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# Risk Factors for Lung Function Decline in a Large Cohort of Young Cystic Fibrosis Patients

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## Abstract

**Objective—**To identify novel risk factors and corroborate previously identified risk factors for mean annual decline in $FEV_1$ percent predicted in a large, contemporary, U.S. cohort of young cystic fibrosis patients.

**Methods—**Retrospective observational study of participants in the EPIC Observational Study, who were *Pseudomonas*–negative and ≤12 years of age at enrollment in 2004-2006. The associations between potential demographic, clinical and environmental risk factors evaluated during the baseline year and subsequent mean annual decline in $FEV_1$ percent predicted were evaluated using generalized estimating equations.

**Results—**The 946 participants in the current analysis were followed for a mean of 6.2 (SD 1.3) years. Mean annual decline in $FEV_1$ % predicted was 1.01% (95% CI 0.85-1.17%). Children with 1 or no F508del mutations had a significantly smaller annual decline in $FEV_1$ compared to F508del homozygotes. In a multivariable model, risk factors during the baseline year associated with a larger subsequent mean annual lung function decline included female gender, frequent or productive cough, low BMI (<66$^{th}$ percentile, median in the cohort), ≥1 pulmonary exacerbation, high $FEV_1$ (≥115% predicted, in the top quartile), and respiratory culture positive for methicillin-

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[6]Appendix 1

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sensitive *Staphylococcus aureus,* methicillin-resistant *Staphylococcus aureus* or *Stenotrophomonas maltophilia*.

**Conclusions—**We have identified a range of risk factors for $FEV_1$ decline in a large cohort of young, CF patients who were *Pa* negative at enrollment, including novel as well as previously identified characteristics. These results could inform the design of a clinical trial in which rate of $FEV_1$ decline is the primary endpoint and identify high-risk groups that may benefit from closer monitoring.

### Keywords

cystic fibrosis; pediatric; lung function; decline; *Pseudomonas aeruginosa*; EPIC Observational Study

## Introduction

The rate of decline in the forced expiratory volume in one second ($FEV_1$) is widely used as a measure of lung disease progression among persons with cystic fibrosis (CF). The rate of $FEV_1$ decline has been shown to predict mortality and to improve with chronic therapies[1-5]. $FEV_1$ decline has slowed with progressive birth cohorts[6], possibly due to more aggressive and standardized care including widespread use of *Pseudomonas* (Pa) eradication regimens. Risk factors for rate of $FEV_1$ decline have been identified, including CF transmembrane conductance regulator (CFTR) genotype, female sex, age, meconium ileus, pancreatic insufficiency, pulmonary exacerbations, respiratory microbiology, high initial $FEV_1$, diabetes, and presence of wheeze or crackles[7-12]. Some of these studies were limited by small sample size, conduct at one or a small number of sites, conflicting results or changes in clinical care since publication. In this exciting era of advances in CFTR modulator therapy, there is renewed interest in rate of $FEV_1$ decline as a clinical trial endpoint, particularly in mild disease. An improved understanding of risk factors for $FEV_1$ decline in a modern cohort with mild disease could help inform the use of rate of decline as a clinical trial endpoint and identify high-risk subgroups in whom more intensive monitoring or treatment might be warranted.

The EPIC Observational Study is a multicenter longitudinal observational study that enrolled *Pa* negative children ≤12 years of age and evaluated a wide range of demographic, clinical and environmental factors, a number of which have not been previously examined. It thus provides a unique cohort in which to evaluate risk factors for $FEV_1$ decline in young patients with relatively mild disease in the era of widespread *Pa* eradication therapy. The purpose of the current study was to identify novel risk factors and corroborate previously identified risk factors for $FEV_1$ decline in this well-characterized, young cohort that was *Pa*-negative at enrollment. Some of the results have previously been presented in abstract form.

## Methods

### Study Participants

The design of the EPIC Observational Study has been described previously[13,14]. Children with an established diagnosis of CF[15] 0 to 12 years of age and with no prior lifetime

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respiratory isolation of *Pa* or *Pa* negative for ≥ 2 years were enrolled at 59 accredited U.S. CF care centers between 2004 and 2006. (Children were also able to enroll in EPIC OBS by virtue of participating in the EPIC Clinical Trial[14], nested in the EPIC OBS cohort. Some of these participants were not *Pa*-negative at enrollment into EPIC OBS and were therefore excluded from the current analysis.) EPIC OBS participants were included in the current analysis if they had at least 3 spirometry measurements obtained after enrollment, as defined below. The first spirometry after enrollment was defined as the baseline spirometry, the 1-year period after the baseline spirometry was defined as the baseline year, and the period starting at the end of the baseline year was defined as the observation period (Figure 1). Spirometry data were only available beginning at age 6. Thus, for children enrolled in the EPIC Observational study prior to age 6, there could be a lag of several years between enrollment into the EPIC Observational Study and the baseline spirometry. Eligible participants were required to have a baseline spirometry and spirometry recorded at least once during the first and fourth years of the observation period. In addition, they were required to have an annual family survey and at least 1 clinical encounter recorded during the baseline year (see Data Collection, below). For families with more than 1 eligible child, a single sibling was randomly selected for inclusion in the analysis. 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

EPIC Observational data were collected at each clinical encounter via the Cystic Fibrosis Foundation National Patient Registry (CFFNPR) and study-specific forms, as previously reported[13]. CFFNPR data included $FEV_1$ for ages 6 and older, results of respiratory cultures obtained as part of routine clinical care, weight and height percentiles, and presence of a pulmonary exacerbation defined as a respiratory illness treated with intravenous antibiotics in either the inpatient or outpatient setting. Respiratory signs and symptoms collected on study-specific encounter forms included: crackles or wheezes on chest auscultation, cough frequency, activity level, and days with activities limited due to cough or shortness of breath. The annual family survey queried families regarding a wide range of exposures including environmental tobacco smoke, daycare, other persons with CF and influenza vaccinations, as well as maternal education and household income[13]. $FEV_1$ was expressed as a percent of the predicted value based on the reference equations of Wang, et al[16] (for males age 6-17 and females age 6-15) and Hankinson, et al[17] (for males ≥18 years of age and females ≥16). The data cut off for this analysis was December 31, 2013.

## Statistical analysis

Predictor variables were evaluated during the baseline year only, and included demographic characteristics obtained from the CF Foundation National Patient Registry, exposures reported on the annual family survey, and clinical data, including respiratory microbiology. The primary outcome was the annualized rate of change in $FEV_1$ % predicted over the observation period, calculated from a linear model using the best reported values of $FEV_1$ % predicted from each age quarter during the observation period, with age centered at the midpoint of each age quarter. Observation time was calculated from end of the baseline year to the date of the latest spirometry measurement reported in the CFFNPR as of 12/31/2013.

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The average annual change in $FEV_1$ % predicted (change in $FEV_1$ % predicted per year of age) was modelled using an extension of the generalized linear model for longitudinal correlated data. Specifically, population-average linear regression models were estimated using generalized estimating equations (GEE) with exchangeable correlation structure and robust variance estimates. A predefined set of predictor variables was evaluated to identify risk factors for decline in lung function. Each risk factor was screened individually in a GEE model that included main effect terms for age in years and the risk factor, and an interaction term between age and the risk factor. The coefficient for each interaction term thus reflects the difference in mean annual change in $FEV_1$ % predicted between participants with the attribute during the baseline year vs. those in the reference category. The significance of each interaction term was assessed by testing the null hypothesis that the coefficient for the interaction term was equal to zero. Risk factors associated with lung function decline when assessed individually ($p<0.10$) were then evaluated together in multivariable GEE models. Risk factors were retained in the final multivariable model if their interaction with age remained statistically significant ($p<0.05$) in the presence of other risk factors. All multivariable GEE models were adjusted *a priori* for *Pa* status (any positive cultures vs. none), and Medicaid status (receiving Medicaid vs. not) during the baseline year. Because we hypothesized that the association of baseline weight percentile, BMI percentile and $FEV_1$ % predicted with annual $FEV_1$ decline was not linear, we categorized each of these predictors into quartiles based on the observed distribution in the cohort. For simplicity, based on the results of these analyses, we categorize weight and BMI percentiles as above or below the median value in the cohort and $FEV_1$ % predicted as above or below the $75^{th}$ percentile. Statistical analyses were conducted using Stata Statistical Software (Release 12, StataCorp, 2011, College Station, TX).

## Results

Figure 2 illustrates selection of the study cohort. Almost 1,800 participants (N=1797) enrolled in the EPIC Observational Study; 114 were excluded due to being *Pa*-positive at enrollment or having their CF diagnosis subsequently reversed. Following assignment of exclusion criteria for the current analysis and excluding siblings, the study cohort comprised 946 participants. Characteristics of the study cohort during the baseline year are detailed in Table 1. As the cohort was enrolled between 2004 and 2006 (prior to universal uptake of newborn screening (NBS) in the U.S. in 2006), only 16.5% of participants were identified by prenatal or NBS. The mean age at enrollment into the EPIC Observational Study was 5.7 (SD 3.6) years. Participants were followed during the observation period for an average of 6.2 (SD 1.3) years, during which time they had an average of 31.4 visits with spirometry recorded (SD 14.5).

Mean annualized rate of decline of $FEV_1$ % predicted for the cohort as a whole was 1.01 (95% CI 0.85-1.17) % per year. Figure 3 displays the effect of risk factors on mean annual change in $FEV_1$ % predicted, from univariate models. When compared to the reference group (F508del homozygotes), participants with 1 or no F508del mutations had significantly less mean annual decline in $FEV_1$% predicted. Similarly, participants diagnosed with CF following prenatal or NBS had significantly less mean annual decline in $FEV_1$ % predicted than those diagnosed conventionally. Characteristics in the baseline year associated with a

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significantly greater annual rate of decline included female sex, pancreatic enzyme use, frequent or productive cough, BMI below the median in the cohort (<66$^{th}$ percentile), 1 or more pulmonary exacerbations and high baseline $FEV_1$ (in the top quartile, ≥115 % predicted). While culturing *Pa* or mucoid *Pa* on one or more occasions during the baseline year was not associated with annual $FEV_1$ decline, isolation of MSSA, MRSA, and *S. maltophilia* were all associated with significantly greater annual decline. A variety of exposures assessed during the baseline year were not significantly associated with mean annual change in $FEV_1$ % predicted, including environmental tobacco smoke exposure, as well as influenza vaccine, wood burning stove use, maternal education, household income and Medicaid status (data not shown).

The results of the multivariate model are shown in Table 2. For the risk factors retained in this model, the direction and magnitude of the effect on annual change in $FEV_1$ % predicted was similar to that seen in the univariate models. Note that, for participants in the reference category for all the included characteristics, the mean annualized change in $FEV_1$ % predicted was not significantly different from zero: mean 0.10 (95% CI, -0.33, 0.52) % predicted/year. The strongest risk factors during the baseline year for subsequent annual decline in $FEV_1$ % predicted were isolation of MRSA from a respiratory culture, $FEV_1$ ≥115% predicted, isolation of MSSA, female sex and homozygous F508del CFTR genotype.

## Discussion

In a large, contemporary cohort of young CF patients who were *Pa* negative at enrollment, we identified a number of important risk factors for rate of decline of $FEV_1$ % predicted. Our cohort was healthier at baseline than earlier cohorts; for example, our mean baseline $FEV_1$ was 104% predicted, compared to mid-80 % predicted in the cohort of Konstan, et al [8]. Similarly, our cohort had a slower mean annual decline in $FEV_{1:}$ 1.01 % per year compared to 1.1 to 2.4 % per year, depending on age, in the cohort of Konstan, et al. Our cohort was enrolled between 2004 and 2006, when *Pa* eradication therapy was already in widespread use. In 2006, 97% of the EPIC Observational sites reported prescribing antibiotics for *Pa* acquisition “often” or “always” on the annual site survey of clinical practices. Nonetheless, we corroborated the work of previous authors in identifying CFTR genotype, pancreatic insufficiency (as measured by pancreatic enzyme use) and pulmonary exacerbations as risk factors for lung function decline. Similar to prior studies, we found parent report of frequent or productive cough and crackles on auscultation of the chest to be risk factors for $FEV_1$ decline[8,9]. In contrast to some, but not all, prior reports, we did not find meconium ileus to be a risk factor.

There have been conflicting results regarding the negative effects of female sex on lung function decline[8,9]; in our study, females did have a significantly larger rate of decline than males even though our cohort was young and had relatively mild disease. This was not due to earlier acquisition of *Pa* among females in our cohort (data not shown). One potential biologic mechanism for poorer lung health in females with CF is upregulation of airway mucus production by estrogen[18, 19], which could worsen mucociliary clearance.

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In this cohort that was *Pa* negative at enrollment and among whom *Pa* eradication treatment was widespread, we found no association between isolation of *Pa* from a respiratory culture in the baseline year and subsequent rate of $FEV_1$ decline, in contrast to studies of cohorts enrolled prior to widespread uptake of *Pa* eradication therapy[8,9]. This result suggests that perhaps chronic *Pa* infection is necessary to affect rate of lung function decline in the contemporary era. Sanders, et al, in a long term follow up study of 132 participants in the Wisconsin Neonatal Screening Trial, found no association between *Pa* in general and $FEV_1$, but did find an association between mucoid *Pa* and $FEV_1$[9], corroborating their prior work showing a strong impact of mucoid, but not non-mucoid, *Pa* on lung function and chest radiograph scores[20]. In our cohort, only 4% of the cohort had mucoid *Pa* at baseline, limiting our power to detect a significant association.

In our cohort, isolation of MRSA, MSSA and *Stenotrophomonas maltophilia* during the baseline year were all associated with a greater rate of $FEV_1$ decline. In fact, MRSA was the strongest risk factor in our multivariable model. Although MRSA has previously been reported to be a risk factor for $FEV_1$ decline in CF[21], to our knowledge MSSA has only been shown to negatively affect $FEV_1$ decline in infants, in a report from the Australian AREST-CF Study[22]. In that study, respiratory cultures were obtained by bronchoalveolar lavage, whereas in our cohort almost all cultures were of the posterior oropharynx, making direct comparisons difficult. Our study suggests that MSSA and its role in CF lung disease in the current era needs to be further investigated, particularly in light of the conflicting results of trials of *S. aureus* prophylaxis [23,24]. To our knowledge, no prior studies have shown *S. maltophilia* to be a risk factor for $FEV_1$ decline. While *S. maltophilia* has long been considered an organism infecting older persons with CF, recent studies have shown that younger age is actually a risk factor for *S. maltophilia* acquisition[25]. In that same study, greater rate of $FEV_1$ decline was found to be a risk factor for *S. maltophilia* acquisition. Our finding of *S. maltophilia* as a risk factor for greater rate of $FEV_1$ decline could be a manifestation of this same association. Clearly, the role of *S. maltophilia* in early CF lung disease deserves further investigation.

The study by Konstan, et al of risk factors for $FEV_1$ decline in the large North American Epidemiologic Study of CF (ESCF) cohort was one of the first to report that a high initial $FEV_1$ (>100% predicted) was associated with a faster rate of decline[8]. Though the mean baseline $FEV_1$ in our contemporary cohort was 104% predicted compared to 85% predicted in the Konstan cohort, this observation nonetheless held true. When $FEV_1$ was expressed as quartiles in our study, an association was found between baseline $FEV_1$ in the highest quartile (≥115% predicted) and a larger mean annual decline in $FEV_1$. These findings suggest that clinicians may not be consistently recognizing and intervening in early drops in $FEV_1$ in their CF patients with high $FEV_1$, as recently demonstrated by Morgan, et al using data from ESCF[26]. In regards to nutritional status, while on average the cohort had a normal BMI (62.7% SD (24.4)), a BMI <66$^{th}$ percentile (below the median in the cohort) was negatively associated with $FEV_1$ annual decline, similar to both Konstan, et al[8] and Sanders, et al[9], who identified poor baseline nutritional status (weight for age and height for age, respectively) as a risk factor for faster rate of decline. Similarly, Yen, et al identified greater weight at age 4 as a predictor of better lung function through age 18 years [27]

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Although a number of investigators have demonstrated an effect of newborn screening on $FEV_1$, to our knowledge ours is the first study to demonstrate a slower annual decline in $FEV_1$ among children identified by newborn screening than those diagnosed conventionally. While encouraging, these results should be interpreted with caution. Participants were enrolled in our study when only selected U.S. states were screening for CF, so unmeasured confounders in terms of different care practices in these states could have contributed to improved outcomes.

While we had the unique ability to examine a number of environmental risk factors for $FEV_1$ decline, we did not detect an association between any of these characteristics (exposure to cigarette smoke, influenza vaccine or other persons with CF; Medicaid status; household income; maternal education) and $FEV_1$ decline. Our findings may be due at least in part to misclassification (particularly for exposure to cigarette smoke), as data were collected via self-report. Prior authors have found an association between influenza season and pulmonary exacerbations[28] rates in CF, and cigarette smoke has recently been shown to produce systemic defects in CFTR function [28]. Socioeconomic status has been shown to affect $FEV_1$ in cross-sectional analyses[29,30].

Strengths of our study include the ability to focus on young patients with generally mild disease in the era of widespread *Pa* eradication therapy, the large size of the cohort enrolled at multiple U.S. sites and followed for a relatively long period, and augmentation of CFFNPR data with EPIC Observational study-specific data. Limitations include potential misclassification of environmental risk factors through annual parent self-report and of characteristics recorded in the CFFNPR such as *Pa* mucoidy. In addition, we were only able to evaluate the association of pulmonary exacerbations requiring intravenous antibiotics on lung function decline; we did not have information on milder exacerbations treated with oral and/or inhaled antibiotics. We chose to evaluate how baseline characteristics predict lung function decline; an alternative and interesting analysis would be to treat each of the predictors as time-varying covariates over the observation period. Finally, as stated above, we relied on oropharyngeal cultures for respiratory microbiology, which have limited diagnostic accuracy compared to lower airway cultures[31].

In summary, we have identified a range of risk factors for $FEV_1$ decline in a large cohort of young, *Pa* negative CF patients with relatively mild disease, including novel as well as previously identified factors. These results could inform the design of a clinical trial in which rate of $FEV_1$ decline is the primary endpoint and identify high-risk groups that may need closer monitoring. Indeed, given that the mean annual rate of $FEV_1$ decline in our contemporary cohort of children was 1.01% predicted per year, perhaps the most relevant conclusion for clinical trial design in this population is that detecting a treatment effect on $FEV_1$ decline would require very large samples and/or long periods of observation.

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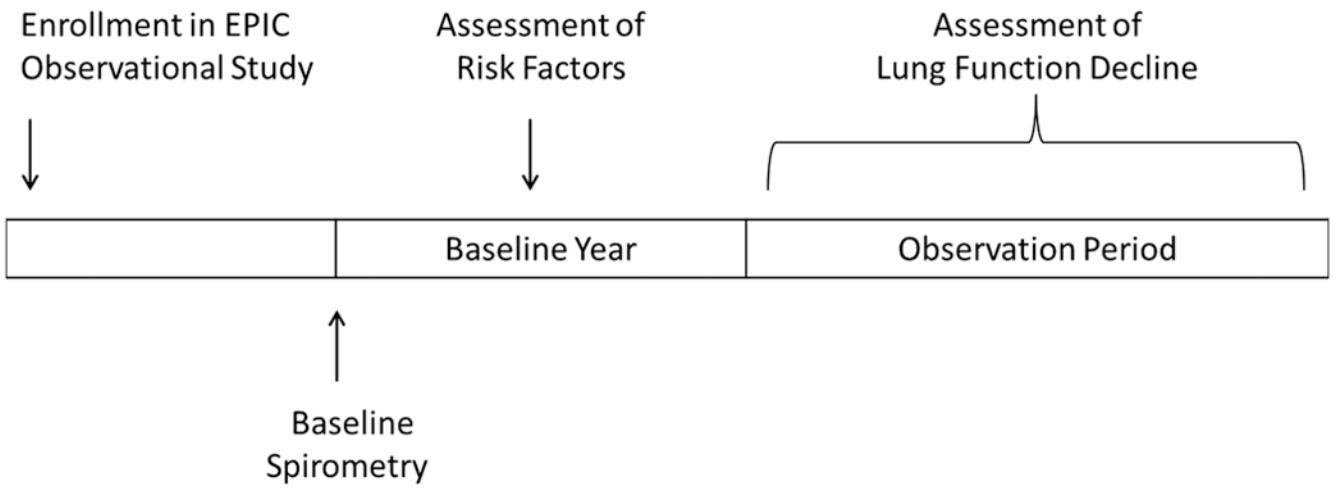


**Figure 1. Schematic of study flow**

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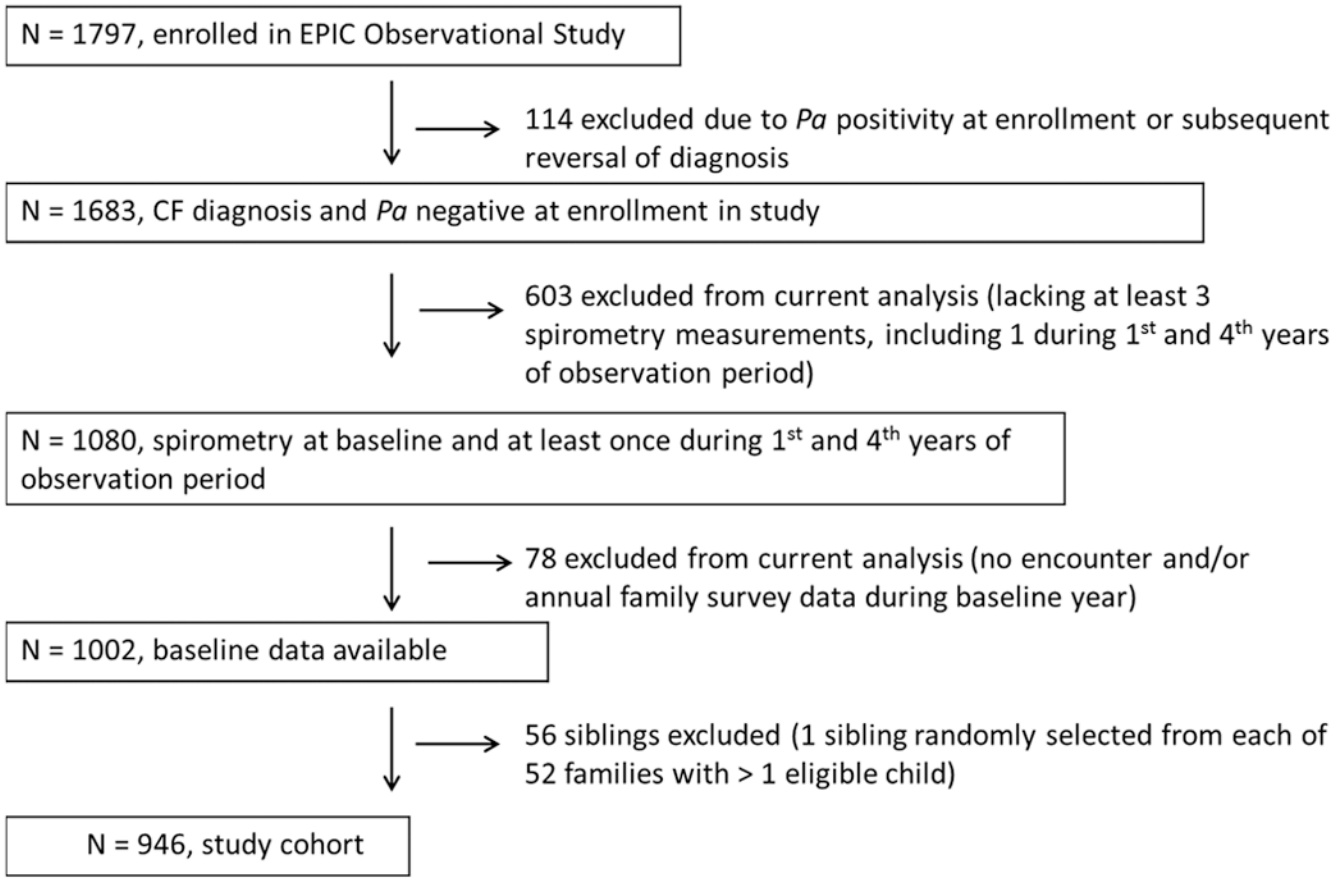


**Figure 2. Selection of study cohort**

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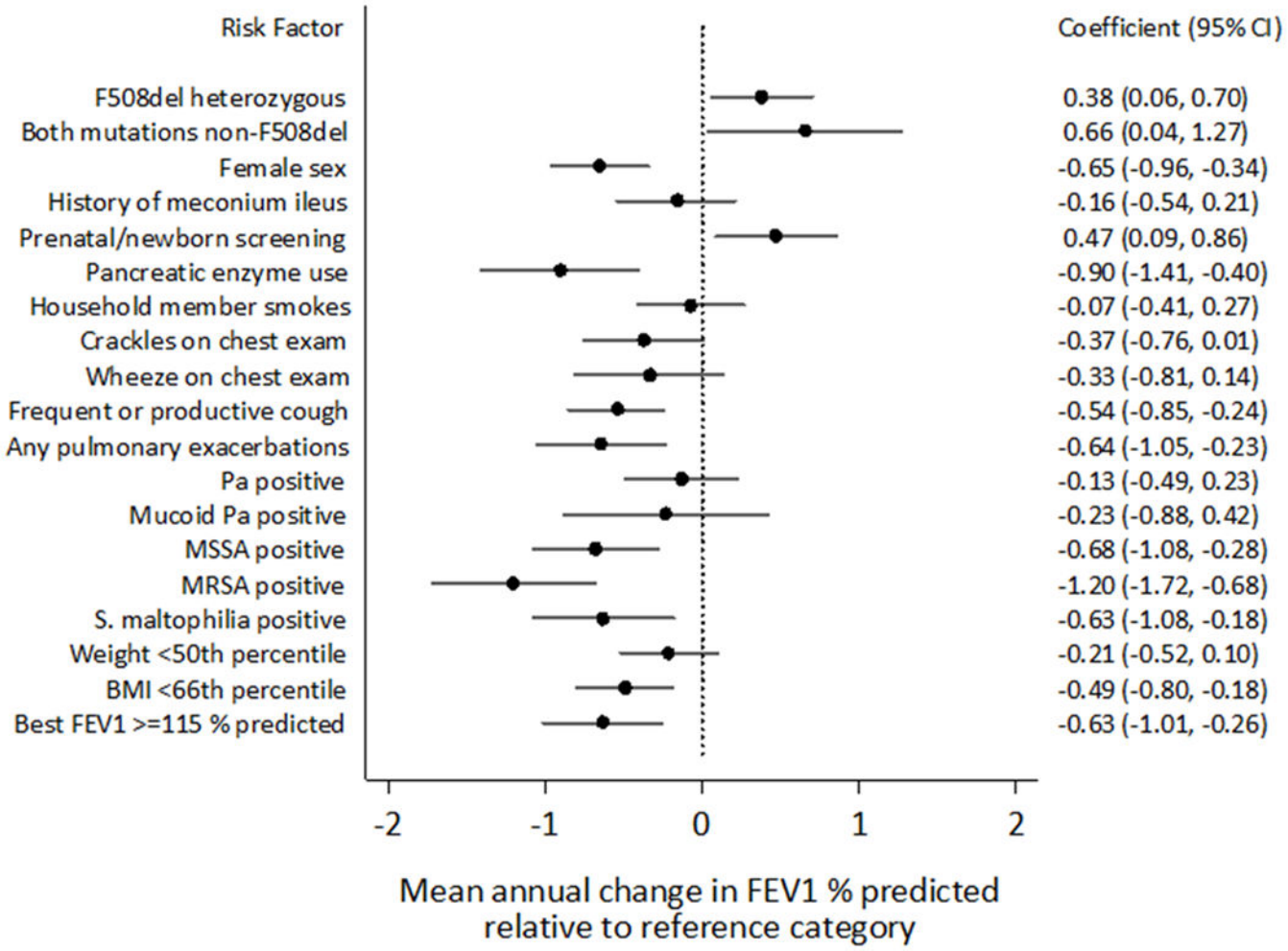


**Figure 3.**

Forest plot of effect of risk factors on annual change in $FEV_1$% predicted, from univariate GEE models. For each risk factor, estimates of mean annual change in $FEV_1$% predicted and associated 95% confidence intervals are displayed for participants with the risk factor relative to participants in the reference category. All risk factors were measured during the baseline year. Based on evaluation of quartiles, best baseline $FEV_1$% predicted was dichotomized at the top quartile value (115%), and best baseline weight and BMI percentiles were dichotomized at the median value ($50^{th}$ and $66^{th}$ percentile, respectively).

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## Table 1
### Participant characteristics evaluated during the baseline year

| | Total Cohort N=946 |
|---|---|
| Age at baseline spirometry, years, mean (SD) | 7.9 (2.0) |
| Female sex, n (%) | 470 (49.7) |
| Caucasian, n (%) | 910 (96.2) |
| Hispanic, n (%) | 31 (3.3) |
| CFTR genotype | |
| F508del homozygous, n (%) | 505 (53.4) |
| F508del heterozygous, n (%) | 358 (37.8) |
| Other/not available, n (%) | 83 (8.5) |
| History of meconium ileus, n (%) | 228 (24.1) |
| Identified by prenatal or newborn screening, n (%) | 156 (16.5) |
| Pancreatic enzyme use, n (%) | 882 (93.2) |
| Household member smokes, n (%)[1] | 261 (27.6) |
| Crackles on chest exam, n (%)[1] | 209 (22.1) |
| Wheeze on chest exam, n (%)[1] | 110 (11.6) |
| Frequent or productive cough, n (%)[1] | 545 (57.6) |
| Pulmonary exacerbation(s), n (%)[1] | 186 (19.7) |
| *P. aeruginosa* (Pa) positive, n (%)[1] | 211 (22.3) |
| Mucoid Pa positive, n (%)[1] | 40 (4.2) |
| Methicillin sensitive *S. aureus* positive, n (%)[1] | 611 (64.6) |
| Methicillin resistant *S. aureus* positive, n (%)[1] | 168 (17.8) |
| *S. maltophilia* positive, n (%)[1] | 137 (14.5) |
| Weight percentile[2], mean (SD) | 50.0 (27.6) |
| BMI percentile[2], mean (SD) | 62.7 (24.4) |
| $FEV_1$ % predicted[2], mean (SD) | 104.4 (15.5) |

[1] Recorded during the baseline year only; does not include data prior to the baseline year.

[2] Best value during the baseline year.

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## Table 2

**Multivariable model of risk factors measured during the baseline year for annual change in $FEV_1$ % predicted[1]**

| Risk Factor | Coefficient | 95% CI | P-value |
|---|---|---|---|
| F508del heterozygous[2] | 0.39 | 0.08, 0.70 | 0.01 |
| Both mutations non-F508del[2] | 0.55 | -0.07, 1.18 | 0.08 |
| Female sex | -0.60 | -0.90, -0.31 | 0.0001 |
| Frequent or productive cough | -0.31 | -0.61, -0.01 | 0.04 |
| Pulmonary exacerbation | -0.47 | -0.89, -0.06 | 0.02 |
| MSSA[3] | -0.68 | -1.05, -0.31 | 0.0004 |
| MRSA[3] | -1.00 | -1.51, -0.49 | 0.0001 |
| *S. maltophilia* positive | -0.50 | -0.93, -0.07 | 0.02 |
| Best BMI <66$^{th}$ percentile | -0.53 | -0.84, -0.23 | 0.001 |
| Best $FEV_1$ ≥115 % predicted | -0.75 | -1.12, -0.38 | 0.0001 |
| Age (yrs) | 0.56 | 0.09, 1.02 | 0.02 |

[1] Results are shown for risk factors that had a significant interaction with age. The coefficient for each risk factor reflects the difference in mean annual change in $FEV_1$ % predicted between participants with the attribute during the baseline year vs. those in the reference category. The coefficient for age reflects the mean annualized change in $FEV_1$ % predicted for participants whose values were in the reference category for all risk factors; coefficients for other main effect terms are not shown. Reference categories included genotype F508del homozygous, male sex, no exacerbations, absence of frequent or productive cough, *S. aureus* negative, *S. maltophilia* negative, BMI ≥66$^{th}$ percentile (the median value in the cohort), and $FEV_1$ <115 % predicted (representing the lower 3 quartiles of $FEV_1$ in the cohort). The final model was adjusted for *P. aeruginosa* status (any positive cultures vs. none) and Medicaid status (on Medicaid vs. not) during the baseline year and reflects data for 931 participants.

[2] The p-value was 0.02 when both genotype terms were tested simultaneously for the overall effect of genotype on annual change in $FEV_1$ % predicted.

[3] *S. aureus* status was assigned to one of 3 mutually exclusive categories: MSSA +, MRSA +, or *S. aureus* negative (reference group). The p-values reflect the fact that the annual change in $FEV_1$ % predicted for both MSSA+ and MRSA+ participants was significantly different than observed for *S. aureus* negative participants.