Regular Smoking and Asthma Incidence in Adolescents

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Rationale: Although involuntary exposure to maternal smoking during the *in utero* period and to secondhand smoke are associated with occurrence of childhood asthma, few studies have investigated the role of active cigarette smoking on asthma onset during adolescence.

Objectives: To determine whether regular smoking is associated with the new onset of asthma during adolescence.

Methods: We conducted a prospective cohort study among 2,609 children with no lifetime history of asthma or wheezing who were recruited from fourth- and seventh-grade classrooms and followed annually in schools in 12 southern California communities. Regular smoking was defined as smoking at least seven cigarettes per day on average over the week before and 300 cigarettes in the year before each annual interview. Incident asthma was defined using new cases of physician-diagnosed asthma.

Measurements and Main Results: Regular smoking was associated with increased risk of new-onset asthma. Children who reported smoking 300 or more cigarettes per year had a relative risk (RR) of 3.9 (95% confidence interval [95% CI], 1.7–8.5) for new-onset asthma compared with nonsmokers. The increased risk from regular smoking was greater in nonallergic than in allergic children. Regular smokers who were exposed to maternal smoking during gestation had the largest risk from active smoking (RR, 8.8; 95% CI, 3.2–24.0). **Conclusions:** Regular smoking increased risk for asthma among adolescents, especially for nonallergic adolescents and those exposed to maternal smoking during the *in utero* period.

Keywords: asthma; epidemiology; smoking

Habitual smoking of tobacco products causes a wide spectrum of adverse impacts on health, including malignant and nonmalignant respiratory disease (1). In contrast to the substantial evidence indicating a causal effect of smoking on the occurrence of most common respiratory diseases, the relationship between regular active cigarette smoking and new-onset asthma, an increasingly common chronic condition, has yet to be firmly established (1).

Although smoking causes pathophysiologic changes in the airways, including inflammation and airway hyperresponsiveness, that support a role for smoking in asthma pathogenesis, the

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Smoking causes a spectrum of adverse health effects; however, the role of active smoking on new onset asthma remains controversial.

What This Study Adds to the Field

Regular cigarette smoking increases the risk for new onset asthma among adolescents, especially among those without allergies or who were exposed to maternal smoking *in utero*.

epidemiologic evidence for an effect of regular active smoking on the onset of asthma is inconsistent with studies showing increased risk, decreased risk, or no association between smoking and asthma (2–14). The 2004 Surgeon General's report on the health consequences of smoking concluded that there is inadequate evidence to infer a causal relationship between smoking and asthma (1). Reasons for the inconsistencies in studies in adults include the difficulty in separation of asthma from chronic obstructive pulmonary disease (COPD) in adult smokers, bias arising from retrospectively defining lifetime smoking histories, and differences in susceptibility for the adverse effects of smoking. Prospective studies of new-onset asthma during the adolescent period of active smoking initiation have the potential to clarify the association between regular cigarette smoking and risk of new-onset asthma and provide a new shorter-term rationale for smoking prevention interventions.

Based on the pathophysiologic effects of smoking and the evidence for rapid onset of lung function deficits and respiratory symptoms, including wheezing after initiation of regular smoking, we hypothesized that the initiation of regular smoking during adolescence increases the risk for new-onset asthma (15). The Children's Health Study (CHS), a longitudinal study of respiratory health among children in 12 southern California communities, offered an opportunity to investigate this hypothesis. We prospectively collected data during annual school visits on demographic factors, medical histories, household exposures, cigarette smoking, and newly diagnosed asthma, and we estimated the relative risk for new-onset asthma associated with regular smoking among school-aged children and adolescents. Some of the results of these studies have been previously reported in the form of an abstract (16).

METHODS

Study Design and Data Collection

The Children's Health Study (CHS) is a prospective study of the determinants of respiratory health among school-aged children in 12 southern California communities. The methods used in the CHS have been described in detail (17, 18). Briefly, children were recruited from public school classrooms from grade four during 1993 and 1996, and from grade seven during 1993, in community schools and followed through high school graduation. The average participation rate of students in each

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classroom was 81%. Parents or guardians of each participating student provided written informed consent and completed a self-administered questionnaire, which provided demographic information, characterized history of prior respiratory illness and its associated risk factors, lifetime tobacco smoke exposure information, and household characteristics. At study entry and in each subsequent year until high school graduation, children completed questionnaires that included asthma symptoms, diagnoses of asthma, and secondhand smoke exposure; children also participated in a private interview about current respiratory health, asthma status, inhaler use, and cigarette smoking. Children who did not complete the questionnaires or interview due to absence during visits at schools were interviewed by telephone by trained staff using the same instruments. Children who moved from a study school area during a school year were interviewed by telephone to collect information for the year that they moved, and were not interviewed in subsequent years. Children who dropped out of the study were censored at the date of their last interview year. Children who reported asthma at any interview were censored at the midpoint of the year of diagnosis. The study protocol was approved by the institutional review board for human studies at the University of Southern California, and written informed consent was provided by a parent or legal guardian for all participants.

Study Cohort

The cohort for this study included CHS participants with no history of asthma or wheezing symptoms from birth to study entry. Children with any history of wheezing at baseline interview were excluded from this analysis to prevent the inclusion of undiagnosed asthma cases. Parental responses on the first questionnaire were used to categorize children's asthma status and wheezing history at study entry. Children were classified as already having asthma at study entry if the adult completing the questionnaire reported that a child had physician-diagnosed asthma or if the child reported a diagnosis of asthma during the initial assessment in-person interview conducted by a trained technician at schools. A child was classified as having a lifetime history of wheezing if the adult completing the questionnaire responded affirmatively to a series of questions about current and past wheezing including, "Has your child's chest ever sounded wheezy or whistling, including times when he or she had a cold?"

New-Onset Asthma

We identified new-onset asthma cases using annual in-person interviews. Subjects who reported a new physician diagnosis in a subsequent year of follow-up were classified as a new-onset asthma case in that year. Because follow-up occurred at approximately yearly intervals and exact date of onset of symptoms or a physician diagnosis was not available, date of diagnosis for each incident case was assigned to the midpoint of the interval between interviews. Children were also interviewed annually about the use of inhaled medications. Using the combined data on new diagnoses of asthma and recent inhaler use, we defined a restricted group of new-onset cases with recent inhaler use for sensitivity analyses.

Personal and Secondhand Smoking Information

Information on exposure to secondhand smoke (SHS) and personal smoking behavior of each child was collected during a private and confidential in-person interview conducted by experienced field staff once a year during school visits. Study subjects were asked to estimate the number of cigarettes they had smoked during the previous 24 h, previous 1 wk, and previous 1 yr before the interview date.

Children who reported smoking any cigarettes in the 24 h/1 wk/1 mo/1 yr before the interview were categorized as smokers. To assess the effect of smoking, participants were categorized into three groups using the reports of weekly smoking: nonsmokers (none), infrequent smokers (one to six cigarettes), and regular smokers (seven or more cigarettes or at least one per day on average) using the amount smoked in the week before the interview. Smoking in the previous year was categorized into four groups: none, 1–99 cigarettes, 100–299 cigarettes, and 300 or more cigarettes (about one per day on average). Because the onset of asthma may occur shortly after the onset of regular smoking and may affect smoking habits, we classified smoking status using data from the year of diagnosis as well as the year before diagnosis.

Exposure to household SHS from birth to study entry and exposure to maternal smoking *in utero* were characterized using the responses from the questionnaire completed by parents or guardians. At entry, information was collected about the current and past household smoking histories of each participant's mother, father, other adult household members, and regular household visitors. *In utero* exposure to maternal smoking (yes or no) was assigned by responses to the question "Did the child's biological mother smoke while she was pregnant with your child? (Include time when she was pregnant but did not yet know she was)." Follow-up information on current household SHS exposure was collected yearly using a questionnaire completed by the child at school.

Sociodemographic and Medical History Information

Ethnicity was defined as non-Hispanic white, Hispanic, African American, Asian, and mixed/other ethnicities. Educational attainment was categorized as a dichotomous variable based on the parent or guardian's completion of high school (grade 12). Household income was categorized into three categories of income. Health insurance coverage (yes or no) was categorized using responses to the question "Does this child have any health plan or health coverage?"

Selected aspects of children's medical histories and family histories of asthma and allergy were collected at study entry. Personal history of allergy included any history of hay fever, allergic rhinitis, 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 allergy was defined as any biological parent or full siblings having been diagnosed with hay fever or allergies. Family history of asthma was defined as any biological parent having been diagnosed with asthma. During annual school visits, students' height and weight were measured and recorded using standard protocols. Body mass index (BMI) was calculated as weight (kg)/height² (m²). We categorized BMI into age- and sex-specific percentiles based on the Centers for Disease Control (CDC) BMI growth charts using 1-mo age intervals. (19) Participants with BMI at or above the 85th percentile were classified as overweight.

Air Pollution Monitoring

We considered the modifying effects of ambient air pollution, household, and indoor exposures. Air pollution monitoring stations were established in each of the 12 study communities beginning in 1994. (17, 18) Each station measured average hourly levels of ozone (O₃), nitrogen dioxide (NO₂), particulate matter (PM₁₀; with an aerodynamic diameter of < 10 µm, and 2-wk integrated PM_{2.5}; with an aerodynamic diameter of < 2.5 µm), and 2-wk integrated levels of vapor acids. For ozone, we computed the annual average of the ozone levels obtained from 10:00 A.M. to 6:00 P.M. (the 8-h daytime average) in each community over the period of follow-up. We classified the communities into low- or high-exposure groups based on long-term average pollution levels at the central monitors, with six communities in each group. For household and indoor exposures, we examined pets (dogs, cats, birds, and other furry animals), pests (roaches), air conditioning, use of a gas stove, household water damage, mold and mildew on household surfaces, houseplants, carpeting in bedrooms, heating source, age of the home, and humidifier use as potential confounding covariates. Participation in team sports was used to assign children's physical activity levels.

Statistical Methods

We fitted Cox proportional hazard regression models with the time scale defined as the follow-up time to investigate the association between regular personal smoking and newly diagnosed asthma. We used stratified baseline hazards in these models to allow for sex- and age (integer years)-specific baseline hazards. All models were adjusted for community of residence and race/ethnicity as fixed effects. For all smoking variables, we fitted time-dependent Cox proportional hazard models using most recent smoking status, smoking status during the year of diagnosis, and smoking status lagged 1 yr before the diagnosis year. The smoking variables were incorporated as time-dependent covariates in the Cox proportional hazard models. We chose to report results from models using the concurrent smoking status because we considered this metric to provide the most valid information on smoking status before diagnosis. The point estimates from the models with 1-yr lag, no lag, and concurrent (the heaviest smoking reported in the year of diagnosis or the previous year) showed consistent effect estimates (*see*

Table E1 in the online supplement). We also investigated the risks associated with SHS exposure using baseline exposure and annual SHS exposure data treated in a time-dependent manner. We considered two SHS variables, including an indicator of any household SHS exposure and a quantitative variable for the number of household smokers. All models were adjusted for community as a fixed effect and race/ethnicity. Additional covariates identified *a priori* as potential confounders were considered for inclusion in the model based on whether their inclusion changed the smoking effect estimate by more than 10%. Heterogeneity of associations among subgroups was assessed by comparing appropriate models with and without interaction terms. Sensitivity analyses were conducted by limiting the case definition to those who reported inhaled medication use. All analyses were conducted using SAS software Version 9 (SAS Institute, Cary, NC). All hypothesis testing was conducted assuming a 0.05 significance level and a two-sided alternative hypothesis.

RESULTS

At study entry, the cohort of children ranged in age from 8 to 15 yr (Table 1). The majority of children were non-Hispanic or Hispanic white. Exposure to maternal smoking during pregnancy was reported for 13.9% of children and exposure to secondhand smoke at study entry was reported for 17.5% of children. Most children had pets and pests in their homes and came from families with parents who reported more than a high school education. About 80% of children had health insurance.

The median and mean follow-up time was 8 yr and 6.3 yr (8 yr possible) for fourth-grade cohorts. For the seventh-grade cohort, median and mean were 5 yr and 4.1 yr (5 yr possible) of follow-up, respectively. For children who developed asthma, follow-up was considered to be complete at the time of diagnosis. Overall, we followed this cohort of children for 75% of the possible time of observation over the 8-yr period of the study. The proportion of possible follow-up time did not vary substantially across any of the subgroups. Based on telephone interviews with the families of subjects who left the study schools, loss to follow-up was mainly due to family moves out of the school catchment area, most of which were due to a change in employment (data not shown).

Over the period of follow-up, approximately 28% of children reported any cigarette smoking during their lifetime (Table 2). Weekly smoking was reported by 13.8% of participants, while 6.9% were classified as regular smokers based on smoking at least one cigarette on average per day (seven or more cigarettes per week). Differences in smoking prevalence were small between children exposed and not exposed to maternal smoking during their *in utero* period; however, more of those exposed were frequent regular smokers.

We ascertained 255 cases of new-onset asthma (males = 104, females = 151) during the cohort follow-up period. The overall incidence rate of asthma was 17.8/1,000 person-years (pyr). Incidence rates were higher among female participants (19.4/1,000 pyr) than male participants (16.0/1,000 pyr).

Regular smoking was associated with increased risk of newly diagnosed asthma (Table 3). Children who smoked seven or more cigarettes per week in the year of diagnosis or previous year had an increase in risk compared with nonsmokers (relative risk [RR], 3.1; 95% confidence interval [95% CI], 1.5–6.2). Consistent with the risk associated with regular frequent smoking assessed on a weekly basis, children reporting regular smoking on a yearly basis (at least 300 cigarettes per year) were at a 3.9-fold increased risk (95% CI, 1.7–8.5) for developing asthma compared with those reporting no smoking in the year of diagnosis or the previous year. We observed an increasing risk of new-onset asthma with the amount smoked for both weekly (p trend = 0.0005) and yearly smoking (p trend = 0.0009). The associations of active smoking with asthma were not substantially affected

TABLE 1. SELECTED BASELINE CHARACTERISTICS OF CHILDREN'S HEALTH STUDY PARTICIPANTS WITH NO HISTORY OF PHYSICIAN-DIAGNOSED ASTHMA OR LIFETIME HISTORY OF WHEEZING AT STUDY ENTRY (FOURTH AND SEVENTH GRADE)

	N (2,609)	Ratio of Observed and Expected Follow-up Time
Age at entry, yr		
8–10	1,731	0.76
11–12	393	0.70
13–15	485	0.76
Race/ethnicity		
White	1,388	0.76
Hispanic	798	0.75
Asian	141	0.82
African-American	138	0.67
Mixed	83	0.73
Other/unknown	61	0.70
Sex		
Female	1,415	0.76
Male	1,194	0.74
Overweight at entry		
No	2,037	0.77
Yes	322	0.73
Parental history of asthma		
No	2,120	0.76
Yes	319	0.74
History of allergy		
No	2,041	0.76
Yes	469	0.75
History of allergic rhinitis		
No	2,127	0.76
Yes	429	0.74
Humidifier use		
No	1,875	0.76
Yes	612	0.74
Maternal smoking during pregnancy		
No	2,165	0.77
Yes	362	0.70
Current maternal smoking at entry		
No	2,318	0.76
Yes	244	0.68
Household SHS exposure at entry		
No	2,100	0.76
Yes	457	0.72
Pests in home*		
No	530	0.73
Yes	1,843	0.76
Dogs in home		
No	1,153	0.75
Yes	1,456	0.76
Pets in home†		
No	617	0.74
Yes	1,992	0.76
Health insurance		
No	459	0.74
Yes	2,101	0.76
Parental Income‡		
≤ \$14,999	362	0.68
\$15,000–49,999	938	0.74
> \$50,000	872	0.78
Parental Education‡		
Less than high school	383	0.72
At least high school	503	0.76
Some college	1,025	0.75
College and above	587	0.77

* Presence of any pests (rats, mice, cockroaches, ant, spiders, termites and others) in the home within 12-mo period before study entry.

† Presence of any pets (dogs, cats, hamster, birds, and others) in the home within last 12-mo period before study entry.

‡ Subtotals are not equal to 2,609 due to missing data for subjects.

TABLE 2. PREVALENCE OF CIGARETTE SMOKING BY SEX, EXPOSURE TO MATERNAL SMOKING DURING PREGNANCY, AND ATOPIC STATUS AT STUDY ENTRY, CHILDREN'S HEALTH STUDY 1993–2003

	Entire Cohort N (%)	Sex		Maternal Smoking during Pregnancy*		Allergy†	
		Female N (%)	Male N (%)	Yes N (%)	No N (%)	Positive N (%)	Negative N (%)
Any lifetime smoking	730 (28.0)	357 (25.2)	373 (31.2)	106 (29.3)	594 (27.4)	237 (27.5)	491 (28.2)
Amount smoked weekly							
1–6 cigarettes	179 (6.9)	78 (5.5)	101 (8.5)	16 (4.4)	152 (7.0)	53 (6.2)	126 (7.2)
7+ cigarettes	180 (6.9)	91 (6.4)	89 (7.4)	37 (10.2)	135 (6.2)	57 (6.6)	122 (7.0)
Amount smoked yearly							
1–99 cigarettes	525 (20.1)	253 (17.9)	272 (22.8)	71 (19.6)	433 (19.5)	173 (20.1)	351 (20.1)
100–299 cigarettes	68 (2.6)	36 (2.5)	32 (2.7)	10 (2.8)	57 (2.5)	25 (2.9)	43 (2.5)
300+ cigarettes	134 (5.1)	66 (4.7)	68 (5.7)	24 (6.6)	102 (4.1)	37 (4.3)	96 (4.3)
Total	2,609	1415	1194	362	2165	862	1741

* History on maternal smoking during pregnancy was unknown for 82 subjects.

† Atopic status was defined by presence or absence of history of allergy, allergic rhinitis, or hay fever at study entry. Information on atopic status was unavailable for six children.

by adjustment for educational attainment, family income, other demographic factors, birth weight, gestational age, health insurance, physical activity levels, family history of asthma, pets, humidifier use, other household characteristics, or exposure to ambient pollutants and indoor combustion sources including secondhand smoke. In sensitivity analyses that restricted the case definition of new-onset asthma to include subjects with recent inhaler use, we found no substantial differences in the magnitude of risk associated with regular smoking in the restricted cohort compared with the analysis of the full cohort (data not shown). Annual household exposure to secondhand smoke was not significantly associated with risk of new-onset asthma (RR, 1.1; 95% CI, 0.9–1.5). The number of household smokers was not associated with the risk of new-onset asthma, and censoring subjects when they became smokers had little effect on these estimates. Restricting the analyses to children without secondhand smoke exposure did not substantially change the risk estimates for regular smoking.

We found evidence for a transgenerational effect of smoking on asthma development. The increased risk for newly diagnosed asthma among regular frequent smokers was largest among children who had been exposed to maternal smoking during their

in utero period (Table 4). Children exposed *in utero* and who became frequent regular smokers (seven or more cigarettes per week) had a greater than eightfold increased risk (RR, 8.8; 95% CI, 3.2–24.0) compared with unexposed nonsmokers. In contrast, children who were not exposed *in utero* showed a small and statistically nonsignificant risk from frequent regular smoking (1.2; 95% CI, 0.4–4.0). The effects of maternal smoking on susceptibility to later life smoking was apparent in those exposed to maternal smoking solely during the *in utero* period (Table 5).

We also found evidence that the effect of regular smoking on new-onset asthma differed by allergy status of the children (Table 6). The observed dose-dependent increasing risk of asthma development was essentially limited to children without any history of allergy at study entry. Compared with children who were nonsmokers and without any history of allergy, children who became regular smokers (seven or more cigarettes per week) and had no history of allergy at study entry were 5.2 (95% CI, 2.4–10.9) times more likely to develop asthma. There was little or no evidence that children who were regular smokers but had a history of allergy were at increased risk of asthma (0.7; 95% CI, 0.1–5.1). We conducted restricted analyses to exclude allergies to food or medicine as well as restricted to children with history of allergic rhinitis or hay fever only, and found no substantial changes in our results. The increased susceptibility to regular smoking associated with nonallergic status and *in utero* exposure to maternal smoking appeared to be independent

TABLE 3. CIGARETTE SMOKING AND RISK OF NEWLY DIAGNOSED ASTHMA, RELATIVE RISK AND 95% CONFIDENCE INTERVAL, CHILDREN'S HEALTH STUDY 1993–2003

	Relative Risk	95% Confidence Interval	p Value for Trend
Any smoking in year of diagnosis	1.3	0.9–2.0	—
Regular smoking			
Amount smoked weekly			
None	1	—	0.0005
1–6 cigarettes	1.8	0.9–3.6	
7+ cigarettes	3.1	1.5–6.2	
Amount smoked yearly			
None	1	—	0.0009
1–99 cigarettes	1.1	0.7–1.7	
100–299 cigarettes	1.8	0.6–5.0	
300+ cigarettes	3.9	1.7–8.5	

Relative risk (Hazard ratio) and corresponding 95% confidence intervals from Cox's proportional hazard model for concurrent smoking with stratified baseline hazard for sex and age (in 1-yr intervals) at study entry. All models are adjusted for race/ethnicity and community of residence.

TABLE 4. JOINT EFFECTS OF ACTIVE SMOKING AND EXPOSURE TO MATERNAL SMOKING DURING PREGNANCY ON NEWLY DIAGNOSED ASTHMA, RELATIVE RISK AND 95% CONFIDENCE INTERVAL, CHILDREN'S HEALTH STUDY 1993–2003

		Maternal Smoking During Pregnancy		Interaction p Value
		Unexposed	Exposed	
Frequent regular smoking*	No	1	0.9 (0.5, 1.4)	0.02
	Yes	1.2 (0.4–4.0)	8.8 (3.2–24.0)	

Relative risks (Hazard ratios) and corresponding 95% confidence intervals were obtained from Cox's proportional hazard model with separate baseline hazard for sex and age (in yr) at study entry. All models are adjusted for race/ethnicity, community, maternal smoking during the children's postnatal period, and numbers of other smokers in the home.

* Smoking at least seven cigarettes in the last week.

TABLE 5. JOINT EFFECTS OF ACTIVE SMOKING AND EXPOSURE TO MATERNAL SMOKING DURING PREGNANCY AND CHILDHOOD ON NEWLY DIAGNOSED ASTHMA, RELATIVE RISK AND 95% CONFIDENCE INTERVAL, CHILDREN'S HEALTH STUDY 1993–2003

		Maternal Smoking during Pregnancy and Childhood		
		Unexposed	During Pregnancy Only	Both
Frequent regular smoking*	No	1 (—)	1.1 (0.6–2.0)	0.7 (0.4–1.2)
	Yes	1.6 (0.6–4.3)	9.9 (2.3–42.5)	6.9 (1.9–25.3)

Relative risks (Hazard ratios) and corresponding 95% confidence intervals were obtained from Cox's proportional hazard model with separate baseline hazard for sex and age (in yr) at study entry. All models are adjusted for race/ethnicity and community.

* Smoking at least seven cigarettes in the last week.

susceptibility factors. Nonallergic children who became regular smokers and who were exposed *in utero* to maternal smoking had 10.6-fold (95% CI, 3.4–32.3) increased risk of asthma compared with nonallergic unexposed nonsmokers. Among atopic regular smokers who were exposed *in utero* to maternal smoking, the risk of asthma was increased 4.1-fold (95% CI, 0.5–33.2) compared with allergic unexposed nonsmokers. Restricting the definition of allergy to hayfever and allergic rhinitis or by excluding food and medication allergies did not substantially change the findings (data not shown).

In further analyses, the association of regular smoking did not vary significantly by sex (interaction p value = 0.26), ethnicity, educational attainment, family income, health insurance, physical activity levels, family history of asthma, presence of household pets, humidifier use, ambient air pollutants, or secondhand tobacco smoke exposure.

DISCUSSION

In the middle of the 20th Century, the late Sir Richard Doll and colleagues provided the first accepted evidence that chronic cigarette smoking causes lung cancer (1). Since these seminal findings, chronic smoking and exposure to secondhand smoke (SHS) have been shown to cause a wide spectrum of diseases and other adverse health outcomes (1). The effects of smoking on asthma, an increasingly important chronic disease, remain to be fully determined. It is clear that smoking and SHS exposure increase the risk for asthma exacerbations (1). In addition to increasing the risk for asthma exacerbations, maternal smoking during pregnancy and early childhood exposure to SHS are associated with increased risk of early life asthma, especially in susceptible populations (20, 21). Smoking also affects the natural history of asthma, as adolescents with a past history of asthma have increased risk for recurrent asthma symptoms after initiating smoking (22, 23). Our results demonstrate a role of regular

active smoking in the development of asthma during adolescence in addition to the adverse impact of tobacco smoke on asthma early in life and upon children with established asthma.

Our findings of increased risk of asthma after the onset of regular smoking during childhood and adolescence is consistent with the large body of evidence showing that active smoking causes adverse respiratory health effects in adolescents and young adults after a short period of regular smoking (1). It has long been recognized that adolescents who begin to smoke regularly show increased symptoms and reduced lung function within the first few years after initiation (15). Although physiologic changes are well documented, the role of active smoking on the onset of asthma soon after smoking initiation has not been extensively studied. Our study addressed some of the issues that may explain the heterogeneity of past studies, including examining asthma at ages when COPD is not prevalent, conducting annual prospective assessments of smoking, and considering susceptibility factors. The results of our study provide clear evidence that regular smoking increases the risk for asthma and that important chronic adverse consequences of smoking are not restricted to those with many pack-years of smoking.

Our research team and other researchers have reported that maternal smoking has transgenerational effects (21, 24–28). Emerging evidence suggests that early life exposure, especially *in utero* exposure to maternal smoking, not only increases the risk for early life asthma, but also increases susceptibility for other adverse respiratory effects during young adulthood (22, 29). Upton and coworkers reported that maternal smoking and personal smoking jointly increase airflow limitation in adults (29). Based on these findings, we hypothesized that exposure to maternal smoking during the *in utero* period increases asthma susceptibility from regular active smoking during adolescence (22). The present study provides additional evidence supporting an important adverse transgenerational effect of maternal smoking on the respiratory health of their children. Given the potential impacts of the transgenerational effects of smoking on asthma occurrence in future years, additional studies are needed to confirm and extend these observations.

We did not investigate the mechanisms that mediate the associations of regular smoking with new-onset asthma; however, the association of new-onset asthma with smoking has strong biological plausibility. Cigarette smoke is a complex mixture that produces a spectrum of pathophysiologic effects in the lung that may mediate the relationship of smoking and new-onset asthma (30). Active smoking has complex acute and chronic effects on pulmonary immune function and proinflammatory responses (31, 32). The effects of smoking may also be mediated by changes in airway function, as smoking causes increased bronchial hyperresponsiveness (BHR) in children and adults without asthma (33). The combined effect of increased BHR and the proinflammatory milieu in smokers may set the stage for the onset

TABLE 6. JOINT EFFECTS OF ACTIVE SMOKING AND ALLERGY ON NEWLY DIAGNOSED ASTHMA, RELATIVE RISK AND 95% CONFIDENCE INTERVAL, CHILDREN'S HEALTH STUDY 1993–2003

Smoking in Previous Week	Children without Allergies	Children with Allergies	Interaction p Value
None	1 (—)	1.1 (0.8–1.4)	0.006
≤ 6 Cigarettes	2.4 (1.1–4.9)	0.7 (0.1–5.1)	
7+ Cigarettes	5.2 (2.4–10.9)	0.7 (0.1–5.1)	

Relative risks (Hazard ratios) and corresponding 95% confidence intervals were obtained from Cox's proportional hazard model with separate baseline hazard for sex and age (in yr) at study entry. All models are adjusted for race/ethnicity, community, maternal smoking during the children's postnatal period, and numbers of other smokers in the home.

of asthma. Smoking may act through nonallergic pathways and have larger effects in those with low lung function, a consequence of maternal smoking during the *in utero* period (34).

The cohort entry criteria and ascertainment of new cases of asthma was based on self-reports of physician diagnosis—a method that may affect incidence rates and relative risk estimates. Asthma is a clinical syndrome with no sensitive and specific diagnostic test available to confirm clinical assessments. Because of the clinical nature of the assessment, physician diagnosis of asthma has been recommended and widely used as a method to classify asthma status in epidemiologic studies; however, this approach has limitations (35, 36). Access to care and differences in practice among physicians has the potential to influence asthma diagnoses (37). Excluding any child with a history of wheezing minimized misclassification of asthma status at entry. In addition, exclusion of cases diagnosed in the first year, a period when unrecognized prevalent cases are likely to be diagnosed, did not substantially change the point estimates for smoking, suggesting that inclusion of undiagnosed cases at study entry that were diagnosed after entry did not account for our results. It has been suggested that smoking causes increased cough and phlegm production that could be misdiagnosed as asthma. In this cohort, smoking was not associated with the prevalence of cough and phlegm production, indicating that such misdiagnosis is likely to be independent of smoking and, therefore, does not account for our findings.

We found that adjustment for factors that mediate access to care including family income, education, and medical insurance did not explain our results, indicating that differential access to care in smokers and nonsmokers was unlikely to substantially bias our results. To further investigate the potential for bias from variation in medical practice, we conducted analyses restricting cases to those who recently used inhaled medication and found little change in the risk estimates. Because the associations with smoking were apparent among the group of cases for which the diagnosis of asthma was most certain, our results are unlikely to be explained by variation in diagnosis. Furthermore, underdiagnosis of asthma in smokers may occur, as physicians may inaccurately attribute post-exercise wheezing or shortness of breath to smoking. However, this practice would result in a bias toward the null and, therefore, would not explain our findings.

Because we did not follow the cohort from birth, we cannot directly determine whether a new diagnosis truly represents an incident case or is a second occurrence of asthma that first occurred during infancy but was not reported by a parent. We sought to limit the inclusion of undiagnosed or unreported cases by excluding participants with any history of wheezing from the analysis. Most early life episodes of wheezing are not due to asthma and therefore limited parental recall of such transient wheezing episodes would not have a major influence on the classification of new-onset asthma during childhood and adolescence.

The incidence rate of physician-diagnosed asthma in the present study (17.8 cases per 1,000 *pyr*) was higher than reported incidence rates of childhood asthma in earlier decades (38–40). An examination of trends in incidence and prevalence indicates that the higher rates in the present study reflect the increasing occurrence of asthma in recent decades in children in Tucson, Arizona and in Europe (8, 22, 41–47).

We assessed smoking behavior by self-report during a confidential interview each year of the study. Although some participants probably did not provide accurate information, the information was collected prospectively and any errors in classification were likely to be independent of subsequent asthma status. Therefore, the use of self-reported smoking histories may have resulted in nondifferential misclassification of smoking sta-

tus that would produce an underestimate of the association of smoking with new-onset asthma.

We did not observe an association of SHS exposure and asthma in this study. Misclassification of SHS exposure as our subjects aged is likely to limit our ability to examine this association, as we did not collect information on exposure in social situations that may be a major contributor to SHS exposure during adolescence. Given the incomplete assessment of SHS during adolescence, the lack of association with asthma should not be over-interpreted. We also observed no statistically significant differences in the effects of active smoking or SHS by GSTM1 genotype.

Conclusions

Regular smoking is associated with a substantial risk for developing asthma during childhood and adolescence. Those who did not have allergies and those previously exposed to prenatal maternal smoking were at the greatest risk. The clinical and public health implications for our findings are far reaching. Effective tobacco control efforts focusing on the prevention of smoking in children, adolescents, and women of childbearing age are urgently needed to reduce the number of these preventable cases of asthma. The substantially increased risk for developing a common activity-limiting chronic disease such as asthma after initiating regular smoking behavior may provide new motivation for adolescents to refrain from smoking.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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