Socioeconomic Status, Smoke Exposure, and Health Outcomes in Young Children With Cystic Fibrosis

Thida Ong, MD,[a] Michael Schechter, MD, MPH,[b] Jing Yang, MS,[c] Limin Peng, PhD,[c] Julia Emerson, MD, MPH,[a] Ronald L. Gibson, MD, PhD,[a] Wayne Morgan, MD,[d] Margaret Rosenfeld, MD, MPH,[a] for the EPIC Study Group

abstract

BACKGROUND: Lower socioeconomic status (SES) and environmental tobacco smoke (ETS) exposure are both associated with poorer disease outcomes in cystic fibrosis (CF), and children with low SES are disproportionately exposed to ETS. We analyzed a large cohort of young children with CF to distinguish the impact of SES and ETS on clinical outcomes.

METHODS: The Early *Pseudomonas* Infection Control Observational study enrolled *Pseudomonas*-negative young children with CF <13 years of age. An enrollment survey assessed SES and ETS exposures. Forced expiratory volume in 1 second (FEV_1), crackles and wheezes, and weight-for-age percentile were assessed at each clinical encounter over at least 4 years. Repeated measures analyses estimated the association of SES and ETS exposures with longitudinal clinical outcomes, adjusting for confounders.

RESULTS: Of 1797 participants, 1375 were eligible for analysis. Maternal education was high school or less in 28.1%, 26.8% had household income <$40 000, and 43.8% had Medicaid or no insurance. Maternal smoking after birth was present in 24.8%, more prevalent in household with low SES. In separate models, lower SES and ETS exposure were significantly associated with lower FEV_1% predicted, presence of crackles or wheezes, and lower weight percentile. In combined models, effect estimates for SES changed minimally after adjustment for ETS exposures, whereas estimates for ETS exposures were attenuated after adjusting for SES.

CONCLUSIONS: ETS exposure was disproportionately high in low SES families in this cohort of children with CF. Lower SES and ETS exposure had independent adverse effects on pulmonary and nutritional outcomes. Estimated effect of SES on FEV_1 decreased minimally after ETS adjustment, suggesting health disparity risks independent of ETS exposure.

[a]*Division of Pulmonary and Sleep Medicine, Department of Pediatrics, University of Washington, Seattle, Washington;* [b]*Division of Pulmonary Medicine, Department of Pediatrics, Virginia Commonwealth University, Children's Hospital of Richmond at VCU, Richmond, Virginia;* [c]*Department of Biostatistics and Bioinformatics, Emory University, Atlanta, Georgia; and Departments of* [d]*Pediatrics and Physiology, Pediatric Pulmonary Center, University of Arizona, Tucson, Arizona*

Dr Ong contributed to data interpretation and drafted the initial manuscript; Drs Schechter, Emerson, and Rosenfeld conceptualized and designed the study, carried out the initial analysis, interpreted the data, and reviewed and revised the manuscript; Drs Gibson and Morgan contributed to data interpretation and critically reviewed the manuscript; Ms Yang and Dr Peng carried out data analysis, contributed to data interpretation, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Among patients with cystic fibrosis, low socioeconomic status (SES) and environmental tobacco smoke (ETS) exposures have both been associated with poorer outcomes. However, limited studies have assessed the role of ETS exposure in health outcomes associated with low SES.

WHAT THIS STUDY ADDS: In a large US cohort of children with cystic fibrosis, we confirm disproportionate ETS exposure in low SES families. The estimated effect of SES on pulmonary and nutritional outcomes decreased minimally after adjustment for ETS, suggesting disparity risks independent of smoke exposure.

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Disparities in health outcomes due to socioeconomic status (SES) are well recognized in many chronic diseases of childhood, including asthma and diabetes. Among patients with cystic fibrosis (CF), refinements in the treatment of CF have resulted in dramatic improvements in nutritional status, lung function, and longevity in the overall population. Nonetheless, there is increased awareness of variation in the severity and progression of CF lung disease among individuals afflicted with this disease.[1] Although CF transmembrane conductance regulator (CFTR) mutations and genetic modifiers play an important role in the heterogeneity of CF outcomes, the role of environmental exposures, such as low SES and environmental tobacco smoke (ETS) exposure, are also of great importance.[2–6] The course of disease in any individual with CF depends on how these influences interact to promote and mitigate the importance of each other.[7]

Studies from both the United Kingdom and the United States have defined a strong association between SES and CF disease outcomes.[2,3,8,9] Low SES is associated with a twofold to threefold higher mortality rate and significantly worse lung function and nutritional status.[3] Regional median family income shows an exposure-response relationship with worsened mortality, lung function, and nutrition, demonstrating that the association is incremental rather than a dichotomous one that affects only the impoverished.[2]

The reason for the SES association with CF outcomes is multifactorial. One link appears to be the correlation between SES and ETS exposure. In 2013, monthly or more frequent tobacco smoke exposure was reported in 23.5% of individuals with CF in the United States.[1] There is a clear relationship between smoking and SES in the general population, and this extends to families of children with CF.[10–12] A dose-dependent association of ETS exposure with poor lung function and growth in children with CF was initially reported in 1990 among attendees of a summer camp and has been confirmed in most (although not all) subsequent reports.[13–16] A recent publication exploring this relationship confirmed the continued high prevalence of ETS exposure in patients with CF, especially those with low SES, and the association with decreased lung function.[17] That analysis found that the relationship between SES and CF outcomes was significantly attenuated by adjustment for ETS exposure, suggesting that the observed association between low SES and lower lung function was in large part due to the greater exposure to ETS among children with low SES. These findings have important implications in understanding health disparities, so we sought to evaluate them further by using a highly characterized, large, contemporary US cohort of patients with CF assembled specifically to study longitudinal outcomes in young children with CF. Specifically, our objective was to evaluate the association of SES and ETS both independently and jointly on longitudinal measures of lung function, presence of crackles or wheezes, and weight-for-age percentile in the Early *Pseudomonas* Infection Control Observational (EPIC OBS) cohort. We hypothesized that we would observe adverse effects of both SES and ETS exposure on clinical status, but that the effect of SES would be significantly attenuated by ETS exposure.

METHODS

Study Participants

The design of the EPIC OBS Study has been described previously.[18,19] Children with an established diagnosis of CF who were 0 to 12 years of age and had no previous lifetime isolation of *Pseudomonas aeruginosa* from respiratory cultures or who were *P aeruginosa* negative for ≥2 years if previously *P aeruginosa* positive were enrolled at 59 accredited US CF care centers between 2004 and 2006.[20] EPIC OBS participants were included in the current analysis if they were enrolled by the end of 2006, had a baseline family survey (see Data Collection section) completed within 1 month of enrollment, and had follow-up data for a minimum of 4 years. Written informed consent was obtained from the family of each participant, and the study was approved by the institutional review board at each participating site.

Data Collection

Study data were collected at enrollment, annually, and at each clinical encounter via study-specific forms and the Cystic Fibrosis Foundation National Patient Registry, as previously reported.[18] This analysis used self-reported (by parent or guardian) data from enrollment on ETS exposures, maternal education, annual household income and insurance status, and encounter-based data on forced expiratory volume in 1 second (FEV_1) (ages 6 and older) and other demographic and clinical characteristics. FEV_1 was expressed as a percentage of the predicted value based on the reference equations of Wang et al[21] and Hankinson et al.[22] The data cutoff for this analysis was December 31, 2010.

Statistical Analysis

SES predictors included mother's education (high school or less, college or more), annual household income (<$40 000, $40 000–$80 000, ≥$80 000), and insurance status (Medicaid, other insurance, no insurance). ETS predictors included history of mother smoking during pregnancy, mother smoking any

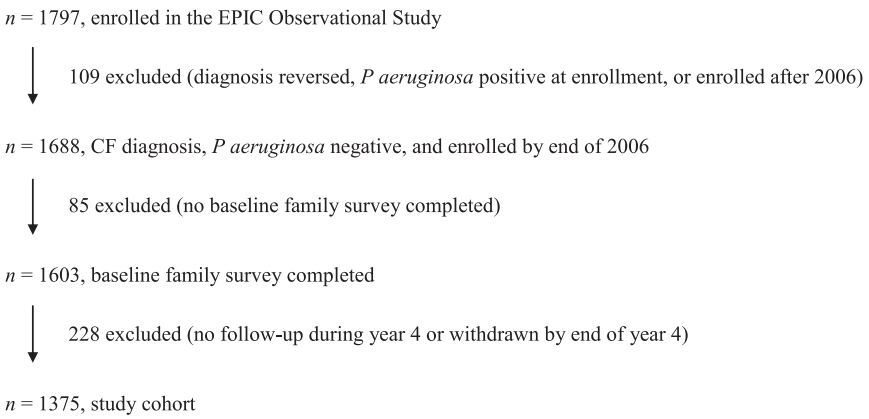

FIGURE 1
Selection of the study cohort.

time after birth of child, household member smoking, and child ever around people who smoked in the past 3 months. The primary outcome was encounter-based measures of FEV_1% predicted during follow-up through 2010, which was year 4 to 6 of the study depending on the year of enrollment.

Repeated measures analyses based on linear mixed models were used to evaluate the effect of potential ETS and SES predictors reported at baseline on longitudinal measures of FEV_1% predicted. A time variable, age in years at each visit, was included in all models to capture the change in FEV_1% predicted over time. A first-order autoregressive autocorrelation working correlation structure was adopted to account for the within-subject correlation among repeated measurements of FEV_1. All models were adjusted for demographic and disease-specific covariates (age, sex, race, ethnicity, CFTR genotype risk group, and diagnosis after pre- or neonatal screening).[23,24]

First, SES and ETS exposures were evaluated separately as predictors of lung function. SES exposures were modeled together to assess their collective effects. Due to concerns for collinearity of ETS exposure variables, the a priori decision was made to evaluate each ETS exposure in separate models. Then, SES and ETS exposures were evaluated in combined models. The estimates of the effect of each SES and ETS exposure from the separate and combined models were compared. Similar repeated measures analyses were conducted to assess the association of SES and ETS exposures with occurrence of crackles or wheezes on chest examination at clinical encounters during follow-up and with longitudinal measures of weight-for-age percentile. For the outcomes of crackles and wheezes, we fitted multivariable longitudinal logistic regression models based on a generalized estimating equations approach with a first-order autoregressive autocorrelation working correlation structure. For the outcome of weight-for-age percentile, we used linear mixed models that included age and a quadratic term of age to accommodate for potentially nonlinear changes of weight percentile over time. Adjusted coefficient or odds ratio (OR) with corresponding 95% confidence interval (CI) estimates were reported for each model, and a $P < .05$ was considered statistically significant. All analyses were performed by using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Figure 1 describes selection of the study cohort. A total of 1797 participants were enrolled in EPIC OBS; 109 were excluded from this analysis cohort because their CF diagnosis was subsequently reversed, they were *P aeruginosa* positive at enrollment, or they were enrolled after 2006; 85 participants were excluded because the baseline family survey was not completed; 228 were excluded because they were not followed for at least 4 years. The resulting cohort for this analysis comprised 1375 participants.

Characteristics of the study cohort at enrollment are summarized in Table 1.

Maternal education was reported to be high school or less in 28.1%, annual household income <$40 000 in 26.8%, and Medicaid or no insurance in 43.8% of participants. Figure 2 shows that children from low SES households characterized by low maternal education, low household income, and/or Medicaid or no insurance had higher percentages with each of the ETS exposures than children from higher SES households.

Impact of SES and ETS on Lung Function

During year 4 of the study, the best value of FEV_1% predicted averaged 101.8 (SD 16.0) among 1065 children ages 6 and older. In models evaluating ETS and SES exposures separately, all SES exposures had significant negative associations with mean absolute FEV_1% predicted during the study period (Table 2, SES model). Similarly, ETS exposures had significant negative associations with mean absolute FEV_1% predicted (Table 2, ETS models 1–4); the most negative association was observed for the mother smoking after the child's birth, which was associated with mean FEV_1% predicted 6.0% lower (95% CI −7.4 to −4.5;

$P < .0001$) compared with children whose mothers did not report smoking after birth.

Associations between SES predictors and FEV_1% predicted were minimally changed when SES predictor variables and ETS exposures were evaluated simultaneously in multivariable models. In contrast, the associations between ETS exposures and FEV_1 % predicted were attenuated to a greater degree. Figure 3 shows the estimates of mean difference in absolute FEV_1% predicted between those exposed and unexposed from the final multivariable models, and for comparison, estimates from the models evaluating SES and ETS exposures separately (from Table 2). The separation between the estimates from the combined models (dark balls and solid lines) and the models evaluating ETS and SES separately (gray balls and dashed lines) indicate the degree to which the effect of the exposure was attenuated in the combined model. All measures of SES and 3 of the 4 measures of ETS exposures (Fig 3B) remained significant independent predictors of lung function in the multivariable models.

Impact of SES and ETS on Chest Examination Findings

Crackles or wheezes on chest auscultation were reported for 22% to 24% of the participants during each of years 1 to 4 on study. We found an increased risk of crackles or wheezes among children from households with lower income, relative to households with the highest level of income (OR 1.4; 95% CI 1.0 to 2.0; $P = .03$ for income <$40 000; and OR 1.3; 95% CI 1.0 to 1.8; $P = .05$ for income $40 000–$79 000). There was also an increased risk of crackles or wheezes among children whose mothers reported smoking after the child's birth (OR 1.4; 95% CI 1.1 to 1.8; $P = .003$) or if the child was ever around smokers (OR 1.3; 95% CI 1.0 to 1.6; $P = .02$). None of these associations remained significant in the multivariate models that simultaneously evaluated SES and ETS.

TABLE 1 Characteristics of the Study Cohort at Enrollment ($n = 1375$)

	n	%
Sex		
Girls	687	50.0
Boys	688	50.0
Age at enrollment,[a] y		
0–<3	364	26.5
3–<6	381	27.7
6–<9	341	24.8
≥9	289	21.0
Race		
Not White	61	4.4
White	1314	95.6
Ethnicity		
Not Hispanic	1280	93.1
Hispanic	46	3.3
Missing	49	3.6
Genotype risk group[b]		
High risk	1074	78.1
Low risk	99	7.2
Unclassified	150	10.9
Missing	52	3.8
Diagnosis by screening[c]		
No	1046	76.1
Yes	297	21.6
Missing	32	2.3
Mother's education		
High school or less	387	28.1
Some college or more	951	69.2
Missing	37	2.7
Annual household income		
<$40 000	368	26.8
$40 000-$79 000	437	31.8
≥$80 000	363	26.4
Missing	207	15.1
Insurance status[d]		
Medicaid or no insurance	602	43.8
Private or other insurance	761	55.3
Missing	12	0.9
Mother smoked during pregnancy		
No	1083	78.8
Yes	189	13.7
Unknown	103	7.5
Mother smoked any time after birth of child		
No	974	70.8
Yes	341	24.8
Missing	60	4.4
Household member smokes cigarettes		
No	966	70.3
Yes	400	29.1
Missing	9	0.6
Child around people smoking in past 3 mo		
Ever	720	52.4
Never	631	45.9
Missing	24	1.7

[a] Mean age at enrollment was 5.7 y (SD 3.5).
[b] CFTR genotype risk group as previously described.[23,24]
[c] Includes newborn or prenatal screening.
[d] Other insurance includes Medicare, military insurance, and insurance not otherwise specified.

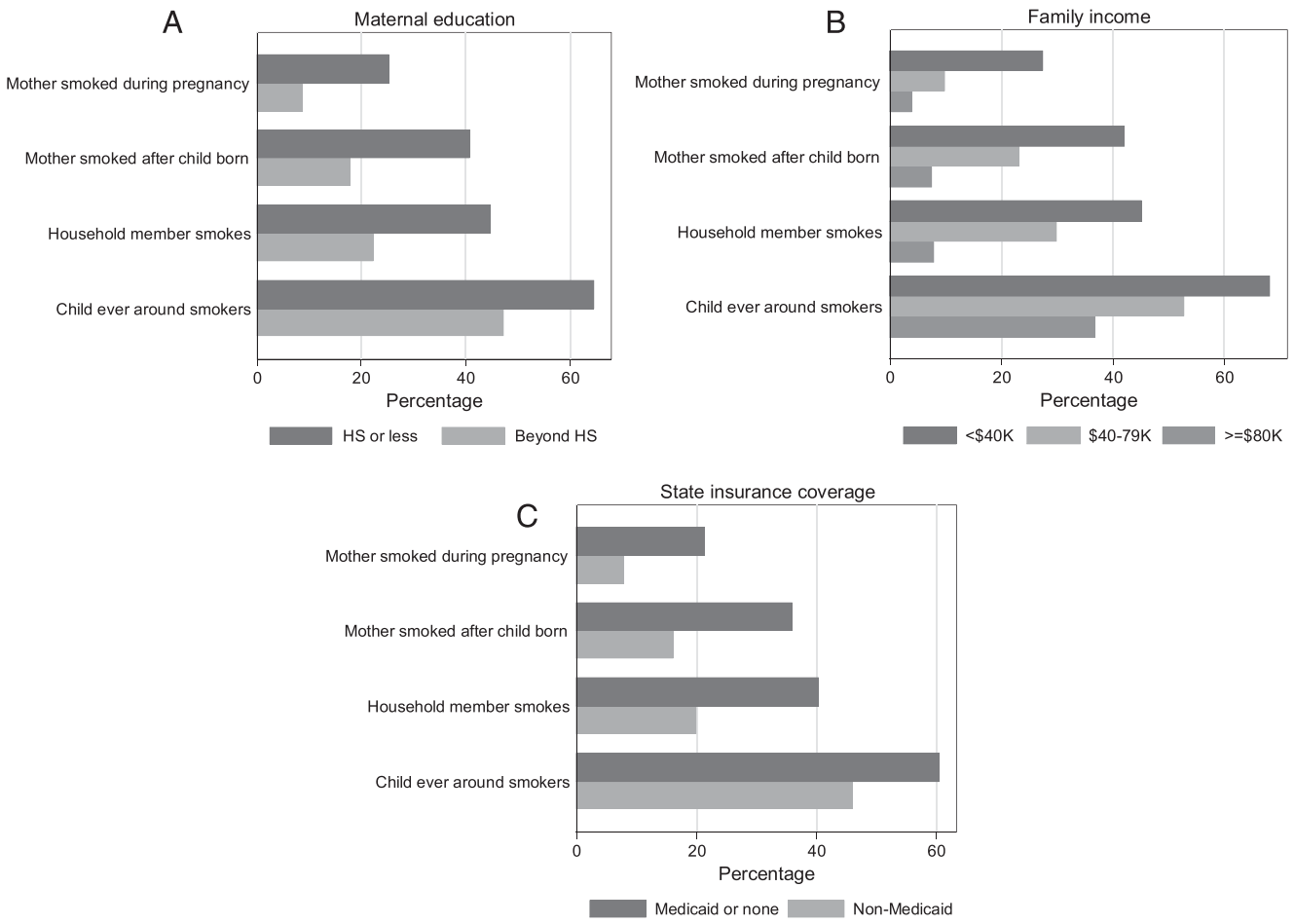

FIGURE 2
Bar charts for each SES variable: A, maternal education; B, family income; C, state insurance coverage, showing the percentage of participants exposed to ETS (as measured by 4 different questions). HS, high school.

Impact of SES and ETS on Weight-for-Age Percentile

During year 4 of the study, mean weight percentile was 50.3 (SD 27.3) among 1371 children. In separate models evaluating the effect of SES and ETS exposures, mother's education level of high school or less was associated with a mean 4.5% lower weight-for-age percentile (95% CI −7.9 to −1.2; $P = .008$) compared with college or more, and household income <$40 000 was associated with a mean 5.7% lower weight percentile (95% CI −9.8 to −1.6; $P = .007$) compared with the highest level of annual household income (Supplemental Table 3). Maternal smoking during pregnancy (−4.3%; 95% CI −7.9 to −0.65; $P = .02$) and after birth (−4.0%; 95% CI −6.9 to −1.1; $P = .007$) were also associated with lower mean weight-for-age percentiles (Supplemental Table 3).

Similar to findings for lung function, the associations between SES predictors and weight-for-age percentile were minimally changed when SES predictor variables and ETS exposures were evaluated simultaneously in multivariable models (Supplemental Table 4). ETS exposures did not remain significant predictors of weight percentile in the combined models.

DISCUSSION

This study examined a large US multicenter longitudinal cohort of young children with CF, by using robust measures of SES and ETS exposure, and confirmed previous reports of the disproportionate exposure to ETS among children in families with low SES as well as the independent association of low SES and ETS exposure with poorer lung function. In multivariable mixed models that simultaneously evaluated the impact of SES and ETS exposures, we found, contrary to our hypothesis, that the strong association between SES and lung function was only minimally affected by adjustment for ETS exposure. The associations between ETS exposures and lung function were more strongly attenuated after adjustment for SES. Our findings suggest that there are SES-related disparities in lung function independent of ETS

TABLE 2 Separate Models to Assess Impact of SES and ETS Predictors on $FEV_{1\%}$ Predicted

Exposure Variable	*n*/Observation[a]	Coefficient[b]	95% CI	*P*
SES model[c]	1050/18 416			
High school education or less		−1.90	−3.60 to −0.19	.03
Household income <$40 000		−5.82	−7.94 to −3.71	<.0001
Household income $40 000–79 000		−3.14	−4.83 to −1.44	.0003
Medicaid or no insurance		−2.49	−4.09 to −0.89	.0024
Age, y		−1.11	−1.46 to −0.76	<.0001
ETS model 1	1160/20 056			
Mother smoked during pregnancy		−4.59	−6.43 to −2.74	<.0001
Age, y		−1.10	−1.44 to −0.77	<.0001
ETS model 2	1197/20 743			
Mother smoked after child's birth		−5.98	−7.44 to −4.52	<.0001
Age, y		−1.11	−1.44 to −0.78	<.0001
ETS model 3	1240/21 607			
Household member smokes		−2.60	−4.03 to −1.16	.0004
Age, y		−1.11	−1.43 to −0.78	<.0001
ETS model 4	1224/21 321			
Child ever around smokers in past 3 mo		−3.21	−4.48 to −1.93	<.0001
Age, y		−1.11	−1.43 to −0.78	<.0001

[a] The numbers of participants and longitudinal observations for each model.

[b] The interpretation of the coefficient estimate for each SES or ETS exposure variable is the difference in mean absolute $FEV_{1\%}$ predicted between those with the exposure and those in the reference group. Each model included age in years at each visit to capture the change in $FEV_{1\%}$ predicted over time. Each model also included covariate adjustment for prespecified demographic and disease characteristics (enrollment age, sex, race, ethnicity, genotype risk group, and diagnosis by screening).

[c] Reference groups for the SES variables include any education beyond high school, income ≥$80 000, and non-Medicaid insurance.

exposure, and similarly, that ETS has impacts on lung function even after taking into account the effects of SES.

We also found a higher risk of crackles and wheezes among children with lower SES or exposure to ETS. The independent effects of SES and ETS on detection of crackles or wheezes did not persist in our combined model, likely due to the high degree of collinearity (overlap) of these characteristics. Finally, we found low SES and exposure to ETS to be associated with poorer weight. Similar to lung function, the strong association between SES and weight percentile was minimally affected by adjustment for ETS exposure, suggesting that there are SES-related disparities in nutrition that are independent of ETS exposure.

The relationship between SES and tobacco use in our cohort mirrored these relationships in the general population.[25] Twenty-five percent of children had exposure to maternal smoking in our cohort, and the prevalence was higher among families with lower SES. These data reflect national trends estimating tobacco use in 26% of adults living below the poverty level compared with 15% among those living at or above this level.[26]

Our analysis supports past reports of associations between both SES and ETS and low FEV_1.[2,3,16,17,25,27,28] The adverse association of low SES on poor lung function in CF is likely driven by multiple factors, including poorer health literacy and adherence and higher prevalence of depression and anxiety.[3,29–31] Decreased access to hospital and CF center care, although an important cause of SES-related adverse health outcomes in other chronic diseases, has not been shown to have a major influence in previous studies in CF.[3,32,33] Nonetheless, lack of access or impaired ability to navigate community resources, such as exercise activities, school advocacy for frequent absences, mental health counseling, parenting and child care support, and nutritional supplements, may limit the effectiveness of referrals generated by the CF team, impeding care delivery downstream.

Our findings differ slightly from those of Collaco and colleagues,[17] who found in their cohort study of 812 twins and siblings with CF that the association between SES and lung function was no longer significant after adjustment for ETS exposure, but that the relationship between ETS and lung function was unaffected by adjustment for SES. Potential explanations for our slightly differing results are differences in our cohorts (ours was younger and *Pseudomonas*-negative at enrollment), different measures of SES and ETS, and different sets of covariates in our multivariable models. Nonetheless, both studies report a similar prevalence of home ETS exposure and support the important adverse effects of low SES and exposure to ETS on health outcomes in CF.

To our knowledge, the detection of crackles or wheezes on chest examination in association with SES or ETS exposures has not been previously examined in CF. The presence of daily respiratory symptoms in CF have been associated with worse health outcomes, including low FEV_1 % predicted and frequency of antibiotic courses.[34–38]

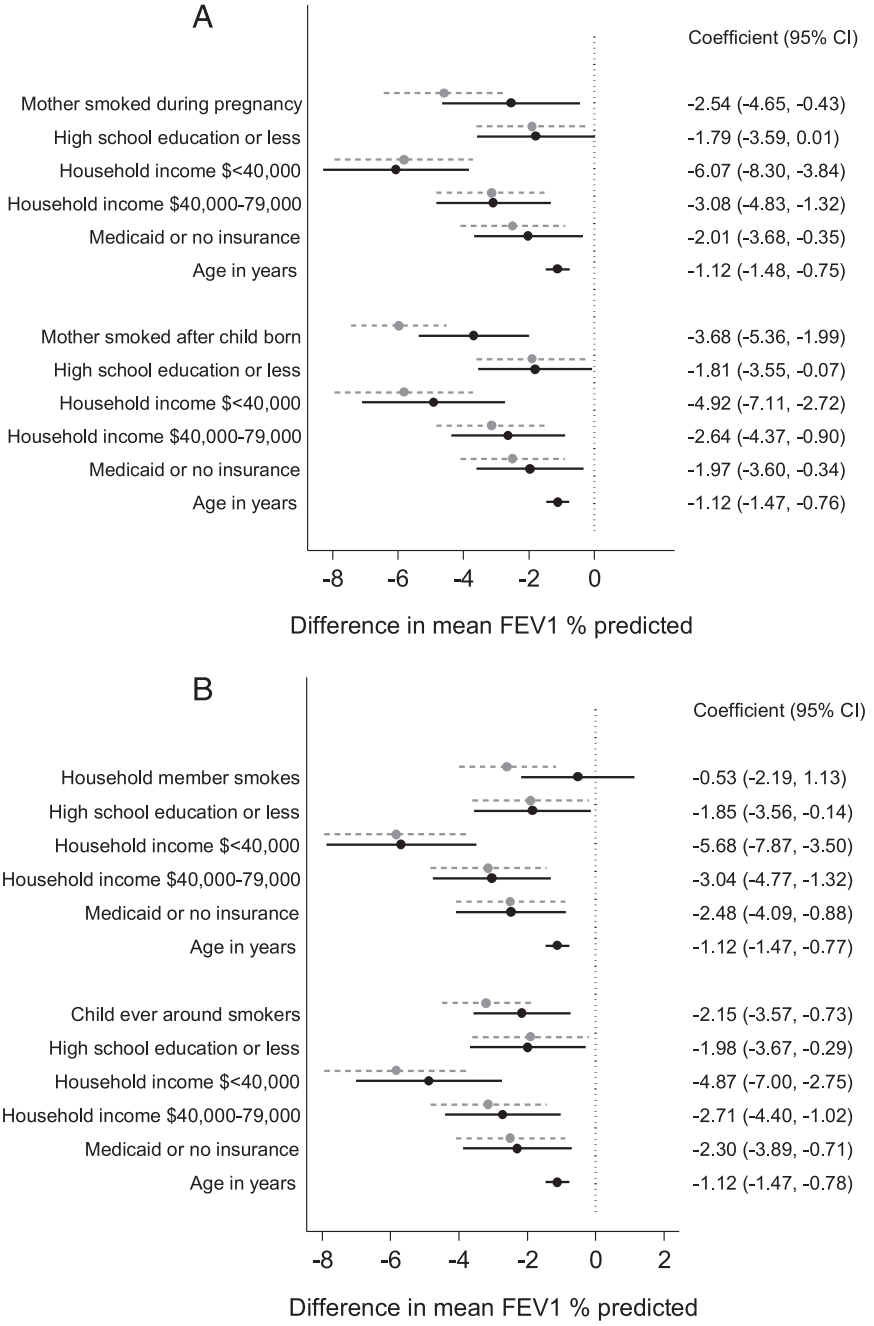

FIGURE 3

Estimates and 95% CIs (black dots, solid lines) for the difference in mean FEV_1 % predicted from multivariable models, including both SES and ETS exposures, and prespecified clinical characteristics. For comparison, gray dots, dashed lines show estimates and 95% CIs from models evaluating SES and ETS exposures separately (Table 2).

SES and ETS impact on growth and nutrition in children with CF has been reviewed.[3,7,39] In our cohort, both SES and ETS exposures were associated with lower weight percentile. Our analyses suggest that the disparities in nutritional outcomes associated with low SES, specifically maternal education level and household income, persist even after taking into account the effects of ETS. Maternal nutritional knowledge specific to CF has previously been reported to predict children's dietary adherence score.[40] Food insecurity, although not assessed in the CF population, has been associated with worse health outcomes in the general population.[41]

A strength of our study is that it includes a range of measures of both SES and ETS. SES disparities vary in degree of health-damaging exposures, including early life conditions, inadequate nutrition, poor housing, air pollution, stress, and health access.[25,28,42] Income, education level, and health insurance status as markers of SES reflect different aspects of the complex relationship of SES disparities and respiratory health. Similarly, ETS exposures may have differential impact based on source, timing, and exposure, including prenatally.[43] Our analysis supports developmental implications of smoke exposure in pregnancy and early childhood. Dose-dependent in utero smoke exposure has been associated with decreased lung function measures in healthy newborns, and infants with CF exposed to ETS have been reported to have more bronchial hyperreactivity.[44,45] Assessment of multiple SES and ETS exposures may better delineate the source of disparities to help target interventions.

An important limitation of our study is self-report of exposures, particularly ETS. Smoking may be underreported due to its social stigma, particularly around children with chronic respiratory disease. The misclassification introduced by self-report would likely attenuate the observed effect size. In addition, our cohort was selected for an absence of *P aeruginosa* infection at enrollment, so our findings may not be generalizable to children with chronic *P aeruginosa* infection. Given the observational nature of this study, we cannot determine the causal nature of relationships between SES and ETS and health outcomes.

CONCLUSIONS

Our study explored prospectively collected data as part of EPIC OBS, a large multicenter longitudinal study, which allowed examination of the effects of SES and ETS exposures on clinical outcomes in young children with CF. Our results indicate that low SES and exposure to ETS are independent risk factors for lower lung function, crackles and wheezes, and lower weight percentile in young children with CF. In addition, the effects of SES on these outcomes are not accounted for simply by disproportionate exposure to ETS among children from families with lower SES. Our findings reinforce the importance of addressing the interrelationship of SES and ETS in CF clinical outcomes analyses and suggest that health care policies addressing SES disparities and fostering smoking cessation could prove beneficial to the lung health of individuals with CF.

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APPENDIX: THE EPIC STUDY GROUP

Albany Medical College, Albany, NY, Paul Comber, MD, PhD and Terese Evens; All Children's Hospital CF Center, St Petersburg, FL, Magdalen Gondor, MD and Kathy Hosler; Baylor College of Medicine, Houston, TX, Peter Hiatt, MD and Omalee Lopez; Brown University Medical School, Rhode Island Hospital, Providence, RI, Karen Daigle, MD; Cardinal Glennon Children's Medical Center, St Louis, MO, Blakeslee Noyes, MD and Freda Branch; Children's Hospital, Boston, MA, Henry Dorkin, MD, Nicolas Fenton, and Kelsey Hill; Children's Hospital & Clinics, Minneapolis, MN, John McNamara, MD and Mary Sachs; Children's Hospital Colorado, Aurora, CO, Stacey Martiniano, MD and Meg Anthony; Children's Hospital of Los Angeles, Los Angeles, CA, Arnold Platzker, MD; Children's Hospital Medical Center of Akron, Akron, OH, Gregory Omlor, MD and Deborah Ouellette; Children's Hospital of Michigan, Detroit, MI, Ibrahim Abdulhamid, MD and Catherine Van Wagnen; Children's Hospital of Milwaukee, Milwaukee, WI, Diana Quintero, MD and Tami Miller; Children's Hospital, University of Birmingham, Birmingham, AL, Hector Gutierrez, MD and Susan Keeling; Children's Hospital of Pittsburgh, Pittsburgh, PA, David Orenstein, MD and Sandra Hurban; Children's Hospital at Westchester Medical Center, Valhalla, NY, Allen Dozor, MD and Armando Ramirez; Children's Medical Center of Dayton, Dayton, OH, Gary Mueller, MD and Sandy Bartosik; Children's Mercy Hospital, Kansas City, MO, Philip Black, MD and Rose Thompson; Children's Specialty Center, Fletcher Allen Health Care, Burlington, VT, Thomas Lahiri, MD and Rose Bergeron; Cohen Children's Hospital, Great Neck, NY, Joan DeCelie-Germana, MD, Lynn Bonitz, and Susan Galvin; Cook Children's Medical Center, Fort Worth, TX, Maynard Dyson, MD and Heather Urbanek; Dartmouth Hitchcock Clinic-Lebanon, Lebanon, NH, H. Alix Ashare, MD and Mary Griffin; Alfred I. DuPont Hospital for Children, Wilmington, DE, Aaron Chidekel, MD and Dana Geiser; Emory University School of Medicine, Atlanta, GA, Hector Gutierrez, MD and Susan Keeling; Helen DeVos Women & Children's Center, Grand Rapids, MI, Susan Millard, MD and Cynthia Gile; Intermountain CF Center, Salt Lake City, UT, Barbara Chatfield, MD and Taylor Block; Johns Hopkins University, Baltimore, MD, Peter Mogayzel, MD, PhD and Carolyn Chapman; Kaiser Permanente Medical Care Program, Oakland, CA, Byron Quick, MD and Julie Lee; Le Bonheur Children's Medical Center, Memphis, TN, Robert Schoumacher, MD and Catherine Horobetz; Massachusetts General Hospital, Boston, MA, Allen Lapey, MD and Henry Dorkin, MD; Medical College of Georgia, Augusta, GA, Kathleen McKie, MD and Heidi Stapp; Memorial Miller Children's Hospital, University of California, Irvine, Long Beach, CA, Felice Adler-Shohet, MD and Jay Lieberman, MD; Milton S. Hershey Medical Center, Penn State University, Hershey, PA, Gavin Graff, MD, Lisa Allwein, and Diane Kitch; Maine Medical Center Cystic Fibrosis Center, Portland, ME, AnneMarie Cairns, DO, Carrie Milliard, and Harmony Renna; Monmouth Medical Center, Long Branch, NJ, Robert Zanni, MD and Bridget Marra; Nationwide Children's Hospital, Columbus, OH, Karen McCoy, MD and Diana Gilmore; Nemours Children's Clinic, Jacksonville, FL, David Schaeffer, MD, Elizabeth DeLuca, and Roslyn Whitley; Northwestern University, Chicago, IL, Adrienne Savant, MD and Zainub Ashrafi; Oregon Health Sciences University, Portland, OR, Alexandra Cornell, MD and Brendan Klein; Rainbow Babies and Children's Hospital, Cleveland, OH, Michael Konstan, MD and Ashlee Parsons; Riley Hospital for Children, Indianapolis, IN, Clement Ren, MD and Lisa Bendy; Seattle Children's Hospital, Seattle, WA, Margaret Rosenfeld MD, MPH, Alan Genatossio, and Sharon McNamara; St Christopher's Hospital for Children, Philadelphia, PA, Laurie Varlotta, MD and Diana Figueroa; St Louis Children's Hospital, St Louis, MO, Thomas Ferkol, MD and Sarah Smith; Stanford University Medical Center, Palo Alto, CA, Richard Moss, MD and Colleen Dunn; SUNY Upstate

Medical University, Syracuse, NY, Christopher Fortner, MD and Donna Lindner; UMass Memorial Health Care, Worcester, MA, Evan Bailey, MD and Karen Longtine; University of California at San Francisco, San Francisco, CA, Dennis Nielson, MD and Courtney Moreno; University of Florida College of Medicine, Gainesville, FL, Terry Spencer, MD; University of Iowa Hospital and Clinics, Iowa City, IA, Richard Ahrens, MD and Mary Teresi; University of Kentucky, Lexington, KY, Jamshed Kanga, MD and Viktoria Bulkley; University of Michigan Health System, Ann Arbor, MI, Samya Nasr, MD and Dawn Kruse; University of Mississippi Medical Center, Jackson, MS, Joseph Maguire, MD; University of Nebraska Medical Center, Omaha, NE, John Colombo, MD and Jill Fahner; University of North Carolina at Chapel Hill, Chapel Hill, NC, George Retsch-Bogart, MD and Rose Cunnion; University of Rochester Medical Center, Rochester, NY, Karen Voter, MD and Judy Sroka; University of Virginia Health System, Charlottesville, VA, Deborah Froh, MD, Mary Alice Blackwell, Patricia Moss, and Christie Aderholt; University of Wisconsin, Madison, WI, Michael Rock, MD and Linda Makholm; Vanderbilt Children's Hospital, Nashville, TN, Rebekah Brown, MD and Stephanie Steen; Women & Children's Hospital of Buffalo, Buffalo, NY, Danielle Goetz, MD and Christine Roach.

ABBREVIATIONS

CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
CI: confidence interval
EPIC OBS: Early *Pseudomonas* Infection Control Observational
ETS: environmental tobacco smoke
FEV1: forced expiratory volume in 1 second
OR: odds ratio
SES: socioeconomic status

Address correspondence to Thida Ong, MD, Division of Pulmonary and Sleep Medicine, Department of Pediatrics, University of Washington, 4800 Sand Point Way NE, M/S OC.7.720, Seattle, WA 98105. E-mail: thida.ong@seattlechildrens.org

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REFERENCES

1. Cystic Fibrosis Foundation Patient Registry. Annual data report to the center directors, 2013. Available at: https://www.cff.org/2013_CFF_Annual_Data_Report_to_the_Center_Directors.pdf. Accessed September 10, 2015
2. Taylor-Robinson DC, Smyth RL, Diggle PJ, Whitehead M. The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study. *Lancet Respir Med*. 2013;1(2):121–128
3. Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *Am J Respir Crit Care Med*. 2001;163(6):1331–1337
4. Goss CH, Newsom SA, Schildcrout JS, Sheppard L, Kaufman JD. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am J Respir Crit Care Med*. 2004;169(7):816–821
5. Boyle MP, Sabadosa KA, Quinton HB, Marshall BC, Schechter MS. Key findings of the US Cystic Fibrosis Foundation's clinical practice benchmarking project. *BMJ Qual Saf*. 2014;23(suppl 1):i15–i22
6. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet*. 2015;16(1):45–56
7. Schechter MS. Nongenetic influences on cystic fibrosis outcomes. *Curr Opin Pulm Med*. 2011;17(6):448–454
8. O'Connor GT, Quinton HB, Kneeland T, et al. Median household income and mortality rate in cystic fibrosis. *Pediatrics*. 2003;111(4 pt 1). Available at: www.pediatrics.org/cgi/content/full/111/4pt1/e333
9. Barr HL, Britton J, Smyth AR, Fogarty AW. Association between socioeconomic status, sex, and age at death from cystic fibrosis in England and Wales (1959 to 2008): cross sectional study. *BMJ*. 2011;343:d4662
10. Nelson DE, Emont SL, Brackbill RM, Cameron LL, Peddicord J, Fiore MC. Cigarette smoking prevalence by occupation in the United States. A comparison between 1978 to 1980 and 1987 to 1990. *J Occup Med*. 1994;36(5):516–525

11. Schuster MA, Franke T, Pham CB. Smoking patterns of household members and visitors in homes with children in the United States. *Arch Pediatr Adolesc Med*. 2002;156(11):1094–1100

12. King K, Martynenko M, Bergman MH, Liu YH, Winickoff JP, Weitzman M. Family composition and children's exposure to adult smokers in their homes. *Pediatrics*. 2009;123(4). Available at: www.pediatrics.org/cgi/content/full/123/4/e559

13. Rubin BK. Exposure of children with cystic fibrosis to environmental tobacco smoke. *N Engl J Med*. 1990;323(12):782–788

14. Campbell PW III, Parker RA, Roberts BT, Krishnamani MR, Phillips JA III. Association of poor clinical status and heavy exposure to tobacco smoke in patients with cystic fibrosis who are homozygous for the F508 deletion. *J Pediatr*. 1992;120(2 pt 1):261–264

15. Kovesi T, Corey M, Levison H. Passive smoking and lung function in cystic fibrosis. *Am Rev Respir Dis*. 1993;148(5):1266–1271

16. Smyth A, O'Hea U, Williams G, Smyth R, Heaf D. Passive smoking and impaired lung function in cystic fibrosis. *Arch Dis Child*. 1994;71(4):353–354

17. Collaco JM, Vanscoy L, Bremer L, et al. Interactions between secondhand smoke and genes that affect cystic fibrosis lung disease. *JAMA*. 2008;299(4):417–424

18. Treggiari MM, Rosenfeld M, Mayer-Hamblett N, et al; EPIC Study Group. Early anti-pseudomonal acquisition in young patients with cystic fibrosis: rationale and design of the EPIC clinical trial and observational study. *Contemp Clin Trials*. 2009;30(3):256–268

19. Rosenfeld M, Emerson J, McNamara S, et al; EPIC Study Group Participating Clinical Sites. Baseline characteristics and factors associated with nutritional and pulmonary status at enrollment in the cystic fibrosis EPIC observational cohort. *Pediatr Pulmonol*. 2010;45(9):934–944

20. Farrell PM, Rosenstein BJ, White TB, et al; Cystic Fibrosis Foundation. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153(2):S4–S14

21. Wang X, Dockery DW, Wypij D, et al. Pulmonary function growth velocity in children 6 to 18 years of age. *Am Rev Respir Dis*. 1993;148(6 pt 1):1502–1508

22. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179–187

23. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet*. 2003;361(9370):1671–1676

24. McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. *Chest*. 2006;130(5):1441–1447

25. Celedón JC, Roman J, Schraufnagel DE, Thomas A, Samet J. Respiratory health equality in the United States. The American Thoracic Society perspective. *Ann Am Thorac Soc*. 2014;11(4):473–479

26. Jamal A, Homa DM, O'Connor E, et al. Current cigarette smoking among adults - United States, 2005-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(44):1233–1240

27. Schechter MS, Margolis PA. Relationship between socioeconomic status and disease severity in cystic fibrosis. *J Pediatr*. 1998;132(2):260–264

28. Adler NE, Rehkopf DH. U.S. disparities in health: descriptions, causes, and mechanisms. *Annu Rev Public Health*. 2008;29:235–252

29. Oates GR, Stepanikova I, Gamble S, Gutierrez HH, Harris WT. Adherence to airway clearance therapy in pediatric cystic fibrosis: socioeconomic factors and respiratory outcomes. *Pediatr Pulmonol*. 2015;50(12):1244–1252

30. Quittner AL, Goldbeck L, Abbott J, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. *Thorax*. 2014;69(12):1090–1097

31. Smith BA, Georgiopoulos AM, Quittner AL. Maintaining mental health and function for the long run in cystic fibrosis. *Pediatr Pulmonol*. 2016;51(S44):S71–S78

32. Schechter MS, McColley SA, Silva S, et al. Association of socioeconomic status with the use of chronic therapies and healthcare utilization in children with cystic fibrosis. *J Pediatr*. 2009;155(5):634–639.e1–4

33. Buu MC, Milla CE, Wise PH. Response. *Chest*. 2016;150(3):753

34. Sanders DB, Emerson J, Ren CL, et al; EPIC Study Group. Early childhood risk factors for decreased FEV1 at age six to seven years in young children with cystic fibrosis. *Ann Am Thorac Soc*. 2015;12(8):1170–1176

35. Konstan MW, Butler SM, Wohl ME, et al; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr*. 2003;142(6):624–630

36. Byrnes CA, Vidmar S, Cheney JL, et al; ACFBAL Study Investigators. Prospective evaluation of respiratory exacerbations in children with cystic fibrosis from newborn screening to 5 years of age. *Thorax*. 2013;68(7):643–651

37. VanDevanter DR, Wagener JS, Pasta DJ, et al. Pulmonary outcome prediction (POP) tools for cystic fibrosis patients. *Pediatr Pulmonol*. 2010;45(12):1156–1166

38. Ren CL, Konstan MW, Rosenfeld M, Pasta DJ, Millar SJ, Morgan WJ; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Early childhood wheezing is associated with lower lung function in cystic fibrosis. *Pediatr Pulmonol*. 2014;49(8):745–750

39. Schechter MS. Non-genetic influences on cystic fibrosis lung disease: the role of sociodemographic characteristics, environmental exposures, and healthcare interventions. *Semin Respir Crit Care Med*. 2003;24(6):639–652

40. Anthony H, Paxton S, Bines J, Phelan P. Psychosocial predictors of adherence to nutritional recommendations and growth outcomes in children with

cystic fibrosis. *J Psychosom Res*. 1999;47(6):623–634

41. Pruitt SL, Leonard T, Xuan L, et al. Who is food insecure? Implications for targeted recruitment and outreach, National Health and Nutrition Examination Survey, 2005-2010. *Prev Chronic Dis*. 2016;13:E143
42. Kerem E, Cohen-Cymberknoh M. Disparities in cystic fibrosis care and outcome: socioeconomic status and beyond. *Chest*. 2016;149(2):298–300
43. Leone FT, Carlsen KH, Folan P, et al; ATS Tobacco Action Committee; American Thoracic Society. An official American Thoracic Society research statement: current understanding and future research needs in tobacco control and treatment. *Am J Respir Crit Care Med*. 2015;192(3):e22–e41
44. Lødrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. *Eur Respir J*. 1997;10(8):1774–1779
45. Kopp BT, Sarzynski L, Khalfoun S, et al. Detrimental effects of secondhand smoke exposure on infants with cystic fibrosis. *Pediatr Pulmonol*. 2015;50(1):25–34