because the asymptotic relative efficiency depends on the sensitivity and specificity of the countermatching variable for the exposure of interest. Power calculations indicated that an *in utero*, countermatched design would be advantageous in the EARS.

In the EARS, we used a more general form of countermatching within the strata of confounding covariates to control for confounding as well as to allow for the potential loss of control subjects because they could not be located. Asthma-free control subjects (n = 570) were countermatched to the *in utero* exposure

a. Cohort: Case-control status by exposure surrogate X

	Counter-matching variable X: Exposed	Unexposed	Total
Cases	D_1	D_0	D
Controls	N_1-D_1	N_0-D_0	N-D
Total	N_1	N_0	N

b. Counter-matched sample: Case-control status by exposure surrogate X

	Counter-matching variable X: Exposed	Unexposed	Total
Cases	D_1	D_0	D
Controls	m_1D-D_1	m_0D-D_0	$D(m_1+m_0-1)$
Total	m_1D	m_0D	$D(m_1+m_0)$

FIGURE 1. Countermatched sampling scheme on exposure surrogate x from a cohort of size N (N_1 exposed and N_0 unexposed) consisting of D case patients (D_1 exposed cases and D_0 unexposed cases). The sample allocations are m_1D-exposed and m_0D-unexposed subjects in the sample including case patients, where m_1D and m_0D are predetermined multiples of total number of cases. The sampling weight of countermatching is

$$\left(\frac{N_1 - D_1}{m_1D - D_1}\right)^{-1}\left(\frac{N_0 - D_0}{m_0D - D_0}\right)^{-1},$$

as m_1D-D_1 exposed control subjects and m_0D-D_0 unexposed control subjects are sampled from the cohort with N_1-D_1 exposed control subjects and N_0-D_0 unexposed control subjects.

status of case patients within the strata of potential confounders including grade, sex, and community of residence using information that was available on the CHS questionnaire. Our cohort had 96 subgroups defined by potential confounding variables (4 grade groups, 2 sexes, and 12 communities). Within each subgroup, the numbers of subjects (*ie*, case patients and control subjects) within each sampling stratum (*ie*, *in utero* exposure status) were as follows: (1) a multiple of the total number of case patients within the subgroup; (2) chosen to yield approximately equal numbers of exposed and unexposed subjects; and (3) increased to account for anticipated nonparticipation.

Covariates

Detailed maternal and household smoking histories, and other asthma risk factor information was obtained by telephone interview with the biological mother. If the mother was not available, the child's father (3.2%), stepmother (2.3%), or guardian (2.2%) was interviewed.

In Utero *Exposure to Maternal Smoking*

Information on smoking status (yes/no) and amount smoked (*ie*, < 0.5 packs, 0.5 packs, 1 pack, 1.5 packs, 2 packs, and > 2 packs) before and during each trimester of pregnancy was collected. If a mother reported that she had smoked during pregnancy, her child was classified as having been exposed to maternal smoking during pregnancy. Using both the CHS baseline questionnaire response and the EARS interview, we categorized mothers into nonsmoker, ex-smoker, quitter during the first trimester, continuous smoker throughout pregnancy, and a mixed group with various other less common patterns of smoking. A mother was defined as a nonsmoker if she had smoked < 100 cigarettes in her lifetime. Ex-smokers were mothers who had smoked at least 100 cigarettes in their lifetime and who quit smoking before they became pregnant with the participating child, including 37 respondents who answered "yes" to smoking during pregnancy in the CHS questionnaire but answered "prior to the pregnancy" in the later EARS interview. The 46 respondents whose answer was "yes" in the CHS entry questionnaire and "no" in the EARS interview were included in a category "other smoking patterns" along with another 15 mothers who reported a less common smoking pattern (*eg*, 4 mothers reported quitting smoking during the second trimester, 2 mothers stopped smoking during the first trimester but started smoking again in the third trimester, 6 mothers smoked during the second and/or third trimester only, and 3 mothers did not specify the pattern). Finally, there were six CHS baseline nonsmokers who reported smoking at the EARS interview. These were included into the smoker category based on the EARS interview response. Because of small numbers, we could not assess the association of quitting during the second trimester and other less common smoking patterns. The smoking intensity for continuous smokers was defined by the most common amount smoked during the three trimesters. (We note that only a small proportion of continuous smokers reported changing their smoking intensity during pregnancy.) Similarly, the smoking intensity for ex-smokers and those who quit smoking during the first trimester was defined by the number of packs of cigarettes smoked during the corresponding period. After reviewing the distribution (< 0.5 packs per day,

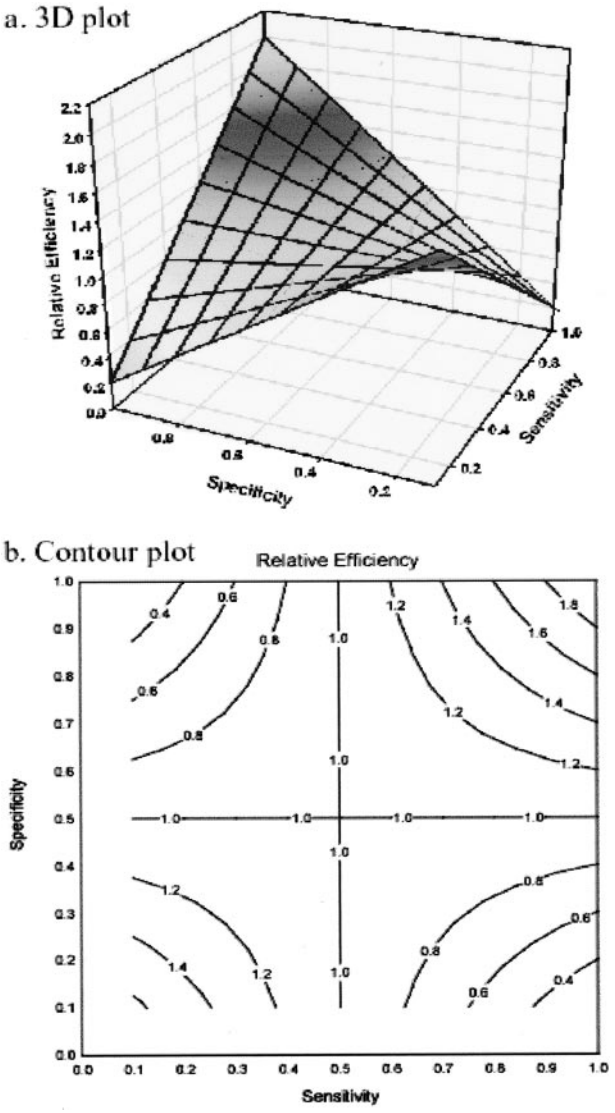

FIGURE 2. The relative efficiencies of 1:1 countermatching compared to 1:1 random sampling with different sensitivity and specificity of the countermatching exposure variable available for the entire cohort and the exposure of interest collected in the nested study. *Top*, *a*: a three-dimensional plot with sensitivity and specificity shown on the x-axis and y-axis, respectively, and relative efficiency shown on the z-axis. *Bottom*, *b*: the contour plot with relative efficiency shown as contour lines.

45.5%; 0.5 packs per day, 21.5%; 1 packs per day, 25.8%; 1.5 packs per day, 2.2%; 2 packs per day, 2.0%; and $>$ 2 packs per day, 3.0%), we categorized the smoking intensity as $<$ 0.5 packs per day or $\geq$ 0.5 packs per day.

SHS Exposure

The SHS exposure was categorized using information about the relationship of the household smoker to the child and the number of household smokers (including those who smoked cigarettes, cigars, or pipes) inside the house on a daily basis during the age intervals birth to 12 months, 13 months to 5 years, and 6 to 10 years. Household smoking patterns were generally constant across the time of interest, so for the purpose of statistical analyses we defined any SHS exposure by the number of persons who smoked inside the home on a daily basis from the child's birth to 1 year of age. We chose the first year because it best characterized exposure before the onset of asthma, as SHS exposure may change after the diagnosis of asthma. Few children (3%) were first exposed after the first year of life.

Transgenerational In Utero *Exposure to Maternal Smoking*

In addition to children's exposure to maternal smoking during pregnancy, we collected information about the smoking habits of the maternal grandmother of each participating child. We defined the term *transgenerational exposure to maternal smoking during pregnancy* using the exposure of the child's mother based on the answer to the question, "Did your mother smoke when she was pregnant with you?" when we interviewed the biological mothers. We also interviewed a subset of maternal grandmothers to assess the agreement with the mother's reports of smoking histories for the grandmother.

Family History of Asthma

Data on the asthma status of parents and siblings and the age at which they had received a diagnosis of asthma were collected. The number of siblings and the family history of asthma among the first-degree relatives (*ie*, parents and elder siblings) were defined at the time when the mother had been pregnant with the participating child.

Statistical Analysis

The ORs and 95% confidence intervals (CIs) of physician-diagnosed asthma were computed using appropriate conditional likelihood logistic regression models given the countermatched sampling method described by Langholz and Goldstein.[22] In addition to the analyses using asthma diagnosis in the first 5 years of life, we also investigated associations for younger age at asthma diagnosis (in the first 3 years of life), and categories of early persistent and transient asthma. The ORs for the association of smoking with, and statistical tests of homogeneity across, early-onset and late-onset childhood asthma, as well as with early-onset persistent asthma, and early-onset transient asthma were computed using a conditional likelihood method for polytomous logistic regression models. Subjects who refused to participate in the EARS or were unavailable for follow-up were considered in the likelihood method by appropriately adjusting the weights under the assumption that participation was based on independent Bernoulli trials.[22] Subjects with missing covariate information were included in the model using missing indicators.[23]

Grade, sex, and community of residence were controlled as strata in the conditional logistic analyses. We further adjusted for ethnicity and gestational age as potential confounding variables. If estimates of the associations changed by at least 10% when a covariate was included in the base model, the covariate was included in the final model. Effect modification was assessed by likelihood ratio test comparing nested models with and without interaction terms. Data were analyzed using a statistical software package (SAS, version 8.2; SAS Institute; Cary, NC), and all tests (p values) were two-sided with $\alpha = 0.05$ as the significance level.

RESULTS

Descriptive Statistics and Crude Risk

Telephone interviews were completed for 691 of the 908 case patients and sampled control subjects.

The participation rates were 72.3% and 82.5%, respectively, for control subjects and case patients. Parents having higher income (≥ $30,000: participating subjects, 64.1%; nonparticipating subjects, 49.8%) and education (some college or more: participating subjects, 57.0%; nonparticipating subjects, 39.1%) at cohort entry were more likely to participate in this study (data not shown). Among the 279 children with asthma, 76.3% (n = 213) received diagnoses in the first 3 years of life, and 81% (n = 226) had persistent asthma.

We assessed the matched univariate ORs that were associated with sociodemographic and other factors (Table 1). Prematurity was associated with increased risk of asthma compared to full-term birth for babies born < 4 weeks early (OR, 1.8; 95% CI, 0.9 to 3.6) and ≥ 4 weeks early (OR, 2.6; 95% CI, 1.2 to 5.8). Family history of asthma was also a risk factor for asthma (ORs: mother with asthma, 2.3; father with asthma, 2.5; siblings with asthma, 1.9). Children were at a 2.6-fold higher risk of asthma (95% CI, 1.8 to 3.8) if any of their first-degree relatives had asthma. Asthma risk was reduced with an increasing number of older siblings in the family (OR, 0.8 per sibling; p = 0.04).

In Utero *Exposure to Maternal Smoking and Postnatal SHS Exposure*

Most pregnant smokers continued smoking throughout pregnancy. The smoking rates were 23% before pregnancy, 19% in the first trimester, 13% in the second trimester, and 12% in the third trimester. About 20% of ever-smokers quit smoking before pregnancy. Among the women who smoked at the onset of pregnancy, only 15% stopped smoking during the first trimester (Table 2). Postnatal SHS exposure occurred in approximately 30% of our study population (exposed to one smoker in the household, 16.8%; exposed to two smokers in the household, 9.9%; and exposed to three and more smokers in the household, 3%). Among mothers with "others smoking in the house," 95% of mothers who smoked during pregnancy continued after birth. Among those without "others smoking in the house," 76% of mothers who smoked during pregnancy continued smoking after birth. Mothers of children with asthma were more likely to have been exposed to *in utero* maternal smoking during their fetal period compared to mothers of nonasthmatic children (34% vs 23%, respectively).

Children with any *in utero* exposure to maternal smoking were at increased risk of asthma (adjusted OR, 1.5; 95% CI, 1.0 to 2.3; first subsection of Table 2). Variation in risk by the detailed smoking patterns defined in the "Materials and Methods" section is

Table 1—*Selected Characteristics by Case Patients and Control Subjects in the EARS

Characteristics	CM		Univariate	
	Case Patients	Control Subjects	OR†	95% CI
Gender				
Girls	102	178	Matching variable	
Boys	177	234		
Age at study entry, yr				
8–9	117	154	Matching variable	
10–11	73	103		
12–13	44	81		
14–18	45	74		
Ethnicity				
Non-Hispanic whites	164	265	1.0	
Hispanics	70	89	1.0	0.6–1.6
African-American	18	22	2.1	0.9–4.8
Others	26	32	1.0	0.5–2.0
Unknown	1	4		
Parental education				
< 12 grades	19	54	1.0	
12 grades	63	101	1.7	0.8–3.5
Some college	137	195	1.8	0.9–3.5
College	24	22	1.5	0.6–3.7
Some graduate	33	32	1.8	0.8–4.2
Unknown	3	8		
Annual family income, US dollars				
< $7,500	17	28	1.0	
$7,500–$14,999	20	58	0.6	0.3–1.7
$15,000–$29,999	40	59	1.2	0.5–2.8
$30,000–$49,999	58	98	1.0	0.4–2.3
$50,000–$99,999	99	102	1.4	0.6–3.2
≥ $100,000	17	20	0.5	0.2–1.5
Unknown	28	47		
Gestational age				
Full term	227	363	1.0	
< 4 wk early	24	28	1.8	0.9–3.6
≥ 4 wk early	26	13	2.6	1.2–5.8
Unknown	2	8		
Family history of asthma‡				
Family members				
Mother with asthma	73	60	2.3	1.4–3.7
Father with asthma	38	22	2.5	1.3–4.9
Sibling with asthma	112	114	1.9	1.3–2.9
Any first-degree relative with asthma	161	158	2.6	1.8–3.8
Number of older siblings				
None	136	191	1.0	
One	94	127	1.0	0.7–1.6
Two	31	62	0.6	0.3–1.0
Three or more	18	32	0.6	0.3–1.2
Trend			0.8§	

*CM = countermatched.
†Models are only adjusted for matching factors.
‡Defined at the time the mother was pregnant with the participating child.
§p = 0.04.

Table 2—*Tobacco Smoke Exposure Patterns Among Participants, OR for Asthma and 95% CI

Smoke Exposure Categories	CM		Cohort Control Subjects	Unadjusted		Adjusted‡	
	Case Patients	Control Subjects		OR	(95% CI)	OR	(95% CI)
Any *in utero* exposure to maternal smoking							
No	227	210	2,254	1.0		1.0	
Yes	52	202	387	1.4	(1.0–2.0)	1.5	(1.0–2.3)
Mother's smoking pattern							
Never smoked	160	106	1,597	1.0		1.0	
Quit before pregnant	55	67	533	0.9	(0.5–1.4)	0.9	(0.5–1.5)
Stopped during first trimester	7	30	56	1.3	(0.5–3.1)	1.2	(0.5–2.9)
Smoked throughout pregnancy	43	162	311	1.4	(1.0–2.1)	1.6	(1.0–2.6)
Other	14	47	145	1.3	(0.6–2.5)	1.3	(0.6–2.6)
Mother's smoking intensity†							
Never smoked	160	106	1,597	1.0		1.0	
Quit before pregnant							
< 0.5 pack/d	23	29	288	0.7	(0.4–1.4)	0.7	(0.3–1.4)
≥ 0.5 pack/d	32	37	240	1.2	(0.6–2.2)	1.3	(0.7–2.4)
Stopped during first trimester							
< 0.5 pack/d	3	9	11	2.0	(0.5–8.1)	1.5	(0.3–6.8)
≥ 0.5 pack/d	4	21	45	1.0	(0.3–3.1)	1.1	(0.3–3.4)
Smoked throughout pregnancy							
< 0.5 pack/d	19	49	111	1.9	(1.0–3.5)	2.2	(1.1–4.3)
≥ 0.5 pack/d	24	108	191	1.3	(0.8–2.1)	1.3	(0.7–2.5)
Any SHS exposure							
No§	183	187	1,865	1.0		1.0	
Yes	96	223	771	1.3	(0.9–1.8)	1.2	(0.8–1.7)
One smoker	54	101	436	1.2	(0.7–1.8)	1.0	(0.6–1.7)
Two and more smokers	42	122	335	1.4	(0.9–2.2)	1.3	(0.8–2.1)
Maternal *in utero* smoke exposure							
No§	141	206	1,505	1.0		1.0	
Yes	94	129	596	2.1	(1.4–3.1)	2.1	(1.4–3.2)

*See legend of Table 1 for abbreviation not used in the text.
†Using sampling probability to estimate the numbers in the full cohort.
‡Models are adjusted for race/ethnicity, gestational age, and SHS exposure, except for the subsection "Any SHS exposure."
§Totals are not equal due to missing values.

given in the second subsection of Table 2. The children of mothers who continued smoking throughout pregnancy were at elevated risk compared to never-smokers (adjusted OR, 1.6; 95% CI, 1.0 to 2.6). The children of mothers who quit smoking prior to pregnancy appear to have an asthma risk that is similar to that of the children of never-smoking mothers (adjusted OR, 0.9; 95% CI, 0.5 to 1.5) and is lower than that of children with mothers who smoked continuously (adjusted OR, 0.6; 95% CI, 0.3 to 1.0). In this study, we could not determine whether the asthma risk of children with mothers who quit smoking during the first trimester was greater than that for children whose mothers never smoked (adjusted OR; 1.2, 95% CI, 0.5 to 2.9) or was less than that for children whose mothers were continuous smokers (adjusted OR, 0.8; 95% CI, 0.3 to 2.1) because of the small number of such subjects.

We did not find evidence of an increasing trend in asthma risk with heavier maternal smoking exposure (third subsection of Table 2). In particular, for children with mothers who smoked continuously throughout pregnancy, the adjusted ORs for asthma diagnosis were 2.2 (95% CI, 1.1 to 4.3) for smoking < 0.5 packs per day and 1.3 (95% CI, 0.7 to 2.5) for those smoking ≥ 0.5 packs per day. As shown in the fourth subsection of Table 2, postnatal SHS exposure was only weakly and nonsignificantly associated with asthma occurrence (having any household smokers: adjusted OR, 1.2; 95% CI, 0.8 to 1.7; having one household smoker: adjusted OR, 1.0; 95% CI, 0.6 to 1.7; having two or more household smokers: adjusted OR, 1.3; 95% CI, 0.8 to 2.1), and the association was further reduced after adjusting for *in utero* exposure to maternal smoking (*eg*, adjusted OR, 0.9; 95% CI, 0.6 to 1.4 for having any household smokers).

In Utero *Exposure to Maternal Smoking and Family History of Asthma*

In utero exposure to maternal smoking and family history of asthma appeared to be independent risk factors for asthma (Table 3). The association of *in utero* exposure to maternal smoking was about the

Table 3—*Multivariable Analysis of the Joint Associations of* In Utero *Exposure to Maternal Smoking and Family History of Asthma With Childhood Asthma, OR, and 95% CI

In Utero Exposure	Family History	No.†	OR	95% CI
Unexposed	No	88/90	1.0	
	Yes	165/26	2.6	1.4–3.8
Exposed	No	56/116	1.3	0.7–2.3
	Yes	97/43	3.6	2.2–6.3

*Models are adjusted for race/ethnicity, gestational age, and SHS exposure.
†Number of countermatched control subjects/case patients.

same in children with a family history of asthma (as indicated by the ratio of ORs, 3.6/2.6 = 1.4) and without a family history of asthma (OR, 1.3; 95% CI, 0.7 to 2.3).

Transgenerational Associations of In Utero *Exposure to Maternal Smoking*

We found a transgenerational association of smoking during pregnancy with childhood asthma risk. A child's risk of asthma was increased if the child's maternal grandmother had smoked during the fetal period of the child's mother (Table 2, fifth subsection). Consistent with a direct effect of *in utero* exposure, we also noted some evidence for an increased risk of asthma in the mother if she had been exposed to maternal smoking during her fetal period (OR, 1.3; 95% CI, 0.9 to 2.0). To further investigate the transgenerational association of *in utero* exposure to maternal smoking, we examined the joint associations of *in utero* exposure to maternal smoking in both the mother and her child (Table 4). When the child's mother had experienced *in utero* exposure to maternal smoking, the child had an increased risk of developing asthma, even if the child had not been exposed to maternal smoking during pregnancy (OR, 1.8; 95% CI, 1.0 to 3.3). If the child and the mother had both been exposed to maternal smoking during pregnancy, compared to no *in utero* exposure to maternal smoking for both, the child was at a higher risk of having asthma (OR, 2.6; 95% CI, 1.6 to 4.5).

Table 4—*Multivariable Analysis of the Joint Associations of Maternal and Child's* In Utero *Exposure to Maternal Smoking With Child's Asthma Risk, OR, and 95% CI

In Utero Exposure to Maternal Smoking				
Mother	Child	No.†	OR	95% CI
Unexposed	Unexposed	118/151	1.0	
	Exposed	27/58	1.3	0.8–2.1
Exposed	Unexposed	165/34	1.8	1.0–3.3
	Exposed	102/36	2.6	1.6–4.5

*Models are adjusted for race/ethnicity, gestational age, and SHS exposure.
†Number of countermatched control subjects/case patients.

Age of Asthma Diagnosis and Asthma Persistence

We further investigated the variation in the associations of *in utero* exposure to maternal smoking by age of asthma diagnosis and asthma persistence. The association of *in utero* exposure to maternal smoking did not vary significantly between children with early-onset transient asthma (OR, 2.0; 95% CI, 0.9 to 4.3) and persistent asthma (OR, 1.5; 95% CI, 1.0 to 2.3). The associations of *in utero* tobacco smoke exposure with the asthma risk for children were not confounded by SHS exposure, family history of asthma, insurance status, parental education, or household income.

Discussion

In an earlier article from the CHS cohort study,[14] we reported an independent association of *in utero* tobacco smoke exposure with asthma risk that appeared to vary by age at asthma diagnosis. We confirmed our previous findings in the present nested case-control study and have shown that *in utero* exposure to maternal smoking was associated with an increased risk of childhood asthma, especially early-onset asthma in the first 3 years of life. There was no statistically significant difference in the association of *in utero* exposure to maternal smoking with transient and persistent asthma. Our finding that *in utero* exposure to maternal smoking increases the risk for asthma is consistent with the evolving evidence that *in utero* exposure to maternal smoking increases asthma risk, exacerbates preexisting asthma, and adversely affects postnatal lung function.[24–30] Interestingly, we also observed a transgenerational association of smoking during pregnancy with the child's asthma risk. The possibility of a transgenerational effect of *in utero* exposure on asthma risk suggests a new etiologic pathway and indicates that the burden from maternal smoking may be underestimated. However, we did not observe a trend of increasing asthma risk with smoking intensity during pregnancy. In our study, smoking cessation during pregnancy was uncommon. Thus, it was not possible to determine the particular time during pregnancy at which *in utero* exposure results in increased risk.

The transgenerational association of *in utero* smoke exposure observed in this study is, to our knowledge, a novel observation. We found that the

risk of asthma was elevated in unexposed children whose asthma-free mothers had been exposed to tobacco smoke *in utero*, suggesting that the associations were not entirely mediated by maternal asthma and maternal smoking during pregnancy. Although we are aware of no published report on this issue, we speculate that one mechanism is the inheritance of asthma susceptibility through epigenetic mechanisms.[31–36] It is possible that by altering DNA methylation patterns in the fetal oocytes, tobacco-derived products may affect both immune function and xenobiotic detoxification mechanisms in the offspring, resulting in an increased susceptibility to asthma affecting one generation to the next. Further studies are needed to investigate this potentially important issue in greater detail.

We did not observe an increasing risk of asthma with an increasing intensity of maternal smoking, which has also been reported by Lux et al[37] in a longitudinal study on wheeze among 8,561 infants who were born in the United Kingdom and had been followed up to 30 months of age. The result suggests that the association with maternal smoking during pregnancy may not be consistent with a linear dose-response relationship. The lack of association between maternal smoking intensity and childhood asthma in the offspring may have been due to the limited sample size of the study and the distribution of exposure. However, the lack of a dose-response relationship could have resulted from the underreporting of smoking by heavy smokers. Since most of the interviews were conducted with biological mothers (92.3%), the misclassification of smoking pattern in the study was reduced. Although self-reported smoking and serum cotinine concentrations are highly correlated,[38] the self-reported smoking histories in our study were collected retrospectively and could not be measured by bioassay. The prevalence of smoking among pregnant women in the EARS was similar to that cited in previous reports. For example, in a large population-based survey from 33 states conducted from 1987 to 1996, Ebrahim et al[39] found that the prevalence of smoking among pregnant women was 16.3% in 1987 and the quitting rate among pregnant women changed little (from 26.3 to 25.2%) during that 10-year period. The smoking percentage among pregnant women in the EARS (first trimester, 19%; second trimester, 13%; third trimester, 12%) was slightly higher, and the smoking cessation rate during pregnancy (15%) in the EARS was lower. The differences are likely to be a result of the fact that children in the EARS had been born between 1975 and 1986, and the maternal smoking prevalence during this period was higher than that in later years.[40] The smoking cessation rate dramatically decreased for few years after 1978 when a "safe" cigarette became a media event.[41] Some participating mothers' responses regarding children's *in utero* tobacco smoke exposure changed between the CHS and the later EARS interviews (conducted up to 7 years apart). To assess the potential effects of the changes in responses, we fitted models using CHS baseline responses and EARS interview responses, and found little difference in the ORs for *in utero* exposure.

A differential misclassification of SHS exposure may occur in case-control studies. We do not believe that bias from the differential misclassification of exposure to tobacco smoke explains our findings. First, to assess the validity of smoking information, we examined the well-established relationship of birth weight and maternal smoking intensity during pregnancy[42] in the EARS participants using birth certificate data on birth weight. We found the anticipated trend in the number of cigarettes smoked during pregnancy with lower birth weight (results not shown). This suggests that the self-report of smoking intensity in our study is likely to be correlated with exposure and that the nonmonotonic dose response is probably not explained by a differential misclassification of smoking amount. We also note that maternal smoking during pregnancy is not widely appreciated as an asthma risk factor. It is not likely that recall bias would arise from prior knowledge about the associations of maternal smoking during pregnancy on asthma. It is more likely that the mothers of children with asthma would deny smoking due to clinical interventions to reduce the effects of SHS on asthma symptoms. This type of misclassification would bias our findings toward the null and would not account for our findings regarding *in utero* exposure. It also appears unlikely that recall bias explains the transgenerational association with grandmaternal smoking because the child's asthma status is unlikely to affect the mother's recall of her mother's smoking habits. To assess the potential for recall bias, we contacted a subset of grandmothers ($n = 26$) directly and found no evidence of systematic misclassification of grandmaternal smoking status (all smokers; 85% confirmed they had not smoked when they were pregnant with the mother of the index child).

We did not observe an independent association of SHS exposure on asthma risk in this study. Substantial evidence indicates that SHS is causally associated with asthma exacerbations.[8,43,44] The association of SHS with asthma risk is less clear. In a metaanalysis conducted by Strachan and Cook,[8] maternal smoking was associated with asthma, and the associations with paternal smoking were less clear. Although maternal smoking in the postnatal period is highly correlated with smoking during pregnancy, the metaanalysis did

not consider the associations with *in utero* exposure, which could explain the association with postnatal maternal smoking. While a growing body of evidence supports an independent role for *in utero* exposure to maternal smoking in onset of asthma, the association of SHS exposure early in life on asthma risk remains uncertain, especially in light of the potential for bias from SHS exposure misclassification.

This nested case-control study was population-based and used an innovative sampling design to efficiently investigate the associations of *in utero* exposure to maternal smoking with asthma occurrence. Although the cohort was large, we found that we could not draw any conclusions about smoking cessation because of the small number of mothers who quit smoking during pregnancy. Because of our sampling of asthma status, we were able to study subsets of asthma such as early-onset persistent asthma, but we could not study categories of wheezing. Our study used early-life prevalent cases at study entry and was subject to the limitations of the cross-sectional studies discussed in Gilliland et al.[14] The diagnosis of asthma in young children is especially difficult (variable), especially in those who are < 3 years of age. However, a variation in asthma diagnosis would likely result in a bias toward the null. Furthermore, we found that asthma that was reported to be transient or persistent had patterns of risk that were similar to the exposures we investigated.

The nonparticipation of subjects in studies is another potential source of bias. Because this study was a nested case-control study, we had some (limited) exposure and outcome information for the entire study base. We used this information to assess the potential for differential nonparticipation to bias our estimates. We found that the associations of *in utero* exposure were essentially the same when we used the binary smoking data or asthma self-reports for the whole cohort and the newly collected data for the EARS participants, suggesting that nonparticipation did not explain our results.

In summary, *in utero* exposure to maternal smoking is an independent risk factor for childhood asthma. Maternal smoking cessation before pregnancy can greatly reduce the risk of childhood asthma, but we could not assess how early in pregnancy the mother must quit to avoid the additional asthma risk. As a public health matter, a woman who smokes should be encouraged to quit smoking, and it is especially important that it occur as soon as she is known to be pregnant. The transgenerational association of grandmaternal smoking during pregnancy with asthma risk is a novel finding that requires confirmation.

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