Ethnic Variability in Persistent Asthma After In Utero Tobacco Exposure

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KEY WORDS

asthma, tobacco, Latino, African American, pregnancy

ABBREVIATIONS

GALA—Genetics of Asthma in Latino Americans
SAGE—Study of African Americans: Asthma, Genes and Environments
FEV₁—forced expiratory volume in 1 second
IgE—immunoglobulin E
OR—odds ratio
CI—confidence interval
SHS—secondhand smoke

All the authors made substantive intellectual contributions to this study, including study design, data acquisition, data analysis, and/or drafting and revision of the manuscript, and all the authors approved the submitted version of the manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: In utero tobacco smoke exposure is associated with childhood asthma, but there are sparse data regarding its effects on asthma severity, especially in Latino and black populations.

WHAT THIS STUDY ADDS: In utero tobacco smoke exposure, but not exposure at other times, is associated with the development of persistent asthma among Latino and black children, which indicates that in utero tobacco smoke exposure has significant consequences for postnatal asthma outcomes.

abstract

BACKGROUND: The effects of in utero tobacco smoke exposure on childhood respiratory health have been investigated, and outcomes have been inconsistent.

OBJECTIVE: To determine if in utero tobacco smoke exposure is associated with childhood persistent asthma in Mexican, Puerto Rican, and black children.

PATIENTS AND METHODS: There were 295 Mexican, Puerto Rican, and black asthmatic children, aged 8 to 16 years, who underwent spirometry, and clinical data were collected from the parents during a standardized interview. The effect of in utero tobacco smoke exposure on the development of persistent asthma and related clinical outcomes was evaluated by logistic regression.

RESULTS: Children with persistent asthma had a higher odds of exposure to in utero tobacco smoke, but not current tobacco smoke, than did children with intermittent asthma (odds ratio [OR]: 3.57; $P = .029$). Tobacco smoke exposure from parents in the first 2 years of life did not alter this association. Furthermore, there were higher odds of in utero tobacco smoke exposure in children experiencing nocturnal symptoms (OR: 2.77; $P = .048$), daily asthma symptoms (OR: 2.73; $P = .046$), and emergency department visits (OR: 3.85; $P = .015$) within the year.

CONCLUSIONS: Exposure to tobacco smoke in utero was significantly associated with persistent asthma among Mexican, Puerto Rican, and black children compared with those with intermittent asthma. These results suggest that smoking cessation during pregnancy may lead to a decrease in the incidence of persistent asthma in these populations. *Pediatrics* 2011;128:e623–e630

Maintaining maternal health during pregnancy is imperative because of the potential adverse effects of poor maternal health on the unborn child. Avoidance of tobacco products during pregnancy is recommended¹ because of their myriad adverse effects on the fetus and in later childhood, including low birth weight, sudden infant death, and adverse pulmonary outcomes.^{2,3} Specifically, in utero tobacco smoke exposure has been identified as an independent risk factor for the development of wheezing,⁴ impaired lung function,^{5–7} and asthma.^{6,8–10} The mechanism by which in utero tobacco exposure causes asthma is not currently established. However, there is speculation that the association between tobacco smoke exposure and asthma development could involve genetic predisposition to the deleterious effects of tobacco smoke, impairment of lung development, altered lung inflammatory responses, or all 3.¹¹ There are limited data on the correlation between in utero tobacco smoke exposure and asthma severity, and there are few studies in which any of these outcomes in minority populations have been investigated.¹²

Postnatal tobacco smoke exposure has well described effects, including adenoid hypertrophy,¹³ increased incidence of tonsillitis and sore throats,¹⁴ and pulmonary outcomes (eg, wheezing, asthma, bronchiolitis, cough, pneumonia, impaired pulmonary function, and chronic bronchitis).^{3,10,15–17} Interestingly, it has been suggested that postnatal tobacco smoke exposure has fewer adverse effects than does in utero exposure,¹⁰ but few studies have been published on this topic.^{3,9,10}

Because of the limited number of studies comparing the effects of in utero and postnatal tobacco smoke exposure on asthma severity, and because such data are even more sparse for minority populations, we sought to elu-

cidate these effects in Latino and black participants recruited in the Genetics of Asthma in Latino Americans (GALA) study¹⁸ and the Study of African Americans: Asthma, Genes and Environments (SAGE).¹⁹ Identification of such effects in minority populations is particularly important because these are the fastest-growing populations in the United States. The US Census Bureau, for example, projects that the Hispanic and black populations will increase by 53.4% and 34.1%, respectively, over the next 4 decades.²⁰ These populations are also disproportionately affected by asthma; black and Puerto Rican children bear some of the highest asthma burdens in the country.^{21–23}

Considering the rapid rate of pulmonary development in utero, we hypothesized that a greater proportion of persistent asthmatics would have in utero tobacco smoke exposure compared with intermittent asthmatics, and that these effects would be greater than those seen with postnatal exposure. Discovering such differences may help identify critical time points to maximize the benefits of appropriately timed smoking prevention and cessation interventions in pregnant women and mothers.

PATIENTS AND METHODS

Study Participants

There were 295 participants previously recruited as part of the GALA study (1998–2001) and SAGE^{18,19} (2001–2003) who were included in the current study. As part of the GALA study, Mexican asthmatic patients were recruited from the San Francisco Bay Area as well as Mexico City, and Puerto Rican asthmatic patients were recruited from New York City and Puerto Rico. Black participants with asthma were recruited from San Francisco as part of SAGE. For the GALA study and SAGE, patients were recruited from community clinics and

hospitals, and recruitment was standardized across all centers.

Eligible subjects for the current study were between ages 8 and 16; had physician-diagnosed asthma or >12% bronchodilator responsiveness; had experienced symptoms of coughing, wheezing, or shortness of breath for at least 2 years; and had all biological parents and grandparents identified as Puerto Rican, Mexican, or black. Subjects with a history of other lung diseases were excluded. Local institutional review boards approved both studies.

Clinical Data Collection

After obtaining age-appropriate informed consent and assent, a trained interviewer administered the modified version of the 1978 American Thoracic Society-Division of Lung Diseases Epidemiology Questionnaire,²⁴ as described previously.¹⁸ Questions used to determine tobacco smoke exposure included (1) Did the child's mother smoke while pregnant with the child? (2) Did the child's mother (father) smoke when the child was under 2 years of age? and (3) Does the child's mother (father) smoke at the present time?

Pulmonary function was evaluated using spirometry performed to American Thoracic Society standards¹⁸ before and 15 minutes after the administration of albuterol, as described previously.¹⁸ Spirometric reference values from Hankinson et al²⁶ were used to determine percent predicted values. The reference values generated for Mexicans were also used for the Puerto Rican subjects because no reference values were available for this ethnic group. Subjects were classified as having either intermittent or persistent asthma on the basis of data gathered from the 1978 American Thoracic Society-Division of Lung Diseases Epidemiology Questionnaire and pulmo-

nary function testing, as described previously.²⁷ The “persistent” classification combined the “mild persistent,” “moderate persistent,” and “severe persistent” classifications of the National Asthma Education and Prevention Program²⁸ into 1 group. Specifically, subjects were classified as having persistent asthma if they met 1 of the following criteria: (1) without respect to medications used, the subject has had daily asthma symptoms for 3 or more months of the year; (2) the subject has experienced nocturnal asthma for >1 night per week for 3 or more months of the past year; and (3) the forced expiratory volume in 1 second (FEV₁) was <80% of the race-corrected predicted value (measured at the study visit).

Statistical Analysis

Participants were stratified according to asthma severity (intermittent versus persistent) followed by comparison of demographic and clinical characteristics. Comparisons were performed with the unpaired 2-tailed *t* test (continuous variables) and the χ^2 test (categorical variables).

The primary end point was the odds of tobacco smoke exposure in utero in persistent versus intermittent asthmatics. This analysis was performed with a single logistic regression model with inclusion of variables for asthma severity, tobacco smoke exposure at 2 time points (in utero and current) via each parent, age, gender, plasma immunoglobulin E (IgE) levels (log-transformed values), BMI, birth weight, history of atopic dermatitis, family history of asthma, ethnicity, birth site, and recruitment center. Secondary end points included the odds of tobacco smoke exposure in the occurrence of the following outcomes: daily asthma symptoms; nocturnal asthma symptoms; wheezing; emergency department visits in the past year; and

FEV₁ of <80% of predicted. Linear regression was used to assess the effect of in utero tobacco smoke exposure on FEV₁ and FEV₁/forced vital capacity. To determine if early-life tobacco smoke exposure affects the association between in utero tobacco smoke exposure and asthma severity, bivariate logistic regression with an interaction term between in utero tobacco smoke exposure and maternal tobacco smoke exposure in the first 2 years of life was performed. This analysis was also performed with the addition of a variable for paternal tobacco smoke exposure in the first 2 years of life. Stata 9.1 software (Stata Corp, College Station, TX) was used for these analyses.

This study involved secondary data analysis, and in turn, sample size calculations were performed to ensure that the study was adequately powered to detect a clinically meaningful difference between participants with intermittent and persistent asthma for the primary end point. With the available sample size of 295, an estimated ρ of 0.2, and R^2 of 0.1, the study was capable of identifying an odds ratio (OR) of 1.55, with an α of 0.05 and a power of 0.80. Although ethnicity was included in the regression models, sample sizes were not adequate for separate subgroup analyses according to ethnicity. G*Power 3.1.2 software²⁹ was used for these analyses. Data from Mexican Americans recruited from San Francisco and Mexicans recruited from Mexico City were combined for analysis, and all these subjects were referred to as Mexicans. Likewise, data from the Puerto Ricans recruited from the island and Puerto Ricans recruited from New York City were combined for analysis, and all these subjects were referred to as Puerto Ricans. Both of the aforementioned combinations were made be-

cause of limited sample sizes within the uncombined populations.

RESULTS

Participant Characteristics

Participants with intermittent asthma and those with persistent asthma differed in that persistent asthmatics had asthma for a longer period of time, lower FEV₁, lower BMI, and a higher serum IgE level. The proportion of black participants was similar between both groups, but in regards to the Latino population, participants with persistent asthma were more likely to be Mexican in comparison to participants with intermittent asthma (Table 1).

Tobacco Smoke Exposure and Asthma Severity

Overall, 27 (9.2%) participants' mothers smoked during pregnancy. After adjusting for the previously noted variables, participants with persistent asthma had a 3.57 times greater odds (95% confidence interval [CI]: 1.14–11.25; $P = .029$) of in utero tobacco smoke exposure compared with participants with intermittent asthma (Fig 1). Current tobacco smoke exposure via the mother or father was not associated with asthma severity.

Maternal tobacco smoke exposure in the first 2 years of life had no effect on the odds of in utero tobacco smoke exposure in persistent versus intermittent asthmatics (OR: 1.06 [95% CI: 0.44–2.57]; $P = .896$). Of participants with persistent asthma, 21 (11%) reported in utero tobacco smoke exposure, and 21 (11%) also reported exposure during the first 2 years of life; however, these groups did not contain the exact same participants, as only 12 (6%) of the participants were exposed to tobacco smoke both in utero and during the first 2 years of life. As seen with maternal tobacco smoke exposure, paternal tobacco smoke exposure in the first 2 years of life also had

TABLE 1 Characteristics of Participants, Stratified According to Asthma Severity

	Intermittent Asthma (N = 101)	Persistent Asthma (N = 194)	P
Age, median (25th–75th percentile), y	10.5 (9.3–11.7)	10.4 (9.2–11.6)	.619
Asthma duration, median (25th–75th percentile), y	6 (3–8)	7 (5–9)	.015
BMI, median (25th–75th percentile)	21.2 (17.9–25.0)	19.7 (16.7–24.1)	.014
Eczema, %	36	55	.232
Ethnicity, n (%)			.043
Black	12 (12)	22 (11)	
Mexican	33 (33)	92 (47)	
Puerto Rican	56 (55)	80 (41)	
FEV ₁ , median (25th–75th percentile)			
L/s	2.1 (1.8–2.4)	1.9 (1.5–2.1)	<.0001
% predicted	93.8 (87.7–101.5)	84.6 (74.8–94.6)	<.0001
Male, %	65.3	58.8	.315
Serum IgE, median (25th–75th percentile), IU/mL	175 (55.6–497.0)	270.5 (83.8–692)	.034
Tobacco smoke exposure, n (%)			
In utero	6 (6)	21 (11)	.1686
Before 2 y of age			
Maternal	11 (11)	21 (11)	.9862
Paternal	22 (22)	48 (25)	.5722
Current			
Maternal	12 (12)	26 (13)	.7586
Paternal	18 (18)	38 (20)	.7436

FIGURE 1

Odds of tobacco smoke exposure for various asthma outcomes. Data are presented as ORs and 95% CIs. ORs were adjusted for variables noted in “Statistical Analysis.”

no effect on the primary outcome (OR: 1.23 [95% CI: 0.75–2.04]; $P = .402$).

Tobacco Smoke Exposure and Asthma-Related Outcomes

A number of asthma-related clinical outcomes, such as the presence of nocturnal symptoms, are associated with asthma severity. To determine if clinically relevant outcomes were associated with tobacco smoke exposure, the odds of tobacco smoke exposure at the previously described time points were calculated for various clinical outcomes (Fig 1). In utero tobacco smoke exposure had a statistically significant association with the presence of daily symptoms (OR: 2.73 [95% CI: 1.02–7.32]; $P = .046$), nocturnal symptoms (OR: 2.77 [95% CI: 1.01–7.63]; $P = .048$), and emergency department visits (OR: 3.85 [95% CI: 1.30–11.34]; $P = .015$) in the past 12 months. Current tobacco smoke exposure via the mother or father was not significantly associated with any of the investigated outcomes.

Although in utero tobacco smoke exposure was associated with persistent asthma and the noted asthma-related clinical outcomes, it was not associated with absolute FEV₁ ($P = .577$), the presence of a FEV₁ <80% of predicted ($P = .645$), or FEV₁/forced vital capacity ($P = .247$).

DISCUSSION

Our results indicate that maternal smoking during pregnancy is strongly associated with persistent asthma in our sample of black, Puerto Rican, and Mexican pediatric asthma patients. Odds of in utero exposure to tobacco smoke were 3.6 times as likely among persistent asthmatics than among intermittent asthmatics. In utero smoking was also associated with daily and nocturnal symptoms as well as asthma-related emergency department visits, and these differences re-

mained after controlling for a number of known risk factors, including current tobacco smoke exposure, ethnicity, plasma IgE, and atopic history. Furthermore, early life tobacco smoke exposure had no effect on the association between in utero tobacco smoke exposure and asthma severity.

In the United States, 13.8% of women in 2005 reported smoking during pregnancy.³⁰ Although the prevalence of maternal smoking during pregnancy has consistently declined during recent years, the 2005 estimate reflects a change of <2 percentage points from 2000.^{30,31} More recently, data from 2008 and 2009 showed that the 1-month prevalence of cigarette smoking among pregnant women was 15.3% as compared with 27.4% for nonpregnant women.³² The high prevalence of maternal smoking during pregnancy, along with the reported 2009 overall rates of cigarette use of 19.2% for black women and 9.8% for Hispanic women,³³ is an issue of concern for the numerous individuals with increased health risks as a result of this preventable exposure.

Maternal smoking during pregnancy is known to vary according to race/ethnicity. In 2007, the percentage of mothers in the United States who smoked while pregnant was lower for Mexican Americans (1.7%) than for Puerto Ricans (7.4%) or black mothers (7.7%).³⁴ These differences in in utero exposure are consistent with the observation that asthma morbidity and mortality are lowest among Mexicans and greatest among Puerto Ricans and blacks.³⁵ Our results indicate that regardless of ethnicity, smoking while pregnant is associated with increased asthma morbidity.

The strong association between tobacco smoke exposure and persistent asthma seems to be seeded during the relatively short 40-week period of pregnancy, underscoring the impor-

tance of tobacco prevention, control, and cessation efforts. Smoking bans have been shown in systematic reviews to increase smoking cessation³⁶ and decrease exposure to secondhand smoke (SHS).³⁷ A number of city and county governments have recently passed successful initiatives to reduce SHS in public outdoor areas. As of October 2010, an estimated 79% of the US population was protected by smoke-free ordinances covering workplaces, restaurants, and/or bars.³⁸ The passage of these initiatives is a success for tobacco control and is a stimulus that may lead to more smoke-free homes.³⁹ However, the efficacy of outdoor smoke-free laws seems to be muted among children with at-home SHS exposures,⁴⁰ particularly because the majority of children's exposure to SHS occurs in homes.^{41,42}

Although cessation of smoking before, during, and after pregnancy is the preferred ideal, our results reveal that abstaining from smoking during pregnancy may significantly reduce the burden of persistent asthma. Nine months of abstinence may also be more acceptable to those who are not considering smoking cessation, but care should be taken to avoid conveying the false impression that abstaining from smoking during pregnancy is just as safe as not smoking at all.

Our findings are tempered by several limitations. Although a prospective study design (eg, birth cohort study) likely could have produced conclusions more robust to certain biases, our study is, to our knowledge, the first in which the effects of in utero tobacco smoke exposure on asthma severity and exacerbations among minority populations have been investigated. Novelty notwithstanding, the retrospective nature of our case-control study design may have introduced biases in ascertainment of exposures. Given that data regarding tobacco

smoke exposure were collected retrospectively, tobacco smoke exposure was not confirmed via objective measures such as the measurement of cotinine, a sensitive measure of tobacco smoke exposure. There is also the potential that parents of persistent asthmatics might have systematically differed in the way they recalled important exposures (eg, smoking during pregnancy) compared with parents of intermittent asthmatics. Respondents of children with more severe disease, for example, may have been influenced by remorse or anxiety to report more or less exposure. Respondents may also have been motivated to give socially desirable responses (ie, to underreport tobacco smoking). However, the reported prevalence of smoking during pregnancy in our study was comparable to national estimates (9.2% in our study; 13.8% nationally³⁰), and the proportion of in utero tobacco smoke exposure in our study population trended in the expected direction (ie, greater among persistent asthmatics than among intermittent asthmatics).

We acknowledge that exposures to tobacco smoke not measured in our study (eg, smoking by nonparent household contacts) also could have affected asthma severity and exacerbations. However, 90% of tobacco smoke exposure in children occurs from parents.⁴³ Given that Latino families are more likely to have intergenerational households compared with white and black families,⁴⁴ it is possible that additional sources of environmental tobacco smoke exposure in our Latino population could have come from caregivers and other relatives living in the home. Nonetheless, in a community-based study of inner-city children with asthma (82% of which were Hispanic or black), 94% of caregivers were parents, and smoking status of these caregivers was more

strongly associated with increased cotinine levels in children than smoking status of other household members.⁴⁵ On the basis of these observations, we assumed in our analyses that parental exposures are generally more common and influential than nonparental exposures for the majority of our study population. Likewise, this supports our use of parental smoking status as a proxy for tobacco smoke exposure in the child.

An additional limitation of our study was that we did not quantify the amount or duration of tobacco smoke exposure, which might have been helpful for estimating dose-dependent effects. Although we did not measure exposures to other sensitizing agents (eg, major indoor allergens), we included terms for serum IgE and atopic dermatitis in regression models as proxies for measuring atopic status in our study population. Accounting for the individuals with atopic status is important in light of the accepted observation that atopic individuals have an increased prevalence of asthmatic symptoms, including wheezing, and hospital visits.⁴⁶ In addition, the generalizability of our findings may be limited because we studied a specific subset of the population (black, Puerto Rican, and Mexican). However, our results are directly pertinent to the segment of the population most affected by asthma.

Our study also has a number of strengths. Recruitment of participants was subject to strict inclusion and exclusion criteria to minimize information biases. Ascertainment bias of dis-

ease status is unlikely, as asthmatic patients in our study were physician-diagnosed and well phenotyped, including by spirometry. Misclassification of race/ethnicity is also unlikely because 1 inclusion criterion required that all biological parents and grandparents identify as the same race/ethnicity. Our use of a multiethnic study population is another strong point of our study, given that the majority of previously published studies have been conducted in white/European populations.

Sixteen years have passed since tobacco use was declared a pediatric disease by the commissioner of the US Food and Drug Administration in 1995.⁴⁷ Yet today, a significant proportion of children still remain exposed to SHS. What can clinicians do to help break the perpetuation of health consequences of smoking? The American Academy of Pediatrics policy statement on tobacco use provides recommendations and guidelines for physicians that cover personal and professional behavior, clinical practice, and advocacy.⁴⁸ Clinicians are recommended, in part, to ask patients about tobacco use during each clinical visit. This screening has been identified by the US Public Health Service as the most important step in addressing tobacco use and dependence.⁴⁹ These recommendations are relevant given that compared with non-Hispanic whites, fewer Hispanic patients are offered screening and counseling for tobacco use during primary care visits,⁵⁰ and black and Latino patients are both less likely to receive tobacco ces-

sation interventions⁵¹ or use nicotine replacement therapy for smoking cessation.⁵²

CONCLUSIONS

Our results reveal that a relatively brief (9-month) period of tobacco smoke exposure during a crucial period of pulmonary development has significant consequences in the subsequent risk for persistent asthma and asthma-related outcomes. This observation lends deeper insight into the correlation between tobacco smoke exposure and asthma, and may hopefully encourage better translation of research on effective smoking prevention and cessation interventions, particularly among women during pregnancy.

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