Environmental Tobacco Smoke and Airway Obstruction in Children With Sickle Cell Anemia

Robyn T. Cohen, MD, MPH; Robert C. Strunk, MD; Joshua J. Field, MD; Carol L. Rosen, MD; Fenella J. Kirkham, MD; Susan Redline, MD; Janet Stocks, PhD; Mark J. Rodeghier, PhD; and Michael R. DeBaun, MD, MPH

Background: The contribution of environmental tobacco smoke (ETS) exposure to pulmonary morbidity in children with sickle cell anemia (SCA) is poorly understood. We tested the hypothesis that children with SCA and ETS exposure would have an increased prevalence of obstructive lung disease and respiratory symptoms compared with children with SCA and no ETS exposure. **Methods:** Parent reports of ETS and respiratory symptom frequency were obtained for 245 children with SCA as part of a multicenter prospective cohort study. One hundred ninety-six children completed pulmonary function testing. Multivariable regression models were used to evaluate the associations between ETS exposure at different time points (prenatal, infant [birth to 2 years], preschool [2 years to first grade], and current) and lung function and respiratory symptoms. **Results:** Among the 245 participants, a high prevalence of prior (44%) and current (29%) ETS exposure was reported. Of the 196 children who completed pulmonary function testing, those with parent-reported infant and current ETS exposure were more likely to have airway obstruction (defined as an FEV₁/FVC ratio below the lower limit normal) compared with unexposed children (22.0% vs 3.1%, $P < .001$). Those with ETS exposure also had a lower forced expiratory flow, midexpiratory phase/FVC ratio (0.82 vs 0.97, $P = .001$) and were more likely to have evidence of bronchodilator responsiveness (23% vs 11%, $P = .03$). Current and prior ETS exposure and in utero smoke exposure were associated with increased frequency of respiratory symptoms. **Conclusions:** ETS exposure is associated with evidence of lower airway obstruction and increased respiratory symptoms in SCA.

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Abbreviations: ETS = environmental tobacco smoke; FEF_{25%-75%} = forced expiratory flow, midexpiratory phase; IUS = in utero smoke; SAC = Sleep and Asthma Cohort; SCA = sickle cell anemia

The adverse pulmonary effects of environmental tobacco smoke (ETS) exposure on children in the general population have been well described.¹ In utero smoke (IUS) exposure has been associated with wheezing, asthma, and reduced pulmonary function in infants and children.^{2,3} Infants with postnatal ETS exposure in the home have increased incidences of wheezing, lower respiratory tract infections, and changes in lung growth and airway flow.^{4,5} Current ETS exposure has been associated with asthma prevalence and severity, with some studies showing an association between it and decreased pulmonary function.^{2,6,7}

The relationship between ETS and pulmonary morbidity among individuals with sickle cell anemia (SCA) is poorly defined. ETS may have particularly adverse consequences for children with SCA because research

in otherwise healthy individuals has demonstrated a relationship between ETS and processes important to the pathogenesis of SCA, including inflammation,⁸ oxidative stress,^{9,10} and endothelial dysfunction.^{11,12} The small amount of published data on the impact of smoke exposure (active and passive) in patients with SCA has been inconsistent, with a few small cohort studies showing associations between smoke exposure and vasoocclusive events,^{13,14} whereas a larger cohort study found no association between active smoking and acute chest syndrome.¹⁵ No studies to date have specifically examined the impact of ETS on lung function in children with SCA or have attempted to identify the relationship between timing of ETS exposure and outcomes.

Given the observations that ETS contributes to pulmonary morbidity in the general population and

potentially increases SCA-related morbidity, we postulate that ETS is associated with increased pulmonary morbidity in children with SCA. Determining the relationship between ETS and morbidity in children with SCA is important because current anticipatory guidance for families of children with SCA does not include prevention of ETS exposure.¹⁶ In this study, we tested the hypothesis that ETS is associated with pulmonary morbidity (airway obstruction and increased frequency of respiratory symptoms) in children with SCA. Evidence to support this hypothesis would provide a strong and specific rationale for educating families about the negative effects of ETS on children with SCA.

MATERIALS AND METHODS

A detailed description of the methods is provided in e-Appendix 1. We conducted a cross-sectional analysis of baseline data collected as part of the Sleep and Asthma Cohort (SAC) study of children aged 4 to 20 years with SCA (HbSS or HbSβ^o).¹⁷ Participants were recruited from pediatric hematology clinics at two sites in the United States (St. Louis, Missouri, and Cleveland, Ohio) and one in London, England. Children were ineligible for participation if they themselves were smokers; receiving long-term blood transfusions or long-term positive airway pressure therapy at the time of enrollment; were participating in a clinical trial for blood transfusions, oxygen, or hydroxyurea; or had chronic lung disease (other than asthma) or structural heart disease. Institutional approval was obtained from participating sites, and informed consent was obtained according to institutional policies.

Participants completed questionnaires and underwent blood sampling for a CBC and total serum IgE level. Spirometry (before and after bronchodilator) was performed by SAC-certified technicians, and procedures were adopted with permission from the Childhood Asthma Research and Education Network.¹⁸ Lower airway obstruction was defined as an FEV₁/FVC below the lower

limit of normal observed in healthy black children.^{19,20} A 12% increase in FEV₁ after albuterol inhalation was considered a positive bronchodilator response.²⁰

Parents were asked eight questions about past and present in-home ETS from the Childhood Asthma Management Program Smoke Exposure Questionnaire.²¹ Questions focused on IUS, ETS exposure in infancy (until the child's second birthday), ETS exposure during the preschool period (age 2 years until starting first grade [age approximately 6 years]), and current exposure. Any ETS was defined as a positive response to any of the questions about ETS exposure at any time point.

Respiratory symptom frequency was assessed with the Childhood Asthma Management Program Respiratory Symptom Questionnaire.²¹ Respondents indicated the frequency of cough or wheeze in several settings, and response options were on an ordinal scale of never, at least once but not monthly, at least once a month but not weekly, at least once a week but not daily/nightly, and almost every day/night.

Statistical Analysis

Characteristics of participants with and without ETS exposure were compared with χ^2 tests for categorical variables, Student *t* tests for normally distributed continuous variables, and Wilcoxon rank sum tests for nonnormally distributed continuous variables. Linear regression models examined the association between ETS exposure and lung function (with data expressed as % predicted values based on age, sex, height, and race^{19,22}). Logistic regression models were used to examine associations between ETS and airway obstruction and bronchodilator responsiveness. Ordinal regression was used to examine associations between ETS and respiratory symptom frequency. In these models, ORs > 1 indicated associations with higher symptom frequency and ORs < 1 indicate associations with lower symptom frequency. The top-two symptom frequency categories (almost every day/night and at least once a week but not daily/nightly) were combined so that statistical criteria (model convergence and proportional odds assumption) would be met for all models. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc) software.

RESULTS

Baseline Characteristics

Of the 252 children enrolled in SAC, 245 (97%) had documented information about ETS exposure from the baseline questionnaire. Eighty-seven percent of questionnaire respondents were the mothers of the study participants. One hundred twenty-six children (51%) had reported in-home ETS during at least one period during their life. Those with ETS at any time point were more likely to have several indicators associated with lower socioeconomic status, including having a primary caregiver who was not married ($P < .0001$), a primary caregiver who did not graduate from high school ($P = .008$), or a family income that was below the median for the study population ($P = .03$). Among those with and without parent-reported ETS exposure, no differences existed in asthma status, family history of asthma, hemoglobin level, WBC count, or total serum IgE levels (Table 1).

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Affiliations: From the Department of Pediatrics (Dr Cohen), Boston University School of Medicine, Boston, MA; Department of Pediatrics (Dr Strunk), Washington University School of Medicine, St. Louis, MO; Blood Research Institute (Dr Field), Blood Center of Wisconsin, Medical College of Wisconsin, Milwaukee, WI; Department of Pediatrics (Dr Rosen), School of Medicine, Case Western Reserve University, Cleveland, OH; Neurosciences Unit (Dr Kirkham) and Portex Respiratory Unit (Dr Stocks), UCL Institute of Child Health, London, England; Department of Medicine (Dr Redline), Harvard Medical School, Boston, MA; Rodeghier Consultants (Dr Rodeghier), Chicago, IL; and Department of Pediatrics (Dr DeBaun), Vanderbilt School of Medicine, Nashville, TN.

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Correspondence to: Michael R. DeBaun, MD, MPH, Vanderbilt-Meharry Center of Excellence in Sickle Cell Disease, Department of Pediatrics, Vanderbilt University School of Medicine, 2200 Children's Way, Room 11206DOT, Nashville, TN 37232-9000; e-mail: m.debaun@vanderbilt.edu

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Timing of ETS Exposure

IUS exposure was reported for 11% (27 of 242) of participants. Forty-four percent (106 of 241) had parent-reported ETS exposure during infancy (between birth and age 2 years), and 43% (104 of 241) had exposure during the preschool period (between age 2 years and first grade). Approximately 29% (70 of 245) of children had current exposure. Most children with ETS exposure during one period of their life had additional exposure during other periods (Table 2). Notably, among children whose parents reported ETS exposure during infancy, only 54% (57 of 106) had current exposure. Similarly, among children with exposure during the preschool years, 58% (60 of 104) had current exposure.

ETS and Lung Function

A total of 196 children aged ≥ 6 years with complete smoke exposure data performed spirometry that was acceptable according to American Thoracic Society standards (Table 1). ETS during the infancy and preschool periods was associated with lower FEV₁/FVC and forced expiratory flow, midexpiratory phase (FEF_{25%-75%})/FVC ratios compared with unexposed children. These findings reflected relatively higher values of FVC and relatively lower values in FEF_{25%-75%} but no significant reduction in FEV₁ among those exposed (Fig 1). Current ETS exposure was also associated with a lower FEV₁/FVC ratio and a higher FVC % (Fig 1). ETS at all time points was associated with an increased odds of having airway obstruction (Fig 2A), whereas maternal smoking during infancy

and the preschool period were associated with having a positive bronchodilator response (Fig 2C). Of 25 children with airway obstruction, 13 had a bronchodilator response of $> 12\%$. Prebronchodilator spirometry among children with IUS exposure was not significantly different from prebronchodilator spirometry among children without IUS exposure. Lung function results were unchanged after adjusting for hemoglobin level, physician diagnosis of asthma, skin test reactivity (as a marker for atopic status), family income, or education (data not shown).

ETS and Respiratory Symptoms

Current ETS exposure was significantly associated with respiratory symptoms, including increased frequency of cough and wheeze with exercise. IUS and current ETS exposure were also associated with more-frequent nighttime awakening because of cough and wheeze. ETS was not associated with daytime cough and wheeze unrelated to exercise (Table 3).

DISCUSSION

The prevalence of parent-reported early life and current ETS exposure among children with SCA was high. ETS exposure during infancy and the preschool period was associated with a lower FEV₁/FVC, a lower FEF_{25%-75%}/FVC, a higher FVC, and airway reactivity in the form of bronchodilator responsiveness. ETS exposure after birth was more consistently associated with lung function than was IUS exposure, although IUS was significantly associated with respiratory

Table 1—Baseline Characteristics of the Study Population, Stratified by Reported ETS Exposure at Any Time Point

Variable	No ETS Exposure (n = 119)	Any ETS Exposure (n = 126)	P Value
Demographics			
Age, y	10 (4-18)	11 (4-18)	.06
Male sex	47.1	52.4	.40
SCD characteristics			
Hemoglobin, g/dL	8.4 (6.0-11.8)	8.2 (6.0-11.4)	.20
WBC ($\times 1,000$ cells)	12.0 (3.4-23.5)	12.0 (3.6-42.2)	.91
Lung function			
No. participants	96	100	...
FVC, % predicted	88.0 (50.7-122.3)	94.4 (61.6-131.9)	<.002
FEV ₁ , % predicted	86.4 (49.8-119.8)	88.6 (55.0-122.6)	.23
FEV ₁ /FVC ratio	0.87 (0.66-1.00)	0.83 (0.63-0.99)	<.001
FEV ₁ /FVC, % predicted	98.5 (75.0-111.9)	94.2 (73.6-110.8)	<.001
FEF _{25%-75%} , % predicted	79.8 (27.8-129.0)	71.7 (27.0-142.4)	.24
FEF _{25%-75%} /FVC ratio	0.97 (0.34-1.84)	0.82 (0.33-1.53)	.001
% change in FEV ₁ after bronchodilator, mean (range)	6.0 (0.1-26.6)	7.8 (0.0-31.7)	.03
Had lower airway obstruction ^a	3.1	22.0	<.001
Had $\geq 12\%$ bronchodilator response	11.1	23.2	.03

Data are presented as mean (range) or % unless otherwise indicated. ETS = environmental tobacco smoke; FEF_{25%-75%} = forced expiratory flow, midexpiratory phase; SCD = sickle cell disease.

^aLower airway obstruction: FEV₁/FVC ratio below the lower limit normal (ie, below the fifth centile compared with healthy subjects of the same age, sex, height, and race/ethnicity).¹⁹

Table 2—Overlap of Participant-Reported (*n* = 126) ETS Exposure at Multiple Time Points

Timing of Exposure	Value
No. participants with IUS exposure	27
Participants with IUS exposure who also had ETS during infancy	26 (96)
No. participants with ETS exposure during infancy	106
Participants with ETS exposure during infancy and the preschool period	93 (88)
Participants with infant ETS exposure who also had current ETS exposure	57 (54)
No. participants with current ETS exposure	70
Participants with current ETS exposure who also had prior ETS exposure	65 (93)

Data are presented as No. (%) unless otherwise indicated. IUS = in utero smoke. See Table 1 legend for expansion of other abbreviation.

symptoms. Current ETS exposure, was associated with current respiratory symptoms, a decreased FEV₁/FVC ratio, and airway reactivity.

Increased FVC has been associated with obstructive lung disease in prior studies. In a study comparing longitudinal changes in lung function of children with mild to moderate asthma to lung function of healthy control subjects, children with mild to moderate asthma had similar FEV₁ values but decreased FEV₁/FVC ratios as a result mainly of higher FVC.²³ Early life exposure to ETS may have particularly long-term consequences because a significant portion of lung development occurs in early childhood, including septation and proliferation of alveoli, increases in the caliber and length of conducting airways, growth and development of the pulmonary vascular bed, and thinning of the smooth muscle component of pulmonary vessel walls.^{24,25} Although patterns of airway growth are strongly influenced by genetic factors, disturbances in the developmental process as a result of early life insults (of which ETS exposure may be one) could disturb normal growth patterns of the developing lung. A more definitive prospective study is warranted to further examine associations between ETS and altered lung development in children with SCD because if true, an ETS intervention should be specifically targeted to parents of newborns with sickle cell disease.

One possible mechanism for this disruption of normal development is through oxidative damage. Studies in humans have demonstrated a reduced antioxidant response in the lungs of newborn infants, potentially resulting in a greater oxidant tissue burden and long-term alterations in structure and function.²⁶ Furthermore, studies have shown higher levels of urine and blood isoprostanes (a marker of oxidative stress) among children exposed to secondhand smoke compared with unexposed children.⁹ Isoprostanes not only have been shown to be a marker of oxidative stress but also

FIGURE 1. Multivariable linear regression models of the association between environmental tobacco smoke (ETS) exposure at different time points and lung function outcomes. A, Association between ETS and FEV₁/FVC %. B, Association between ETS and FEF₂₅₋₇₅/FVC ratio. C, Association between ETS and FVC %. D, Association between ETS and FEV₁ %. E, Association between ETS and FEF₂₅₋₇₅ %. F, Association between ETS and % change in FEV₁ after albuterol. Data are presented as the unstandardized (β) estimate (95% CI) and *P* value. FEF₂₅₋₇₅ = forced expiratory flow, midexpiratory phase.

FIGURE 2. A, B, Multivariable logistic regression models of the association between ETS exposure at various time points and the presence of airway obstruction (FEV₁/FVC % below the lower limit of the 95% CI for age) (A) and bronchodilator responsiveness (> 12% improvement in FEV₁ after receiving albuterol) (B). Data are presented as ORs, with error bars representing 95% CIs. See Figure 1 legend for expansion of abbreviation.

are bioactive compounds with deleterious effects on pulmonary physiology, including bronchoconstriction²⁷ and nonspecific airway hyperresponsiveness.²⁸ This could explain why children with SCA, already subject to increased oxidative stress,²⁹ also have a tendency toward airway obstruction and airway hyperresponsiveness, even in the absence of classic atopic asthma.

A surprising finding in the present study is that IUS exposure was not consistently associated with lung function outcomes, which is in contrast to prior studies^{30,31} of children without SCA. Applicability of those studies to the current cohort is limited for several reasons. Many of these studies were conducted in newborns who did not yet have postnatal ETS exposure. Because most infants whose mothers smoked during pregnancy will continue to have ETS exposure after birth, effects of IUS will be exacerbated by subsequent exposure.^{3,32} Perhaps the most compelling reason for a lack of an

association is the length of time that passed between the mothers' pregnancy and the ascertainment of the exposure. The average age of the study participants at the time the smoke exposure history was obtained was 10 years.

This study had a number of strengths, including objective measurements of lung function according to a standardized research protocol with centralized overreading. The major limitations of this study were related to methods of ascertaining ETS exposure among participants. ETS questions were answered primarily by the participants' mothers, which may underestimate the extent of current ETS exposure either because of reporting bias if it is perceived to be more socially acceptable to report previous ETS in a child's home rather than current exposure or because of parental unawareness of their child's exposures outside their own home.³³ The data for approximately 50% of children with prior exposure who no longer have current exposure raise questions about underreporting of current exposure, which may have biased the results toward the null. Another possibility is that parents of children with milder disease tended to continue to smoke, whereas those of the sickest children did not, a phenomenon known as the healthy smoker effect.³⁴ In addition, the questions only pertained to in-home exposure and may not adequately ascertain all possible opportunities for ETS exposure, including in the car, other people's homes, and public places. The small number of participants with reported IUS exposure (11%) reduces the ability to detect a true difference when one exists.

In summary, this study demonstrates that early exposure to ETS is associated with airway obstruction in children with SCA. Future evaluations of this prospective cohort will include more extensive ETS questionnaires administered to both parents and participants and questions about exposures not only in the home but also in the car, work environments, and public places as well as around having friends who smoke.^{35,36} Objective validation of current ETS exposure with the use of cotinine analysis and biomarkers of oxidative stress and inflammation will also be obtained to

Table 3—Ordinal Regression^a Models of the Association Between ETS at Different Time Points and Frequency of Respiratory Symptoms During the Previous 6 Mo

Symptom	IUS Exposure		ETS Exposure From Mother During Infancy (0-2 y)		Current ETS Exposure	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Daytime cough/wheeze with exercise	2.3 (1.2-4.6)	.01	2.8 (1.5-5.1)	< .001	1.7 (1.0-2.8)	.03
Daytime cough/wheeze unrelated to exercise	1.0 (0.06-2.1)	.94	0.9 (0.5-1.7)	.67	1.1 (0.7-1.8)	.78
Nighttime cough/wheeze causing awakening	2.4 (1.2-4.8)	.01	1.3 (0.7-2.3)	.47	2.4 (1.4-4.1)	.002

See Table 1 and 2 legends for expansion of abbreviations.

^aORs > 1 indicate associations with higher symptom frequency, and ORs < 1 indicate associations with lower symptom frequency.

more comprehensively assess the impact of this potentially preventable risk factor in children with SCA.

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Additional information: The e-Appendixes can be found in the "Supplemental Materials" area of the online article.

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