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# Lung Function Decline From Adolescence to Young Adulthood in Cystic Fibrosis

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## SUMMARY

**Background—**Despite improving survival in cystic fibrosis (CF) patients, there is a mortality peak in early adulthood. Defining risk factors that predict significant worsening of lung disease in young adulthood may identify opportunities to improve outcomes in adults.

**Methods—**We identified 4680 patients in the Epidemiologic Study of Cystic Fibrosis 1994–2005 with data in both adolescence (age 14.0–17.4 years) and young adulthood (age 18.5–22.0 years) and analyzed 2267 who had ≥5 encounters and ≥5 measurements of forced expiratory volume in 1 second ($FEV_1$) spanning ≥1 year during both adolescence and young adulthood, and ≥1 encounter with weight and height and ≥1 $FEV_1$ measurement age 17.5–18.5 years. We compared the annualized rates of decline in $FEV_1$ during adolescence and young adulthood stratified by best

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Disclosure of Conflict of Interest

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$FEV_1$ around age 18. Logistic regression was used to identify risk factors associated with substantial decline (>20 points) in $FEV_1$% predicted in young adulthood.

**Results—**Annual rate of decline was greater in young adulthood than in adolescence. Risk factors for substantial decline included slower rate of $FEV_1$ decline, greater $FEV_1$ variability, faster body mass index (BMI) decline, male sex, chronic inhaled antibiotics, *Haemophilus influenzae* detection, and absence of multidrug-resistant *Pseudomonas aeruginosa* in adolescence, and lower than expected $FEV_1$ and BMI around age 18.

**Conclusions—**Decline in lung function accelerates in young adults with CF, especially in those with early stage lung disease. Adolescents at risk for substantial decline in lung function in young adulthood have higher $FEV_1$ and worse nutritional status, among other identifiable risk factors.

### Keywords

Transition; nutrition; risk factors; youth; *H. influenzae*; *P. aeruginosa*

## INTRODUCTION

Young adulthood is an important and vulnerable period for patients with cystic fibrosis (CF). Often around age 18, many CF patients have taken over responsibility for managing their disease and are transitioning their care from pediatric to adult health care providers.[1] It is generally recognized that young adulthood is also a time of significant acceleration of morbidity and mortality in CF. The median age at death for patients with CF in the U.S. in 2009 was 26.1 years according to the Cystic Fibrosis Foundation Patient Registry.[2] The median forced expiratory volume in 1 second ($FEV_1$) in 13- to 18-year-old CF patients was relatively preserved at 93.6 % predicted, whereas it was 65.3 % in those over 18 years. In addition, there was a difference in the percentage of patients with full adherence to recommended CF care guidelines for clinic attendance and recommended health screenings across age groups: 72.9% for 6- to 18-year-old CF patients and 58.4% for CF patients over 18 years.[2] We hypothesized that there are identifiable risk factors in adolescence associated with accelerated lung function decline during early adulthood that can direct intervention and care. Our first aim was to compare the rate of pulmonary function decline during adolescence and young adulthood. The second aim was to identify adolescent risk factors for substantial pulmonary function decline in young adulthood.

## METHODS

Data from the Epidemiologic Study of Cystic Fibrosis (ESCF), a large, prospective observational study of CF patients in the United States and Canada between 1994 and 2005, were used for this analysis.[3] The study was approved by the Copernicus Group institutional review board (tracking number OVA 1-03-008) and local institutional review boards as applicable. Participants or their guardians provided informed consent. Patients were eligible for this analysis if they had at least five encounters and five $FEV_1$ measurements spanning at least 365 days during both adolescence (defined as age 14.0–17.5 years) and young adulthood (defined as age 18.5–22.0 years), plus at least one additional encounter that recorded weight, height, and at least one $FEV_1$ measurement between ages 17.5 and 18.5

years. All $FEV_1$ measurements were included in the analyses, regardless of whether a pulmonary function test was taken at the time of clinical stability.

We estimated the annualized rate of $FEV_1$ decline during adolescence and young adulthood using a mixed-effects model with random slopes and intercepts for each period. This is similar to the approach used in Ren et al[4] and Konstan et al.[5] The selection of 3.5 years for the "before" and "after" periods was based on a desire to have patients with enough data to establish trend lines over a reasonably long span of time (necessitating a longer time) and wanting to keep the time reasonably short so that we could evaluate "local" effects that could be approximated by a linear trend. Patients were stratified into four categories based on best $FEV_1$ around age 18 (age 17.5 to 18.5 years) <40% predicted, 40 to <70% predicted, 70 to <100% predicted, and ≥100% predicted. Values for $FEV_1$% predicted were calculated from the equations of Hankinson.[6]

To define a substantial decline in $FEV_1$, the decline during adolescence was first extrapolated to obtain a fitted (predicted) value at age 18. This was compared to a fitted value at age 22 extrapolated from the rate of decline during young adulthood (Figure 1). A substantial decline was defined as a decrease of 20 or more points in $FEV_1$% predicted between the fitted value at age 18 and the fitted value at age 22.

Multivariable logistic analysis was used to assess risk factors during adolescence associated with substantial decline in $FEV_1$ in young adulthood. The analytical approach was to select *a priori* a handful of key variables to be included in the model regardless of statistical significance and then to test other variables for statistical significance at the $\alpha$=0.05 level. Once the model using $\alpha$=0.05 was developed, we then used backward stepwise analysis with $\alpha$=0.01 to determine the sensitivity of the remaining variables to the presence of the variables that were not significant or had borderline significance. The variables selected for inclusion regardless of statistical significance were a history of cirrhosis or the presence of cough, sputum production, or crackles at any visit during adolescence. Other clinical, demographic, and health care utilization variables were tested statistically. These included sex, race and ethnicity, socioeconomic status (using state insurance status at any time during the years studied as proxy), medical conditions, $FEV_1$ during adolescence and around age 18, nutritional status based on body mass index (BMI) *z*-score, microorganisms detected by respiratory tract culture, prescribed routine therapies, and annualized number of clinic visits and intravenous (IV) pulmonary exacerbations. The time-varying variables were summarized over the adolescent period (age 14.0–17.5 years) or around age 18 (age 17.5–18.5 years). The evaluation of number of pulmonary exacerbations was limited to patients treated by IV antibiotics and did not include patients treated by inhaled or oral antibiotics, in part due to data limitations in ESCF. Outlier or clearly erroneous values for $FEV_1$ and for the various predictors were set to missing before the analysis. (Appendix A in the online data supplement presents and defines all of the variables.)

Some additional sensitivity analyses were performed. One sensitivity analysis evaluated the effect of including in the model patients who had at least three data values during adolescence and young adulthood (in addition to those who met the original criterion of at least five data values). ESCF covers more than a decade and there have been a number of

changes in the treatment of CF during that period, although the use of longitudinal patient-specific data mitigates the effect of any possible secular trend. As a separate sensitivity analysis, the year of the 18th birthday was added as an explanatory variable.

Analyses were performed using SAS Version 9.1 or later (SAS Institute, Inc., Cary, NC).

## RESULTS

A total of 6515 ESCF patients had at least one pulmonary function test and one encounter that included assessment of BMI in the year around the 18th birthday (17.5–18.5 years). Of these, 1835 had no encounters in either the adolescence or young adulthood period, and an additional 2413 did not meet the data requirements (≥5 encounters and ≥5 $FEV_1$ measurements spanning ≥365 days) for adolescence or for young adulthood, leaving 2267 patients for the analysis cohort (Figure 2). However, 338 of the excluded patients did have sufficient data to allow inclusion in a supplemental cohort for a sensitivity analysis (≥3 encounters and ≥3 $FEV_1$ measurements spanning ≥365 days). Patient demographics and clinical characteristics during adolescence and around age 18 are shown in Table 1 for the patients in the analysis cohort, the 338 patients evaluated in the supplemental cohort, and the 2075 who had some data in adolescence and young adulthood but could not be included in the model (the ineligible cohort). In the analysis cohort, the annualized rate of $FEV_1$ decline was greater in young adulthood (−2.68% predicted per year) than during adolescence (−1.59% predicted per year). The more rapid decline in young adulthood was attributable to patients with $FEV_1$ ≥70% predicted at age 18, who constituted 61.7% of the cohort. Patients with lower $FEV_1$% predicted showed a slower rate of decline in young adulthood than in adolescence (Figure 3 and Table 2).

Of the 2267 patients, 667 (29%) had a substantial decline in $FEV_1$% predicted (20 points) from age 18 to age 22. The logistic regression model predicting a substantial decline in lung function was developed iteratively. In preliminary modeling, the aspect of lung function around age 18 that best predicted the likelihood of a significant drop in young adulthood was the difference between the lowest measured $FEV_1$ between ages 17.5 and 18.5 and the extrapolated $FEV_1$ value at age 18 (using the line fitted from age 14.0 to 17.5). The rate of decline in $FEV_1$ during adolescence and the variability of $FEV_1$ around that fitted line were both also strong predictors. BMI was also a strong predictor, even after adjusting for these three aspects of $FEV_1$. The most significant predictor related to BMI was obtained by subtracting the extrapolated BMI *z*-score value at age 18 from the highest (rather than the lowest) measured value around age 18. At this juncture, we enforced parallelism between BMI and $FEV_1$ by including the rate of decline in BMI during adolescence and the variability around the fitted BMI line regardless of statistical significance.

Risk factors in adolescence associated with substantial decline in young adulthood included higher $FEV_1$ around age 18 (relative to the extrapolated value), slower rate of decline in $FEV_1$% predicted, greater variability in $FEV_1$% predicted, and/or a faster rate of decline in BMI. Additionally, $FEV_1$ and/or BMI around age 18 that were lower than expected based on fitted values were also associated with substantial decline (Table 3). Neither variability in BMI nor the variables selected *a priori* (cough, sputum production, crackles, and cirrhosis)

were statistically significant. Only four additional variables were significant predictors of substantial decline: male sex, the presence of *Haemophilus influenzae* on respiratory tract culture, and the percentage of encounters at which chronic inhaled antibiotics were prescribed (i.e., indicated as used for prophylaxis or for chronic suppressive therapy). The presence of multidrug-resistant *Pseudomonas aeruginosa* was associated with a lower likelihood of substantial decline. Other demographic, clinical, and health care utilization characteristics described in Appendix A were not predictors of substantial decline; these included the use of insulin/oral hypoglycemic agents (a proxy for CF-related diabetes).

Backward stepping using $\alpha$=0.01 removed the nonsignificant variables first, then the chronic inhaled antibiotics and *P. aeruginosa* variables, and finally the variability of $FEV_1$. The remaining variables were all statistically significant at $\alpha$=0.01 and had odds ratios nearly the same as when the other variables were included in the model (data not shown).

The sensitivity analysis that included the 338 patients with at least three data values during adolescence and young adulthood in addition to the original 2267 patients resulted in no material changes. The sensitivity analysis that included year of the 18th birthday as an additional covariate also resulted in no material changes. The effect of chronic inhaled antibiotic therapy was strengthened slightly; other coefficients were essentially unchanged.

## DISCUSSION

In this large cohort of adolescent CF patients, we have demonstrated an acceleration of lung function decline in early adulthood. This decline is attributable to adolescents with early stage lung disease by $FEV_1$ criteria, i.e., those with $FEV_1 \geq 70\%$ predicted around age 18. This is consistent with our previous finding that higher $FEV_1$ is a risk factor for $FEV_1$ decline in children and adolescents.[7] Furthermore, patients at greatest risk of a substantial, clinically meaningful $FEV_1$ decline in young adulthood can be identified by specific risk factors, most notably several aspects of $FEV_1$ and BMI during adolescence.

Adolescents with a slower rate of $FEV_1$ decline had a greater risk of substantial decline in young adulthood. In addition, if a patient's lowest $FEV_1$ around age 18 was lower than expected based on the estimated value at age 18 from the fitted line during adolescence, the patient was at further risk of a substantial decline. This suggests that acceleration in decline detectable at age 18 precedes and predicts a substantial drop in lung function by age 22. Even after accounting for the slope of $FEV_1$ and the $FEV_1$ around age 18, increased variability in $FEV_1$ was predictive of substantial decline. Patients with a faster rate of BMI decline had a greater risk of substantial decline in lung function. Acceleration in BMI decline, defined by the difference between measured highest BMI at age 18 and the extrapolated trend line of BMI, also predicted a substantial drop in lung function. Thus, estimating the risk for substantial decline between age 18 and 22 years requires assessment of several aspects of both $FEV_1$ and BMI during adolescence.

The finding that adolescent patients with higher $FEV_1$ are at risk for accelerated decline in $FEV_1$ in young adulthood is important new information for both pediatric and adult CF care providers and suggests opportunities for improving care. It has been previously shown that

patients with higher $FEV_1$ receive fewer therapies, including therapies that have been shown to increase or maintain lung function and reduce the frequency of pulmonary exacerbations.[8] Moreover, patients with fewer symptoms and normal or near-normal pulmonary function are less likely to receive vigilant monitoring or intervention,[8] and may be less attentive to self-care. Normal developmental patterns of adolescence, including striving for normality by disregarding or avoiding treatment recommendations, may be reinforced by measurably early stage lung disease.[9] These factors are difficult to study, but the implications for clinical practice are highly relevant. Practitioners, families, and patients should be aware that high $FEV_1$ and minimal decline in $FEV_1$ during adolescence do not predict the same stable course during young adulthood, but are actually risk factors for increasing decline and substantial loss of lung function in the ensuing years.

The other two aspects of $FEV_1$ found to be independent risk factors relate to variability. The difference between the lowest $FEV_1$ around age 18 and the extrapolated $FEV_1$ at age 18 encompasses both curvature and short-term variability. A longer-term measure of variability is the standard deviation of $FEV_1$ measures around the trend line during adolescence. Both are independent risk factors for substantial decline in $FEV_1$ in young adulthood. After controlling for these variables, we found that the frequency of IV-treated pulmonary exacerbations was not an independent predictor of substantial decline in $FEV_1$. This is somewhat surprising given that pulmonary exacerbation is a known risk factor for lung function decline.[7,10] A long-standing issue in CF clinical care has been the lack of a commonly held definition of pulmonary exacerbation. Mirroring this conundrum, data collection at the many study sites demonstrated variability in making the clinical diagnosis of pulmonary exacerbation; only treated exacerbations were recorded in ESCF. We assume that exacerbations, treated or untreated, account for much of the variability in $FEV_1$. Thus the standard deviation of $FEV_1$ measures around the trend line may in fact be largely a measure of frequency and severity of pulmonary exacerbations, whether or not identified or treated. This could explain why a measure of treated exacerbations was not an independent risk factor.

In a recent analysis using ESCF, Liou et al[11] demonstrated that a substantial number of patients have relatively large individual year-to-year changes in $FEV_1$% predicted from early adolescence through early adulthood that are not accurately represented in median $FEV_1$ population data for this group. The ages of greatest risk were the early teen years rather than the early adulthood we chose to evaluate in this study. It would be valuable to see if the risk factors in those earlier teen years are similar to those we report here.

Nutritional status is a strong, independent predictor of survival in CF in both children and adults[12] and is also correlated with $FEV_1$% predicted values.[13] We found that the most relevant nutritional status predictors of substantial decline in $FEV_1$% predicted were a faster rate of decline in BMI during adolescence or a lower than expected BMI around the 18th birthday compared with the extrapolated BMI based on slope of decline during adolescence. These variables are related, but have independent effects on the likelihood of substantial decline even after adjusting for several aspects of $FEV_1$. These findings, taken together, suggest more vigorous monitoring of nutritional status and more nutritional intervention

during adolescence, even in those with early stage lung disease, could reduce $FEV_1$ decline in the following years.

Having more encounters documenting use of chronic inhaled antibiotics during adolescence was associated with a greater risk of substantial decline in young adulthood. Inhaled antibiotics are indicated for chronic suppressive treatment of *P. aeruginosa*; however, *P. aeruginosa* infection was not, in itself, associated with risk of substantial decline. Chronic use of inhaled antibiotics may be a marker of more advanced disease.

*H. influenzae* is frequently present in respiratory tract cultures of young patients with CF; prevalence peaks at over 30% in the preschool years but then decreases to less than 10% during adulthood.[2] *H. influenzae* can be part of normal respiratory flora in healthy children, but is a significant pathogen in other disorders, notably chronic obstructive pulmonary disease. *H. influenzae* has not been previously reported to be associated with more rapid decline in lung function in CF. However, this is the first report to specifically study pulmonary function changes in discrete time periods during late adolescence and early adulthood and demonstrates that presence of this organism predicts decline in lung function. We do not believe that *H. influenzae* is simply a marker of milder disease, as it remained significant in the predictive model even after adjustment for $FEV_1$ and its derived variables. *H. influenzae* has a number of properties that would suggest the potential for significant pathogenicity in the CF lung, including biofilm formation.[14] This finding, which may have implications for antimicrobial selection and recommendations in CF, deserves further evaluation.

The presence of *P. aeruginosa* in respiratory tract cultures has been previously reported to be associated with more rapid decline in lung function, especially when mucoidy is present.[15,16] However, we did not find that presence or absence of *P. aeruginosa* or of mucoid *P. aeruginosa* was predictive. This may reflect the very high rate of *P. aeruginosa* infection (86%) in this adolescent cohort. We did find that substantial lung function decline in the adult period was less likely to occur in patients with multidrug-resistant *P. aeruginosa.* We previously reported that ESCF sites with $FEV_1$ in the highest quartile had a higher use of IV antibiotics and a higher rate of multidrug-resistant *P. aeruginosa* on respiratory cultures than sites in the lowest $FEV_1$ quartile.[17] Thus, the decreased risk for decline seen in the group with multidrug-resistant *P. aeruginosa* might be a marker of more frequent antibiotic therapy leading to better overall outcomes.

Male sex was associated with an increased risk of substantial decline in the early adult period. This contrasts with earlier reports indicating that female sex is a risk factor for morbidity and mortality in CF in patients 1–20 years of age.[18] However, the effect of sex has been seen primarily in patients up to age 10,[18] and several recent reports have suggested the resolution of the gender gap in CF mortality.[19–21] Young men with CF use fewer prescribed therapies;[22,23] while ESCF did not measure adherence, this sex-related difference is a plausible reason for this finding.

This study has several limitations. Only patients who had at least five visits in the 3.5 years before and after the year around the 18th birthday were included in the analysis cohort. This

allowed more rigorous assessment of longitudinal patterns of pulmonary function, nutritional status, and other clinical factors, but reduced the available cohort. These data may not reflect the clinical course of patients who are seen less frequently. In addition, the requirement of data during young adulthood introduces at least some potential survivor bias. The fact that the sensitivity analysis using the supplemental cohort gave similar results provides some reassurance on these points. In addition, the sensitivity analysis addressing the possibility of a secular trend did not materially change the results.

In conclusion, the rate of $FEV_1$ decline accelerates in young adults with CF, most notably in those with high pulmonary function ($FEV_1$ ≥70% predicted). Other risk factors in adolescence associated with substantial decline in young adulthood include lower BMI and variability in either $FEV_1$ or BMI. This combination of risk factors is of concern given our understanding of adolescent cognition and behavior in regard to health. CF clinicians should have a heightened awareness for adolescents with these risk factors, while implementing strategies to assist these patients in understanding risk, embracing preventative strategies, and adopting positive behaviors that may slow progression of disease as they transition to adulthood.

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## ABBREVIATIONS

| | |
|---|---|
| **BMI** | body mass index |
| **CF** | cystic fibrosis |
| **ESCF** | Epidemiologic Study of Cystic Fibrosis |
| **$FEV_1$** | forced expiratory volume in 1 second |
| ***H. influenzae*** | *Haemophilus influenzae* |
| **IV** | intravenous |
| ***P. aeruginosa*** | *Pseudomonas aeruginosa* |

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## Appendix A: Variables Considered in the Development of the Model

- Demographic characteristics (age at diagnosis, gender, race in four categories, genotype, mother's highest level of education completed, median household income based on zip code, and insurance status)
- Comorbid conditions (defined as whether the patient has ever had any of the following conditions, and if so, the number of encounters and percentage of encounters at which they were present in adolescence and around age 18: allergic bronchopulmonary aspergillosis, asthma, atypical mycobacteria, cirrhosis, elevated liver function test, hemoptysis, use of insulin/oral hypoglycemics, nasal polyps, pneumothorax, portal hypertension, and sinusitis)
- Pulmonary function tests (defined using $FEV_1$% predicted as a 4-group categorization of best value around age 18, the best or worst or mean value in adolescence, the best or worst or mean value around age 18, ever/never or percentage of tests not marked stable in adolescence, difference between best and worst value around age 18, difference between best or worst value around age 18 and the fitted age 18 value from adolescence, difference between best or worst value around age 18 and the value nearest to 18th birthday, slope of values in adolescence, and residual standard deviation in adolescence)
- Clinical signs and symptoms (defined as whether the patient has ever had any of the following conditions, and if so, the number of encounters and percentage of encounters at which they were present in adolescence and around age 18: cough, crackles, and sputum production)
- Height/weight (defined as best/worst and mean/median in adolescence and around age 18: height-for-age percentile/*z*-score, and weight-for-age percentile/*z*-score)
- Body mass index (defined as best/worst, first/last, median, mean, slope [adolescence only], and residual standard deviation [adolescence only] for actual, percentile, and *z*-score in adolescence and around/nearest age 18 and differences in these measures between adolescence and around age 18; last and first, worst/best/mean and predicted at age 18; and nearest to and predicted at age 18)
- Microorganisms (defined as >8 cultures in adolescence and ever cultured, number of cultures, and percentage of cultures in adolescence and around age 18 for *Burkholderia cepacia, Haemophilus influenzae, Pseudomonas aeruginosa* (PA) [multidrug-resistant, mucoid, non-mucoid, and any], *Stenotrophomonas maltophilia, Staphylococcus aureus* (SA), methicillin-resistant SA (MRSA), and combinations of these occurring in the period and concurrently, including SA without PA, multidrug-resistant PA without SA, multidrug-resistant PA with concurrent SA, non–multidrug-resistant PA without SA, non–multidrug-resistant PA with concurrent SA)

- Use of therapies (defined as whether the following therapies were ever used, and if so, the number of encounters and percentage of encounters at which they were prescribed in adolescence and around age 18: airway clearance techniques, enteral supplements, chronic inhaled antibiotics, chronic oral antibiotics, inhaled bronchodilators, oral bronchodilators, mast cell stabilizers, inhaled corticosteroids, oral corticosteroids, and dornase alfa)
- Health care resource utilization (defined as total counts in adolescence and around age 18 for encounters, stable encounters, sick encounters, cultures, and categorization of pulmonary function tests per year in adolescence)
- IV exacerbations (defined as intravenous antibiotic treatment for pulmonary exacerbation ever having occurred, number of occurrences, and rate in adolescence and around age 18)

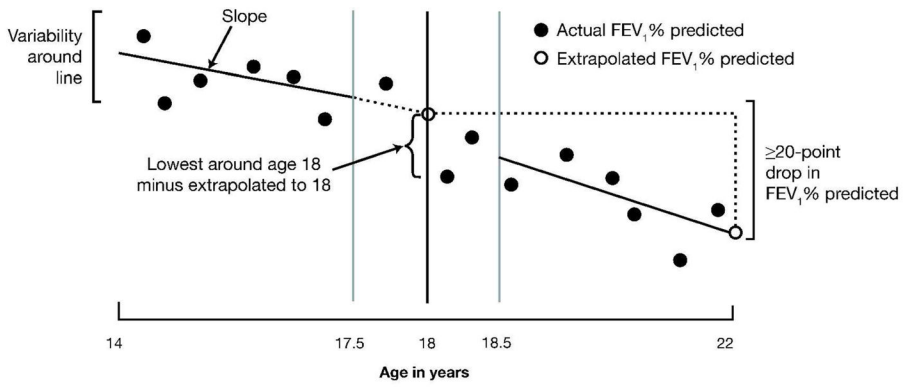


**Fig. 1.**
Timeline and $FEV_1$ assessments.

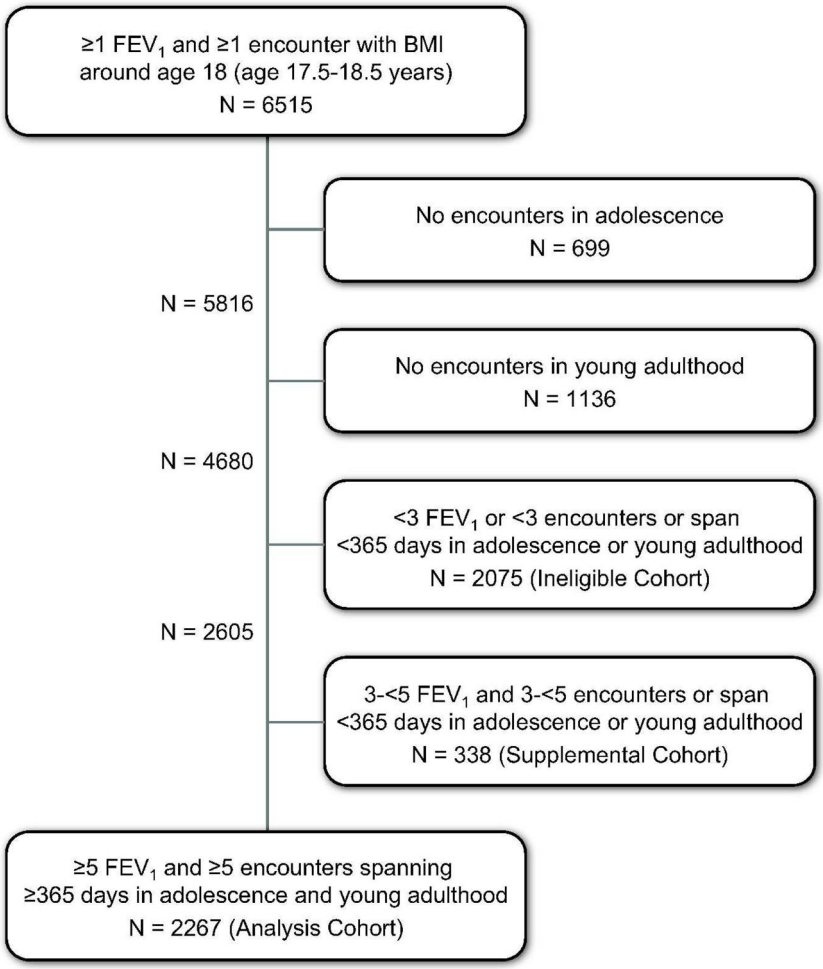


**Fig. 2.**
Patient disposition.

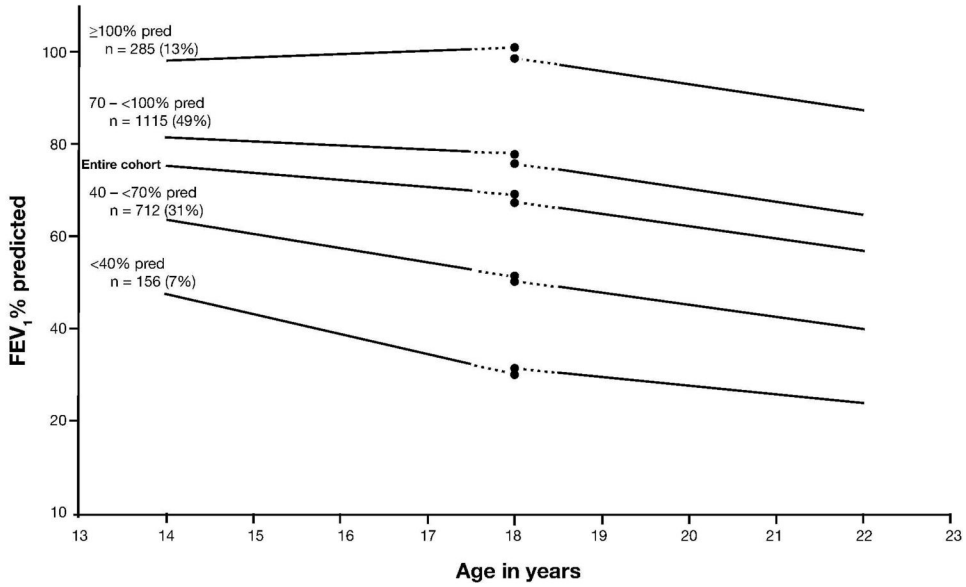


**Fig. 3.**

$FEV_1$ % predicted by age and CF severity.

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**TABLE 1**

Patient Demographics and Clinical Characteristics[1]

| Demographics | | Analysis Cohort (≥5) (2267) N (%) | Supplemental Cohort (≥3) (338) N (%) | Ineligible Cohort (≥1) (2075) N (%) |
|---|---|---|---|---|
| Gender[2] | Male | 1172 (52) | 205 (61) | 1107 (53) |
| | Female | 1095 (48) | 133 (39) | 968 (47) |
| Race[3] | Caucasian | 2127 (94) | 314 (93) | 1914 (92) |
| | African American | 59 (3) | 9 (3) | 56 (3) |
| | Hispanic | 66 (3) | 11 (3) | 81 (4) |
| | Other (mixed) | 14 (1) | 4 (1) | 23 (1) |
| State insurance | Yes | 695 (31) | 64 (19) | 433 (21) |
| | No | 1023 (45) | 170 (50) | 742 (36) |
| | Unknown | 549 (24) | 104 (31) | 900 (43) |
| **Clinical characteristics during adolescence** | | | | |
| Comorbidities during adolescence | Allergic bronchopulmonary aspergillosis | 197 (9) | 11 (3) | 132 (6) |
| | Asthma | 927 (41) | 80 (24) | 637 (31) |
| | Atypical mycobacteria[4] | 49 (2) | 1 (0) | 29 (1) |
| | Insulin or oral hypoglycemic use (CFRD) | 305 (13) | 22 (7) | 231 (11) |
| | Nasal polyps[5] | 821 (36) | 110 (33) | 546 (26) |
| | Sinusitis[6] | 1034 (46) | 123 (36) | 723 (35) |
| | Pneumothorax[3] | 27 (1) | 3 (1) | 20 (1) |
| | Hemoptysis | 206 (9) | 9 (3) | 144 (7) |
| | Cirrhosis[3] | 79 (3) | 8 (2) | 69 (3) |
| Best $FEV_1$ in the year around the 18th birthday | <40% predicted | 156 (7) | 15 (4) | 233 (11) |
| | 40%–69% predicted | 712 (31) | 84 (25) | 615 (30) |
| | 70%–99% predicted | 1115 (49) | 178 (53) | 941 (45) |
| | ≥100% predicted | 284 (13) | 61 (18) | 286 (14) |
| Best BMI percentile in the year around the 18th birthday | >25th percentile | 585 (26) | 67 (20) | 604 (29) |

| Demographics | | Analysis Cohort (≥5) (2267) N (%) | Supplemental Cohort (≥3) (338) N (%) | Ineligible Cohort (≥1) (2075) N (%) |
|---|---|---|---|---|
| | 10th–25th percentile | 452 (20) | 72 (21) | 413 (20) |
| | <10th percentile | 1230 (54) | 198 (59) | 1053 (51) |
| Clinical symptoms at any encounter during adolescence | Cough[5] | 2265 (100) | 337 (100) | 2030 (98) |
| | Sputum production[6] | 2233 (99) | 322 (95) | 1919 (92) |
| | Crackles | 1721 (76) | 172 (51) | 1261 (61) |
| Microbiology during adolescence | 8 or fewer cultures during adolescence | 1597 (70) | 299 (88) | 1654 (80) |
| | *Pseudomonas aeruginosa* | 1945 (86) | 236 (70) | 1560 (75) |
| | *P. aeruginosa, mucoid*[6] | 1607 (71) | 182 (54) | 1200 (58) |
| | *P. aeruginosa, non-mucoid*[6] | 1786 (79) | 205 (61) | 1356 (65) |
| | *P. aeruginosa, multidrug resistant* | 362 (16) | 22 (7) | 251 (12) |
| | *Haemophilus influenzae*[5] | 631 (28) | 99 (29) | 478 (23) |
| | *Staphylococcus aureus*[5] | 1572 (69) | 247 (73) | 1319 (64) |
| | *S. aureus, methicillin resistant* | 138 (6) | 8 (2) | 164 (8) |
| | *Stenotrophomonas maltophilia* | 318 (14) | 21 (6) | 246 (12) |
| | *Burkholderia cepacia*[3] | 121 (5) | 12 (4) | 110 (5) |
| Maintenance therapy use in adolescence | Airway clearance | 2210 (97) | 307 (91) | 1795 (87) |
| | Dornase alfa | 1706 (75) | 176 (52) | 1359 (65) |
| | Inhaled bronchodilator[6] | 2157 (95) | 284 (84) | 1810 (87) |
| | Inhaled mast cell stabilizer[6] | 791 (35) | 67 (20) | 484 (23) |
| | Oral antibiotics[2] | 702 (31) | 59 (17) | 629 (30) |
| | Inhaled antibiotics | 1305 (58) | 114 (34) | 976 (47) |
| | Enteral supplements[2] | 250 (11) | 19 (6) | 267 (13) |
| **Health care interventions during adolescence**[7] | | | | |
| Routine encounters | Mean annualized rate ± SD/year | 3.5 ± 1.6 | 2.5 ± 1.5 | 3.3 ± 2.2 |
| Exacerbations requiring IV antibiotics during adolescence | Mean annualized rate ± SD/year[2] | 0.8 ± 1.1 | 0.3 ± 0.7 | 0.8 ± 1.2 |
| | No exacerbations in adolescent period | 726 (32) | 219 (65) | 1021 (49) |

CFRD, cystic fibrosis–related diabetes; SD, standard deviation

[1] Except as noted, cohort differences are statistically significant at $P < 0.05$ by chi-square test (for frequency variables) or by Tukey-adjusted mean comparisons (for continuous variables).

[2] The ineligible cohort is not statistically different from the analysis cohort.

[3] No cohorts are statistically different.

[4] The ineligible cohort is not statistically different from the supplemental or analysis cohorts.

[5] The supplemental cohort is not statistically different from the analysis cohort.

[6] The ineligible cohort is not statistically different from the supplemental cohort.

[7] For the ineligible cohort, very short time spans led to unreasonable extrapolated rates, so encounter rates >15/yr (n=28) and IV exacerbation rates >10/yr (n=11) were set to missing.

## TABLE 2

Intercepts ($FEV_1$ % Predicted at Age 18), Slopes ($FEV_1$ % Predicted/Year), and 95% Confidence Intervals for Figure 3

| **$FEV_1$ % predicted** | **Adolescence** | | **Young Adulthood** | |
|---|---|---|---|---|
| | **Intercept at age 18 yr** | **Slope (% pred/yr)** | **Intercept at age 18 yr** | **Slope (% pred/yr)** |
| Entire cohort | 69.02 (68.48, 69.57) | −1.09 (−1.36, −0.82) | 67.48 (66.95, 68.01) | −2.68 (−2.88, −2.49) |
| ≥100 | 100.65 (99.10, 102.20) | −3.39 (−4.16, −2.61) | 98.29 (96.76, 99.83) | −2.76 (−3.34, −2.19) |
| 70–<100 | 77.81 (77.03, 78.58) | −1.92 (−2.31, −1.54) | 75.67 (74.90, 76.43) | −2.78 (−3.06, −2.50) |
| 40–<70 | 51.15 (50.19, 52.12) | 0.38 (−0.09, 0.85) | 50.28 (49.34, 51.22) | −2.67 (−3.01, −2.32) |
| <40 | 30.24 (28.21, 32.27) | 2.34 (1.31, 3.36) | 31.35 (29.34, 33.37) | −1.88 (−2.64, −1.11) |

$FEV_1$, forced expiratory volume in 1 second

**TABLE 3**

Multivariate Risk Model of Factors in the Adolescent Period Influencing Substantial Decline in the Adult Period (N=2267)

| | Odds Ratio | 95% Confidence Interval | Risk of a substantial decline is higher if … |
|---|---|---|---|
| **Variables (*P* <0.01)** | | | |
| Difference between fitted $FEV_1$ % predicted at age 18 and lowest measured $FEV_1$ around age 18 | 0.95 | 0.94–0.96 | Worst $FEV_1$ around age 18 is low compared with fitted value at 18 |
| Slope of $FEV_1$ (% predicted per year) during adolescence | 1.06 | 1.04–1.09 | Rate of decline during adolescence is less severe |
| Difference between fitted BMI *z*-score at age 18 and highest measured BMI *z*-score around age 18 | 0.62 | 0.50–0.78 | Best BMI around age 18 is low compared with fitted value at 18 |
| Slope of BMI (*z*-score per year) during adolescence | 0.48 | 0.30–0.78 | Rate of BMI decline during adolescence is more severe |
| Female | 0.74 | 0.60–0.90 | Patient is male |
| Presence of *Haemophilus influenzae* on any culture during adolescence | 1.40 | 1.12–1.73 | *H. influenzae* is ever present |
| **Variables (*P* <0.05)** | | | |
| Percentage of encounters recording inhaled antibiotics during adolescence | 1.71 | 1.03–2.82 | Inhaled antibiotics are recorded more often |
| $FEV_1$% predicted variability (SD around fitted line) during adolescence | 1.04 | 1.01–1.07 | Variability around the adolescent trend line is greater |
| Presence of *Pseudomonas aeruginosa* (multidrug resistant) on any culture during adolescence | 0.74 | 0.56–0.99 | *P. aeruginosa* (multidrug resistant) is never present |
| **Variables (not statistically significant)** | | | |
| BMI *z*-score variability (SD around fitted line) during adolescence | 0.99 | 0.52–1.90 | Variability around the BMI trend line is greater (NS) |
| Cirrhosis reported at any encounter during adolescence | 1.35 | 0.82–2.24 | Cirrhosis is ever reported (NS) |
| Percentage of encounters with occasional or daily cough during adolescence | 2.28 | 0.93–5.61 | Cough is recorded more often (NS) |
| Percentage of encounters with crackles during adolescence | 0.84 | 0.54–1.29 | Crackles are recorded less often (NS) |
| Percentage of encounters with occasional or daily sputum during adolescence | 0.87 | 0.53–1.44 | Sputum is recorded less often (NS) |

BMI, body mass index; $FEV_1$, forced expiratory volume in 1 second; NS, not significant; SD, standard deviation