Early Childhood Risk Factors for Decreased FEV_1 at Age Six to Seven Years in Young Children with Cystic Fibrosis

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Abstract

Rationale: There are limited objective measures of the severity of lung disease before children are able to routinely perform spirometry, generally at age 6 years. Identifying risk factors for reduced lung function at age 6 provides opportunities to intervene and slow the progression of cystic fibrosis (CF) lung disease.

Objectives: To evaluate early childhood predictors of lung function at age 6–7 in a large U.S. CF cohort in the current era of widespread early eradication therapy for *Pseudomonas aeruginosa* (*P. aeruginosa*).

Methods: Participants were children with CF enrolled before age 4 in the Early *Pseudomonas* Infection Control (EPIC) Observational Study, a multicenter, longitudinal study that enrolled *P. aeruginosa*–negative children not exceeding 12 years of age. Linear regression was used to estimate the association between potential early childhood risk factors and the best FEV_1% predicted at age 6–7 years.

Measurements and Main Results: Four hundred and eighty-four children (of 1,797 enrolled in the EPIC Observational Study) met the eligibility criteria for this analysis. Mean (SD) age at enrollment was 2.0 (1.3) years. In a multivariable model adjusted for age at enrollment, the following risk factors were significantly associated with lower mean (95% confidence interval) FEV_1% predicted at age 6–7: weight percentile less than 10% during the year of enrollment (–5.3 [–9.1, –1.5]), *P. aeruginosa* positive during the year of enrollment (–2.8 [–5.7, 0.0]), crackles or wheeze during the year of enrollment (–5.7 [–9.4, –1.9]), mother's education of high school or less (–4.2 [–7.3, –1.2]), and mother smoked during pregnancy (–4.4 [–8.8, 0.1]).

Conclusions: In this large U.S. cohort, we identified several early childhood risk factors for lower FEV_1 at age 6–7 years, most of which are modifiable.

Clinical trial registered with www.clinicaltrials.gov (NCT00097773).

Keywords: cystic fibrosis; lung function; microbiology; tobacco smoke pollution

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*Participating clinical sites and investigators are listed in the online supplement.

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Children with cystic fibrosis (CF) can begin to develop lung disease within the first few months of life (1). However, there are limited objective measurements available to determine the severity of lung disease before children are reliably able to perform spirometry, generally at age 6 years (2). The ability to identify risk factors for low FEV_1% predicted (FEV_1 expressed as a percentage of the predicted normal value) at age 6 could provide opportunities to intervene and slow the progression of CF lung disease. Previous studies have identified risk factors for low FEV_1% predicted at age 6, including female sex, poor nutritional status, viral infections, persistent infection with *Pseudomonas aeruginosa* (*P. aeruginosa*), respiratory symptoms, pulmonary exacerbations, and low socioeconomic status (3–8). It is unclear whether these risk factors remain applicable in the current era, as children with CF born today are more likely to be detected by newborn screening (NBS) and treated more aggressively with antibiotics and CF-specific therapies, and to undergo eradication therapy when *P. aeruginosa* is isolated from respiratory cultures (9–11).

The Early *Pseudomonas* Infection Control Observational Study (EPIC OBS) is a multicenter, prospective observational cohort study of risk factors for the acquisition of *P. aeruginosa* and outcomes associated with *P. aeruginosa* in young U.S. children with CF enrolled between 2004 and 2006 (12). The study collected data on potentially modifiable risk factors for low FEV_1% predicted at age 6–7 that have not previously been evaluated, including daycare attendance, breastfeeding, and environmental tobacco smoke exposure, as well as potentially modifiable risk factors that have been studied previously, for example, nutritional status, infection with *P. aeruginosa*, respiratory symptoms, and pulmonary exacerbations. The objective of the current analysis was to evaluate early childhood risk factors for low lung function at age 6–7 years in the EPIC OBS cohort. Our hypothesis was that children with lower lung function at age 6–7 would have potentially modifiable risk factors in the first few years of life. Portions of this work have been presented in abstract form.

Methods

Study Participants

The design of the EPIC OBS has been described previously (12). Children with an established diagnosis of CF (13) and not more than 12 years of age were enrolled at 59 accredited U.S. CF care centers between 2004 and 2006. Requirements for inclusion in the current analysis included the following: enrolled in EPIC OBS before age 4 years, no prior lifetime respiratory isolation of *P. aeruginosa* or *P. aeruginosa* negative for at least 2 years before enrollment, spirometry measurements reported during at least two clinic visits between age 6 and 7 years, and encounter and family survey data available during the first year enrolled in EPIC OBS. Written informed consent was obtained from the parent(s) or guardian of each participant, and the study was approved by the institutional review board at each participating site.

Data Collection

Study data were collected at each clinical encounter via the Cystic Fibrosis Foundation National Patient Registry (CFFNPR) and study-specific forms (12). CFFNPR data collected at each encounter included results of respiratory cultures obtained as part of routine clinical care, weight and height percentiles, and FEV_1% predicted (beginning at age 6). Data collected on study-specific encounter forms included the following: physician report of crackles or wheezes on chest auscultation; and parent report of cough frequency, activity level, days with reduced levels of activity due to cough or shortness of breath, and antibiotic use. Potential risk factors reported by parents on the annual family survey included maternal education, household income, immunizations, any exposure to environmental tobacco smoke, breastfeeding, wood-burning stoves, and swimming pools or hot tubs in the previous year. FEV_1 was expressed as a percentage of the predicted value for a healthy reference population based on the equations of Wang and colleagues (14). The data cutoff for the current analysis was December 31, 2013.

Statistical Analysis

The primary end point for all analyses was the single best value of FEV_1% predicted at age 6–7 years. Univariate and multivariable linear regression models with robust variance estimates were used to evaluate the primary end point in relation to potential risk factors measured during the year of enrollment in EPIC OBS. Risk factors measured during the year of enrollment included exposures reported on the annual family survey; growth measurements (mean weight, height, or body mass index percentile during the year of enrollment), respiratory culture results, respiratory signs and symptoms, and oral and inhaled antibiotic treatments reported at clinical encounters; and episodes of pulmonary exacerbations treated with intravenous antibiotics and reported in the CFFNPR. The statistically significant predictors (defined as $P < 0.05$) from initial univariate screening were evaluated in multivariable linear regression models. Risk factors that remained statistically significant in the presence of other risk factors were retained in the final multivariable models. All models were adjusted for age at enrollment in EPIC OBS as a continuous variable. All statistical computations were performed with Stata software (version 12.1, 2011; StataCorp LP, College Station, TX).

Results

Participant Characteristics

A total of 484 children enrolled in the EPIC OBS met the criteria for inclusion in the current analysis (Figure 1). Eligible children were born between 2001 and 2006 and diagnosed with CF at a mean (SD) age of 3.6 (0.6) months. Mean age at study enrollment was 2.0 (1.3) years and mean observation time in the study before age 6 was 4.0 (1.3) years. The majority of participants were white (95.2%), non-Hispanic (90.1%), and reported using pancreatic enzyme supplements (90.5%). In the enrollment year, mean (SD) percentiles were 40.6 (26.9) for weight and 38.0 (25.6) for height. A small percentage of subjects had poor nutrition (i.e., <10th percentile for age) as measured by weight percentile (14.5%) or height percentile (17.6%).

Lung function data at age 6–7 years were available from a mean of 5.9 (1.8) quarterly clinic visits per child. There were 18 children with only two visits; the time range between these two visits was 60 days to 1.4 years. The mean best FEV_1% predicted at age 6–7 years was 108.9 (15.3)% predicted. Table 1 describes the mean best FEV_1% predicted at age 6–7 by baseline characteristics of the study cohort. Mean best FEV_1% predicted at age 6–7 differed significantly by mode of diagnosis (diagnosed by newborn or prenatal screening vs. other presentations), mother's education level, insurance status (Medicaid

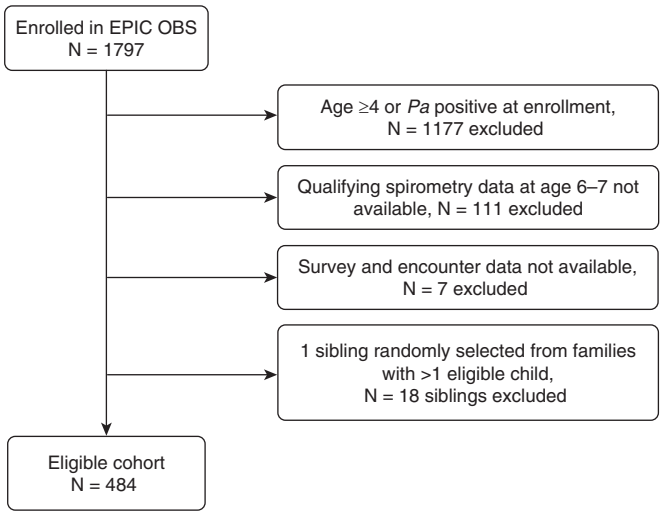

Figure 1. Study flow chart of cohort for the current analysis. EPIC OBS = Early *Pseudomonas* Infection Control Observational Study; *Pa* = *Pseudomonas aeruginosa*.

vs. non-Medicaid), and weight and height percentile in the enrollment year (<10th percentile vs. ⩾10th percentile).

In the year of enrollment, most participants reported frequent or productive cough at one or more encounters, but there were few children with decreased activity compared with their peers or activity limited by shortness of breath (Table 2). Despite having no prior lifetime respiratory isolation of *P. aeruginosa* or being *P. aeruginosa* negative for at least 2 years before enrollment, 30.8% of subjects had at least one culture positive for *P. aeruginosa* in the year of enrollment. *P. aeruginosa* was reported to be mucoid in 2.3% of subjects. The majority of participants received the influenza vaccine in the enrollment year and had at least one course of oral antibiotics recorded. Mean best FEV_1% predicted at age 6–7 differed significantly by presence of wheeze or crackles on chest examination or isolation of *P. aeruginosa* from a respiratory culture at one or more encounters during the enrollment year, intravenous antibiotics prescribed during the enrollment year, and cigarette exposure during the enrollment year or a mother who smoked while pregnant (Table 2).

Impact of Early Childhood Risk Factors on Lung Function at Age 6–7 Years

In simple regression models adjusted only for age at enrollment, the following risk factors from the enrollment year were significantly associated with mean best FEV_1% predicted at ages 6–7 years: mean weight less than 10th percentile, any clinic visit with wheezes or crackles reported on examination, a culture positive for *P. aeruginosa*, treatment with intravenous antibiotics, maternal education, any smoking exposure, or a mother who smoked during pregnancy. In a multivariable regression model, age at enrollment, poor nutrition, *P. aeruginosa*–positive respiratory cultures, mother's education, and having wheezes or crackles reported on examination remained statistically significant; having a mother

Table 1. Demographic characteristics of participants and best FEV_1% predicted at age 6–7 years

Risk Factor	Baseline, n (%)*		Best FEV_1% predicted at age 6–7, Mean (SD)			*P* Value
	Participants with Risk Factor	Participants without Risk Factor	Participants with Risk Factor	Participants without Risk Factor	Mean Difference (95% Confidence Interval)	
Age enrolled, 2 to <4 yr	237 (49.0)	247 (51.0)	107.9 (16.0)	109.9 (14.6)	−1.9 (–4.7, 0.8)	0.17
Female	241 (49.8)	243 (50.2)	108.1 (15.6)	109.7 (15.0)	−1.5 (–4.2, 1.2)	0.28
F508del homozygous†	254 (52.5)	219 (45.2)	110.0 (15.0)	107.9 (15.6)	2.1 (–0.7, 4.9)	0.14
Diagnosed by screening‡	168 (34.7)	300 (62.0)	111.1 (15.0)	107.8 (15.6)	3.2 (0.4, 6.1)	0.03
Meconium ileus‡	127 (26.2)	341 (70.4)	109.0 (14.0)	109.0 (15.9)	−0.0 (–3.0, 2.9)	0.98
Mother's education high school or less§	133 (27.5)	345 (71.3)	105.4 (15.3)	110.2 (15.1)	−4.8 (–7.9, –1.7)	0.002
Household income <$40,000§	150 (31.0)	284 (58.7)	107.1 (16.3)	109.8 (14.7)	−2.7 (–5.8, 0.4)	0.09
Medicaid recipient§	211 (43.6)	267 (55.2)	107.2 (16.2)	110.1 (14.5)	−2.9 (–5.7, –0.1)	0.05
Weight < 10th percentile‖	70 (14.5)	414 (85.5)	104.3 (15.5)	109.7 (15.1)	−5.4 (–9.3, –1.5)	0.007
Height < 10th percentile‖	85 (17.6)	399 (82.4)	105.2 (17.0)	109.7 (14.8)	−4.5 (–8.4, –0.6)	0.02
Body mass index < 10th percentile‖	8 (3.4)	229 (96.6)	105.1 (17.1)	108.0 (16.0)	−2.9 (–14.3, 8.5)	0.62

*All percentages reflect a denominator of 484 participants with the exception of body mass index (which was assessed only in 237 children ⩾ 2 yr of age at enrollment). Mean differences and *P* values reflect simple linear regression models.
†Genotype data were missing for 11 participants.
‡Diagnosis by screening includes prenatal and newborn screening. Data related to diagnosis by screening and meconium ileus were missing for 16 participants.
§Education and income reflect family survey data reported during the year of enrollment. Medicaid status reflects data reported in the Cystic Fibrosis Foundation National Patient Registry during the year of enrollment. Items with missing data included education (n = 6), income (n = 50), and Medicaid status (n = 6).
‖Weight, height, and body mass index percentiles reflect the mean of best quarterly values during the year of enrollment.

Table 2. Risk factors reported at one or more cystic fibrosis clinic visits in the year of enrollment and best FEV_1% predicted at age 6–7 years

Risk Factor	Risk Factor Status as Reported during Baseline Year, n (%)*		Best FEV_1% Predicted at Age 6–7, Mean (SD)			*P* Value
	Participants with Risk Factor	Participants without Risk Factor	Participants with Risk Factor	Participants without Risk Factor	Mean Difference (95% Confidence Interval)	
Frequent or productive cough	282 (58.3)	202 (41.7)	108.4 (16.0)	109.6 (14.3)	−1.3 (–4.0, 1.5)	0.36
Less active relative to peers	73 (15.1)	393 (81.2)	108.6 (14.5)	108.9 (15.4)	−0.3 (–3.9, 3.4)	0.88
Activity limited by shortness of breath†	139 (28.7)	345 (71.3)	109.0 (15.8)	108.9 (15.1)	0.1 (–2.9, 3.2)	0.93
Wheeze on chest examination	71 (14.7)	413 (85.3)	103.8 (18.7)	109.8 (14.5)	−5.9 (–10.5, –1.4)	0.01
Crackles on chest examination	61 (12.6)	423 (87.4)	103.4 (21.2)	109.7 (14.1)	−6.3 (–11.8, –0.9)	0.02
Pa-positive culture	149 (30.8)	335 (69.2)	106.5 (16.3)	110.0 (14.8)	−3.4 (–6.5, –0.4)	0.03
Methicillin-resistant *Staphylococcus aureus*–positive culture	42 (8.7)	442 (91.3)	106.0 (16.5)	109.2 (15.2)	−3.2 (–8.4, 1.9)	0.22
Oral antibiotics prescribed‡	411 (84.9)	73 (15.1)	109.1 (15.4)	107.8 (14.9)	1.3 (–2.4, 5.0)	0.49
Inhaled antibiotics prescribed‡	146 (30.2)	338 (69.8)	108.0 (16.7)	109.3 (14.7)	−1.3 (–4.4, 1.9)	0.43
intravenous antibiotics prescribed‡	156 (32.2)	328 (67.8)	106.0 (16.5)	110.3 (14.5)	−4.2 (–7.3, –1.2)	0.006
Dornase alfa prescribed	225 (46.5)	259 (53.5)	109.1 (16.3)	108.7 (14.4)	0.4 (–2.3, 3.2)	0.75
Influenza vaccine received	408 (84.3)	67 (13.8)	109.3 (15.3)	107.2 (15.6)	2.0 (–2.0, 6.1)	0.32
Household member smoked	159 (32.8)	323 (66.7)	107.8 (15.4)	109.4 (15.3)	−1.6 (–4.6, 1.3)	0.27
Any smoking exposure	230 (47.5)	247 (51.0)	107.3 (15.0)	110.6 (15.3)	−3.3 (–6.1, –0.6)	0.02
Mother smoked while pregnant	52 (10.7)	414 (85.5)	103.3 (15.2)	109.5 (15.0)	−6.1 (–10.5, –1.8)	0.006
Wood-burning stove used in home	44 (9.1)	437 (90.3)	107.0 (18.3)	109.2 (15.0)	−2.3 (–7.8, 3.3)	0.42
Swimming pool used	359 (74.2)	125 (25.8)	108.4 (15.7)	110.3 (14.2)	−1.9 (–4.9, 1.1)	0.21
Hot tub used	60 (12.4)	423 (87.4)	107.9 (13.3)	109.0 (15.6)	−1.1 (–4.7, 2.6)	0.56
Others with CF in same home	77 (15.9)	406 (83.9)	106.1 (16.9)	109.4 (15.0)	−3.3 (–7.3, 0.7)	0.11
Daycare > 9 h/wk	221 (45.7)	253 (52.3)	107.7 (15.1)	109.7 (15.4)	−1.9 (–4.7, 0.8)	0.17
Breastfed§	88 (35.6)	154 (62.3)	111.2 (13.5)	109.2 (15.1)	2.0 (–1.8, 5.7)	0.30
Palivizumab received§	111 (44.9)	113 (45.7)	111.6 (13.5)	108.2 (15.8)	3.4 (–0.4, 7.3)	0.08

Definition of abbreviations: CF = cystic fibrosis; *Pa* = *Pseudomonas aeruginosa.*

*Respiratory symptoms, chest examination findings, and associated treatments reflect study-specific encounter data. Culture findings reflect Cystic Fibrosis Foundation National Patient Registry (CFFNPR) culture data. Intravenous antibiotics reflect CFFNPR data on episodes of hospitalization or home intravenous antibiotics for a pulmonary exacerbation. Vaccines, smoking exposures, other environmental exposures, and breastfeeding reflect the most recent family survey collected during the year of enrollment. Participants were considered as having the risk factor if reported at one or more clinic visits or at the most recent family survey during the first year enrolled. All percentages reflect a denominator of 484 participants, with the exception of breastfeeding and palivizumab (which were assessed only in participants < 2 yr of age). Participant numbers (percentages) that sum to less than 484 (100%) indicate that there were missing data. Mean differences and *P* values reflect simple linear regression models.

†Activity limited by at least 1 day/month by shortness of breath or cough.

‡At least one course reported during the year of enrollment.

§Breastfeeding and palivizumab are reported for participants enrolled at age less than 2 years (n = 247). Participant numbers (percentages) that sum to less than 247 (100%) indicate that there were missing data.

who smoked during pregnancy was borderline significant and was retained in the final model (Table 3). There were no statistically significant interactions between age at enrollment and any of the other risk factors in the final model.

An additional analysis was performed with the 413 participants who had encounter data collected at enrollment and during at least four quarterly clinic visits between enrollment and age 6. Among these participants, the mean (SD) number of quarterly clinic visits was 12.5 (4.9). Oral and inhaled antibiotics were recorded at a mean (SD) of 53.1 (25.1)% and 16.8 (22.2)% of quarterly clinic visits. Neither the percentage of quarterly clinic visits with oral antibiotics nor the percentage of quarterly clinic visits with inhaled antibiotics was statistically significant when added to the multivariable model (data not shown).

Discussion

The EPIC Observational Study is a U.S. national prospective study designed to define risk factors for age at initial acquisition of *P. aeruginosa* (12). Participants were enrolled between 2004 and 2006, when *P. aeruginosa* eradication therapy was already in widespread use: in 2006, 97% of the EPIC OBS sites reported prescribing antibiotics for *P. aeruginosa* acquisition "often" or "always" on the annual site survey of clinical practices. In addition, data were collected on potential risk factors that have not been previously evaluated. Thus, this study provides an important opportunity to evaluate new risk factors and corroborate previously identified risk factors for reduced lung function at early school age in a large, contemporary U.S. cohort. We found that poor nutrition, the presence of abnormal chest sounds, and acquisition of *P. aeruginosa* in the year of enrollment, as well as mother's educational status and maternal smoking during pregnancy, were risk factors for low FEV_1% predicted at ages 6–7 years. These results may enable clinicians to target young patients at risk for low lung function and address risk factors that (with the exception of mother's educational status) are potentially modifiable.

Table 3. Multivariable linear regression model of baseline risk factors associated with best FEV_1% predicted at age 6–7 years

Risk Factor*	Mean Difference in Best FEV_1% Predicted†	95% Confidence Interval	*P* Value
Age at enrollment on study	−1.3	−2.4, −0.3	0.01
Weight percentile < 10% during year of enrollment	−5.3	−9.1, −1.5	0.006
P. aeruginosa positive during year of enrollment	−2.8	−5.7, 0.0	0.05
Crackles or wheeze during year of enrollment	−5.7	−9.4, −1.9	0.003
Mother's education high school or less	−4.2	−7.3, −1.2	0.007
Mother smoked during pregnancy	−4.4	−8.8, 0.1	0.055

*The multivariable model was based on observations for 461 participants.
†For age at enrollment, the mean difference in best FEV_1% predicted reflects the mean difference per 1-year increase in age. For categorical covariates, the mean difference in best FEV_1% predicted reflects the mean difference relative to the reference category. Reference categories included weight percentile equal to or greater than 10%, *P. aeruginosa* negative, no sounds on chest examination, mother's education beyond high school, and no smoking during pregnancy.

Our analysis also supports previous reports that have described associations between low FEV_1% predicted at age 6 years and low socioeconomic status (7, 15). Schechter and colleagues used data from the CFFNPR from 1994 and reported that low socioeconomic status, as indicated by being a recipient of Medicaid, was associated with lower FEV_1% predicted, including at age 6 years. In our cohort, the relationship between Medicaid status and FEV_1% predicted at age 6 years was similar to the relationship between maternal education and FEV_1% predicted at age 6 years, although Medicaid status did not reach statistical significance in our multivariable model. The mechanism(s) for this association are unclear, but may involve differences in disease self-management, tobacco smoke exposure, psychological stress, and exposure to environmental pollutants (16–19). Access to care does not appear to explain these associations in the United States, as prescriptions for chronic CF therapies, treatment of pulmonary exacerbations, and rates of hospitalization are not reduced among patients with lower socioeconomic status (20, 21).

We have previously reported that maternal smoking was associated with lower FEV_1% predicted in the year of enrollment for EPIC OBS participants (22). Others have described cross-sectional (23–27) and longitudinal associations (18) between lower lung function and second-hand smoke exposure, but the effect of maternal smoking during pregnancy on lung function in children with CF has not to our knowledge been examined elsewhere. The effect of maternal smoking during pregnancy has been shown to be associated with lower lung function in healthy infants and adolescents and more symptoms in young children with asthma (28–30). Our results will need to be corroborated in other cohorts, but encouraging mothers known to be expecting a child with CF, for example, with positive results on prenatal screening, to stop smoking may provide benefit to later lung function.

Our analysis supports previous reports that have described associations between low FEV_1% predicted at age 6 years and poor nutrition (4, 8). Using data from the Epidemiologic Study of Cystic Fibrosis (ESCF) from 1994 to 1996, Konstan and colleagues found that children with weight below the fifth percentile at age 3 years had an FEV_1% predicted at age 6 years that was a mean 5–16% lower than that of children with weight above the fifth percentile (4). VanDevanter and colleagues used ESCF data from 1994 to 2005 to develop a prediction score for low FEV_1% predicted at age 6 years (8). They reported that children with weight below the 10th percentile at a stable clinic visit between ages 2 and 5 were likely to have FEV_1% predicted at age 6 years 4–10% lower than for children with weight above the 10th percentile. We found a similar magnitude of association between children with weight below the 10th percentile during the year of enrollment and FEV_1% predicted at age 6 years (mean 6% predicted lower than for children with weight above the 10th percentile), even though the mean FEV_1% predicted at age 6 years in our cohort (108% predicted) was substantially higher than in either ESCF cohort (97–100% predicted). We did not evaluate the fifth percentile as a cutoff point, as only 31 children had weight below the fifth percentile during the year of enrollment.

Several studies have demonstrated that young age at initial *P. aeruginosa* acquisition is an important risk factor for the development of more severe CF lung disease (6, 31–33). It is likely that the earlier acquisition of *P. aeruginosa* allows more time for phenotypes to develop that are associated with pulmonary exacerbations and/or lower FEV_1% predicted, for example, mucoidy (34, 35). Our prior primary analysis of the entire EPIC OBS cohort found no modifiable risk factors for *P. aeruginosa* acquisition (12). In contrast to the findings of the current analysis, Zemanick and colleagues found, among EPIC OBS participants at least 6 years of age, no significant change in the slope of FEV_1% predicted after initial acquisition of *P. aeruginosa* (36). Reasons for the difference in findings from the same overall cohort include the different age ranges of the two analyses, the fact that Zemanick and colleagues evaluated rate of FEV_1 decline whereas the current analysis evaluated best value of FEV_1% predicted in a 1-year period, and the fact that we had a longer mean observation period (mean, 4.0 vs. 2.6 yr). They did find that acquisition of *P. aeruginosa* was associated with an increased rate of pulmonary exacerbations and the presence of crackles or wheeze on physical examination, both of which are risk factors for FEV_1 decline (37, 38).

Previous analyses have also described associations between FEV_1% predicted at age 6 years and the presence of respiratory signs or symptoms (e.g., daily cough or crackles or wheeze on auscultation), the frequency of oral antibiotics, and the frequency of pulmonary exacerbations treated with intravenous antibiotics (4, 5, 8, 39). In our study, the presence of crackles or wheeze on auscultation in the year of enrollment

was associated with FEV_1% predicted at age 6 years. A retrospective analysis of data from the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study described an association between the frequency of new respiratory symptoms in the first 2 years of life and lower FEV_1 *z* scores at age 6 years (5). A more recent analysis from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) cohort did not find an association between respiratory symptoms or the number of days of hospitalization in the first 2 years of life and lung function at ages 4–8 years, although their study had only 56 participants (6). Neither the frequency of treatment with oral or inhaled antibiotics in the enrollment year, or between enrollment and age 6 years, was associated with FEV_1% predicted in our study. Unfortunately, we did not collect data on either the indication or duration of antibiotics, so our analysis of antibiotic exposure is somewhat limited.

Our study made use of data collected prospectively as part of EPIC OBS, a large study conducted at multiple U.S. CF centers. None of the other environmental risk factors we were able to investigate (including receiving the influenza vaccine or palivizumab, daycare attendance, breastfeeding, and environmental tobacco smoke exposure) were associated with statistically significant differences in FEV_1% predicted. These exposures were all self-reported, and thus open to misclassification. Given our sample size, we were also limited in our ability to compare degrees of exposure (e.g., duration of breastfeeding). This limitation was amplified for the first 2 years of life, because we could assess risk factors only among the subjects enrolled before age 2 years. Limitations of our data include varying degrees of missingness and the potential for misclassification. Given the observational nature of the study, we can describe only associations between environmental exposures and lung function, and cannot determine causality. The generalizability of our results may be limited in that at the time of enrollment in the EPIC OBS, newborn screening for CF was not yet universal in the United States. The diagnosis of CF via NBS allows more opportunities to intervene to avoid malnutrition, but without proper infection control NBS can be a risk factor for infection with *P. aeruginosa* (40).

In conclusion, we have reported on risk factors for low FEV_1% predicted at age 6–7 years. Our results reinforce the importance of delaying acquisition of *P. aeruginosa* and avoidance of poor nutrition and demonstrate that low socioeconomic status, presence of abnormal chest sounds, and *in utero* smoke exposure are also associated with low FEV_1% predicted at age 6–7 years. Although the ability to modify smoke exposure or low socioeconomic status may be limited, our results may assist clinicians in targeting these young patients who are at risk for low lung function with more aggressive therapy, closer monitoring, and by supporting their families' empowerment and disease self-management—factors associated with improved outcomes in children with CF (41). ■

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