

Chapter 2

Epidemiology of cystic fibrosis lung disease progression in adolescence

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1. Introduction

Physiological and emotional changes that challenge all adolescents can be accompanied by accelerated progression of lung disease in the adolescent with cystic fibrosis (CF), leading to irreversible morbidity and increased risk of mortality. In this chapter, the epidemiology of lung disease progression in adolescents with CF and the physical and psychosocial factors that may influence this process will be reviewed. The published literature on the epidemiology of adolescent CF lung disease is currently dominated by studies of North American populations that are followed in the US CF Foundation (CFF) Patient Registry [1] and the Epidemiologic Study of Cystic Fibrosis (ESCF) [2]. There is reason to believe, however, that adolescent CF experiences and outcomes vary to some degree from country to country as a result of differences in genetic backgrounds, healthcare delivery systems, clinician practice patterns, available treatments and cultural behaviours among adolescents, peers and families. A comprehensive analysis of the epidemiology of adolescents with CF would ideally include comparisons across all countries with adolescent CF populations. Whenever possible, epidemiological data from as many different countries as possible will be included in this review.

2. Assessing pulmonary disease progression by spirometry

Today, more than 80% of CF deaths result directly or indirectly from loss of pulmonary function [1], although only a small fraction of these deaths occur among adolescents. In

2010, 7.4% of all patient deaths reported in the 2010 US CFF Patient Registry occurred among patients 12–17 years old, comprising only 0.63% of the 12–17-year-old US CF population [1]. Despite the relative rarity of death in the adolescent CF population, there is an increased probability of irreversible loss of lung function during adolescence [3] that increases the subsequent risk of mortality [4].

When characterising CF lung disease, there has been a traditional emphasis on spirometry, and in particular forced expiratory volume in 1 sec (FEV_1) and the fraction of FEV_1 present compared with a reference population ($FEV_1\%$ predicted) [5]. As $FEV_1\%$ predicted is lost, lung disease stage advances and predicted 2-year survival decreases [4]. It is important to note, however, that inflammation-induced lung damage precedes the ability to detect functional loss by spirometry. Air trapping, bronchial wall thickening, and bronchiectasis can be detected in infants with CF by high-resolution computed tomography [6–9] and chest X-ray [10]. Similarly, ventilation inhomogeneity can be discerned well before spirometric changes [11–13]. Unfortunately, there are relatively few published data describing the epidemiology and progression of early structural or ventilation changes in the CF lung, whereas spirometric data are widely available. Although Rosenthal [14] has suggested that the reliance by the clinical community on FEV_1 as an indicator of CF health status is questionable, the measure remains an influential driver of patient management, including (but not limited to) defining lung disease stage [5] and disease aggressiveness phenotype [5,15], supporting the diagnosis of pulmonary exacerbation [16], evaluating response to exacerbation management [17–22] and demonstrating treatment efficacy in controlled CF clinical trials [23–28]. Several different normative equations have been employed to estimate the fraction of FEV_1 an individual retains compared with a reference population of the same sex, height and age ($FEV_1\%$ predicted) [29]. In this chapter, unless otherwise stated, $FEV_1\%$ predicted values will be determined using the reference equations of Wang et al. [30] for females up to age 15 years and males up to age 17 years, with the reference equation of Hankinson et al. [31] for older individuals.

3. Variability of lung disease progression

Not surprisingly, individuals with CF who die at younger ages experience greater average rates of FEV₁ loss over their lifetimes compared with those who die at older ages [32]. However, rates of FEV₁ decline are not constant across all ages [3,33]. Only a minority of children with CF experience substantial FEV₁ loss by the age of 6 years. For example, 91.0% of 3456 children in an ESCF study had an FEV₁ ≥70% predicted at age 6 years, with 83.3% having an FEV₁ ≥80% predicted and 68.1% with an FEV₁ ≥90% predicted [34]. Unfortunately, mean rates of FEV₁ decline increase as children get older, with an ESCF analysis of children 6–18 years of age identifying FEV₁ decline rates of 1.12% predicted/year for 6–8-year olds (n=1811; *p*=0.369), 2.39% predicted/year for 9–12-year olds (n=1696; *p*=0.0060) and 2.34% predicted/year for 13–17-year olds (n=1359; *p*=0.042) [3].

4. FEV₁% predicted versus age

Individuals with CF advance through progressive stages of lung disease. However, CF lung disease progression is heterogeneous, with the age at which an individual reaches a given lung disease stage providing an indication of the relative aggressiveness of his or her lung disease phenotype [5]. Heterogeneity of CF lung disease stage (as FEV₁% predicted) within the adolescent population suggests that individual FEV₁ decline rates vary broadly prior to adolescence (**Fig. 1**).

Changes in FEV₁ distributions observed in successively older adolescent groups in **Fig. 1** are consistent with lung disease progression continuing during adolescence. For example, 37.7% of 12- and 13-year-olds followed in the US CFF Patient Registry had a best recorded FEV₁ ≥100% predicted in 2010 compared with 30.8% of 14- and 15-year-olds and only 20.9% of 16- and 17-year-olds (**Fig. 1**). Similarly, 12.2% of the youngest adolescents had a best FEV₁ <70% predicted in 2010, whereas 18.4% of 14- and 15-year-olds and 26.7% of 16- and 17-year-olds found themselves in the same situation. However tempting it is to employ such cross-sectional data to infer lung disease progression, they are inadequate to estimate rates of FEV₁ decline from year to year. Accurate estimation of decline rates during adolescence requires longitudinal analyses

of the same population over time to avoid bias introduced by demographic differences between age groups as well as patients entering or leaving the population due to new diagnoses, relocations or deaths.

5. Lung disease aggressiveness phenotypes

In 2006, Schluchter et al. divided homozygotes for the most common *CFTR* mutation, F508del, from the US CFF Patient Registry into quartiles by FEV₁% predicted at each age to create a topographical map of age versus FEV₁ in order to identify F508del homozygotes with the most and least aggressive CF lung disease phenotypes [15]. These investigators demonstrated that ~95% of patients identified as having a 'mild' or 'severe' phenotype based on mapping (**Fig. 2A**) remained in their respective phenotypic zones during subsequent years [15]. The potential utility of disease aggressiveness phenotypes in the management of the entire CF population has been reviewed [5]. Interestingly, adolescents with CF who are under 15 years of age and have relatively high FEV₁% predicted prove difficult to categorise using the aggressiveness phenotype algorithm (**Fig. 2A**), as their disease progression 'fate' has yet to be fully realised. For these individuals, the extent to which their FEV₁ is preserved or lost during adolescence determines whether their disease phenotype will ultimately be categorised as 'mild' or 'intermediate' in aggressiveness (**Fig. 2B**).

6. Risk factors for adolescent pulmonary function decline

As noted previously, cross-sectional analyses of adolescent CF populations (**Fig. 1**) suggest substantial heterogeneity in lung disease progression. To identify risk factors associated with variability in lung disease progression in children with CF, Konstan et al. identified 11 demographic or clinical parameters (of the 28 initially studied) that exhibited significant univariate associations with rate of FEV₁ decline in any of three age groups: 6–8 years, 9–12 years and 13–17 years [3]. These 11 parameters were incorporated into a multivariate model to predict rates of FEV₁ decline over 5–6 years. The parameters retained included: clinical presentations (sex, sputum production, crackles, wheeze and sinusitis); objective measures (FEV₁% predicted, culture history for *Pseudomonas*

aeruginosa, weight-for-age [WFA] percentile, and liver function test [LFT] results); and intervention histories (treatment with intravenous [IV] antibiotics for pulmonary exacerbation and prescription of pancreatic enzyme supplements) [3]. Seven of these parameters were found to be statistically significant with respect to predicting rate of FEV₁ decline in adolescents ages 13–17 years: baseline FEV₁% predicted ($p<0.001$), sex ($p=0.002$), WFA percentile ($p=0.021$), sputum production ($p=0.003$), crackles ($p=0.010$), past IV antibiotic treatments for exacerbation ($p<0.001$) and pancreatic enzyme use ($p=0.041$). Parameter estimates and their 95% confidence intervals from this model are shown in **Fig. 3**.

Using **Fig. 3**, an individual's future rate of FEV₁ decline is estimated by summing his or her parameter status estimates. For example, the estimated future rate of FEV₁ change for a 13-year-old boy with an FEV₁ of 95% predicted, a WFA in the 55th percentile and no *P. aeruginosa* infection, sputum production, crackles, wheeze, sinusitis, prior year history of exacerbation treated with IV antibiotics or elevated LFT, but who requires pancreatic enzyme supplements would be $(-2.34) + (-0.37) + (-0.3) + (0.13) + (-0.41) + (0.33) + (0.18) + (-0.04) + (0.0) + (0.42) + (0.02) + (-0.04) = -2.42\%$ predicted/year.

With this method, the effects of differences in a single parameter on the rate of lung function decline can be assessed, all other parameters being equal. For example, overall adolescent male FEV₁ decline rates are predicted to be 0.61% predicted/year greater than female decline rates (**Fig. 3**). This result may seem counterintuitive given previous reports of more aggressive CF lung disease progression among females compared with males [35], but the contribution of other parameter estimates may offset these differences, and FEV₁ decline rate calculations for individuals require summation of all parameter estimates.

7. Lung disease progression: nature versus nurture?

Some parameters captured in the rate of FEV₁ decline modelling (**Fig. 3**) suggest underlying biological factors that are markers for lung disease and are for the most part beyond the influence of clinicians. Sputum production and crackles suggest exaggerated airway inflammation and obstruction, and it is not surprising that these symptoms are

associated with more rapid FEV₁ decline. Similarly, some individuals with CF carrying at least one 'mild' *CFTR* mutation are pancreatic sufficient and do not require pancreatic enzyme supplementation [36,37]. These individuals also enjoy a relatively greater overall survival compared with those with two 'severe' *CFTR* mutations [38,39]. In this context, it is not surprising that rates of FEV₁ decline are higher in individuals prescribed pancreatic enzyme supplements than in those not prescribed supplements.

Relationships between FEV₁ decline rates and other parameters may be more complicated than they first appear. For example, an association between history of pulmonary exacerbation and future FEV₁ decline makes intuitive sense, as it has recently been suggested that a substantial portion of patients with CF treated for pulmonary exacerbation fail to recover associated FEV₁ loss [20]. However, by sheer numbers, more pulmonary exacerbations in North America are treated with inhaled and/or oral antibiotics than with IV antibiotics [40], and thus a clinician's decision to choose IV antibiotics to treat an exacerbation may include a subjective assessment of his or her patient's disease status and risk of progression, as well as an objective assessment of exacerbation severity.

Finally, relationships between some parameters and FEV₁ decline rates seem counterintuitive and inexplicable in strictly biological terms, and these may provide insight into variations in standards of care. For example, it is difficult to rationalise a biophysical relationship between the presence of wheeze and a reduced FEV₁ decline rate (a relationship that was observed to be statistically significant in younger children and nearly so in adolescents [3]). However, if one postulates that the presence of wheeze may increase the rigour of pulmonary management and/or treatment adherence, then wheeze can be viewed as an indirect marker of better pulmonary care and it would make sense for it to be associated with better FEV₁ outcomes. The most striking example of a counterintuitive relationship between a parameter's status and estimated future rate of FEV₁ decline can be found with FEV₁% predicted itself, where greater baseline lung function is associated with greater future decline. Understanding that patients with the very lowest FEV₁% predicted values have little room for further lung function decline (i.e. there is a basement effect), there is no biological basis from which to conclude that the very highest lung function levels should cause accelerated FEV₁ decline. However, it has been documented that CF clinicians can be more hesitant to

prescribe chronic pulmonary therapies to healthier adolescents [41,42] and also that healthier patients can be less motivated to adhere to prescribed therapies [43]. Furthermore, it has been shown that the responsibility for adherence shifts more and more towards the adolescent and away from their parents/caregivers, creating a potential for reduced adherence [44]. Viewed in this context, better lung function may be a marker for less rigorous management/adherence and in turn a marker for increased risk of FEV₁ decline. Interestingly, this phenomenon appears to extend beyond adolescence and into young adulthood, where higher FEV₁ values have also been associated with a greater risk of near-term lung function decline [45].

Evidence that clinician and patient behaviours affect adolescent lung disease progression is largely indirect, but substantial. First, at least three chronic CF pulmonary therapies have been shown to reduce mean rates of FEV₁ decline: high-dose ibuprofen [46–48], inhaled corticosteroids [49], and dornase alfa [50]. It follows that a clinician's decision to prescribe or not prescribe such therapies has the potential to impact future FEV₁ decline, as does a patient's decision to be adherent to these therapies or not. Second, the tendency to prescribe chronic pulmonary therapies has been shown to be heavily influenced by lung disease stage, with the proportion of patients prescribed therapies increasing with decreasing FEV₁% predicted [41,42]. If clinicians are less inclined to prescribe therapies that reduce the rate of lung function decline in patients with better lung function [41,42], it is perhaps not surprising that these patients are at relatively greater risk of FEV₁ decline.

Additional evidence that clinical practice may play a role in adolescent lung disease progression can be found in comparisons of FEV₁ distribution among adolescents from different countries, where practice patterns presumably differ to some extent (**Fig. 4**). Although simple in premise, such comparisons must be tempered by recognition of the potential for bias introduced by differing patient genetic backgrounds, CF diagnostic methods, and death rates. Perhaps more importantly, such comparisons are complicated by fundamental differences in CF registry data collection across geographical regions that can be challenging to transcend [51]. Beyond the obvious problem of comparing data collected in different (but proximal) years (**Fig. 4**), it should be noted that regional registries do not employ a uniform standard for calculating FEV₁% predicted; the UK CF Registry data in **Fig. 4** are calculated using the normative equations of Knudson et al.

[52], whereas data from the other regions are calculated using the equations of Wang [30] and Hankinson [31]. Furthermore, assigning a single pulmonary function value for each patient in a given year is, in itself, a somewhat arbitrary practice, and varies by region. For the most part, data in **Fig. 4** employ the 'best recorded' FEV₁% predicted that year, with exceptions being data contributed to the ECFS Registry by France (N=898), which reported the final FEV₁ measure of the year, and Germany (N=950), which reported the FEV₁ closest to the patient's birthday. Finally, the UK CF Registry records pulmonary function from an 'annual encounter'.

Given the many caveats associated with demographic comparisons across geographical areas [51], **Fig. 4** does suggest that there is geographical variability in CF lung health in adolescents, and it is not unreasonable to conclude that how children with CF have been managed in these regions has at least partially contributed to these differences.

A final indication that differences in patient management can influence adolescent lung disease progression can be found in a comparison of US adolescent lung disease distributions between 1995 and 2010. Again, cross-sectional comparisons of different adolescent CF populations of the same age may be prone to bias due to an inability to account for demographic differences. Recognising these caveats, the percentage of 12- and 13-year-olds in the US CFF Patient Registry with an FEV₁ ≥100% predicted increased from 22.4% to 37.7% between 1995 and 2010, while the percentage of 16- and 17-year-olds with FEV₁ ≥100% predicted nearly doubled from 11.4% to 20.9% over the same time period (**Fig. 5**).

Incremental improvements in the pulmonary health of adolescent CF populations are remarkably consistent between 1995 and 2010 and coincide with a decrease in signs and symptoms of respiratory disease in adolescents [53]. Perhaps not coincidentally, a steady increase in the use of chronic pulmonary therapies within the adolescent ESCF population also occurred between 1995 and 2005, with prescriptions for inhaled antibiotics increasing from 8.0% to 50.0%, prescriptions for inhaled corticosteroids increasing from 18.1% to 53.5%, and prescriptions for dornase alfa increasing from 57.5% to 76.0% (**Fig. 6**) [42]. Increased use of chronic pulmonary therapies over this time period are notable because they occurred in a population with improving lung

function [53] against the trend that prescription of these therapies is lower in patients with higher FEV₁% predicted than in those with lower FEV₁ values [41,42]. Observed increases in pulmonary health in the US adolescent CF population are likely also related to the remarkable improvements in the nutritional status, growth and stature of younger children with CF that has been achieved in recent decades [1].

8. Conclusions

Inexorable lung function loss and premature death are characteristic of a majority of individuals with CF. However, mean rates at which lung function is lost are not constant across an individual's lifetime or between individuals of the same age. Progressive damage to CF airways can begin early in life, but the most common measure of lung disease in CF, FEV₁% predicted, is only modestly affected in early childhood. Mean rates of FEV₁ decline increase as children with CF get older. By adolescence, overall rates of FEV₁ decline are roughly double what they had been when individuals were 6–8 years of age. Despite an overall increase in the rate of lung disease progression at the population level immediately prior to and during adolescence, individual rates of FEV₁ decline can vary widely, creating a distribution of lung disease stages at a given age.

Although adolescence is characterised by an increased risk of CF lung disease progression, remarkable improvement in the pulmonary health of adolescents with CF has been realised over recent decades. Circumstantial evidence that clinician and patient behaviour can have a substantial impact on lung disease progression (e.g. through more rigorous use of chronic pulmonary therapies) suggests that the potential for further improvement in the pulmonary health of adolescents with CF remains.

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Fig. 1. Heterogeneity of FEV₁% predicted among US adolescents with cystic fibrosis (CF). Distributions of adolescents followed in the 2010 CF Foundation Patient Registry [1] stratified by their best recorded FEV₁% predicted in 2010 for different age groups. Patients were assigned to age groups based upon their age on their 2010 birthday, and the percentages shown total 100% within each age group.

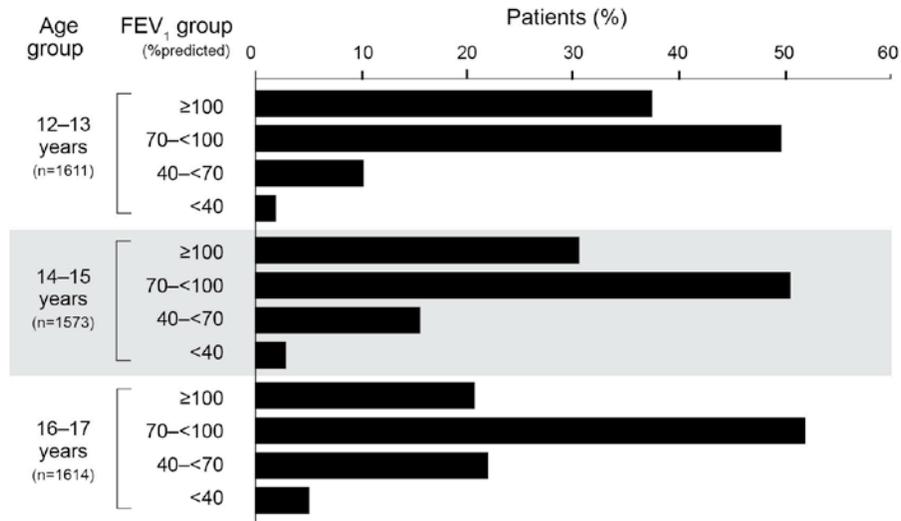


Fig. 2. Topographical mapping of cystic fibrosis (CF) lung disease phenotypes. Panel A: disease aggressiveness phenotype map adapted from Konstan et al. [5]. Patients with a 'severe' lung disease phenotype (black zone) are at greater risk for mortality at a younger age, whereas those with a 'mild' disease phenotype (grey zone) are more likely to survive to older ages. The adolescent CF population is found between the vertical dotted lines. Panel B: disease aggressiveness among CF adolescents 12–17 years of age. The disease aggressiveness phenotype of a 14-year old with an FEV₁ of 100% of his or her predicted value (circle 'a') is uncertain and dependent on rate of FEV₁ decline over the subsequent 2 years (circles 'b' versus 'c').

Adapted from Journal of Cystic Fibrosis, Volume 8S, Konstan MW, Wagener JS, VanDevanter DR, Characterizing aggressiveness and predicting future progression of CF lung disease, pages 8S:S15-S19, copyright 2009, with permission from Elsevier.

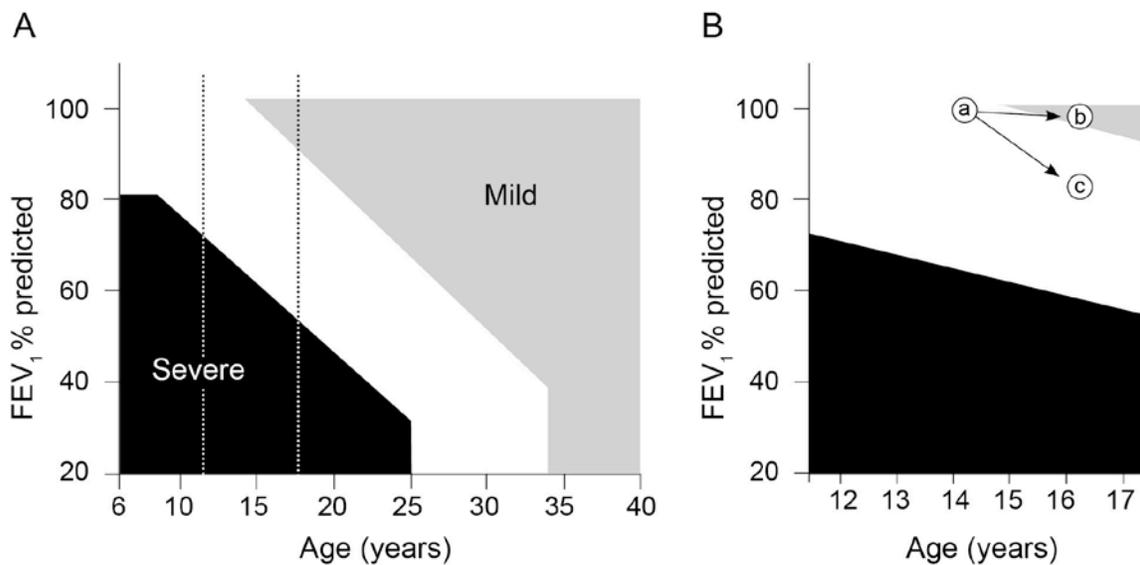


Fig. 3. Multivariate modelling of FEV₁ decline rates in adolescents with cystic fibrosis (CF) aged 13–17 years [3]. Parameters are shown in the left column. n = number of patients included in the model with a given parameter value. Bars are 95% confidence intervals (CI). Dotted vertical line is the overall estimate for rate of FEV₁ decline for the population (2.34% predicted/year). LFT = liver function tests; WFA = weight for age. Adapted from Journal of Pediatrics, Volume 151 Number 2, Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, Stokes DC, Wohl MB, Wagener JS, Regelmann WE, Johnson CA, Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis, pages 134–139, copyright 2007 with permission from Elsevier.

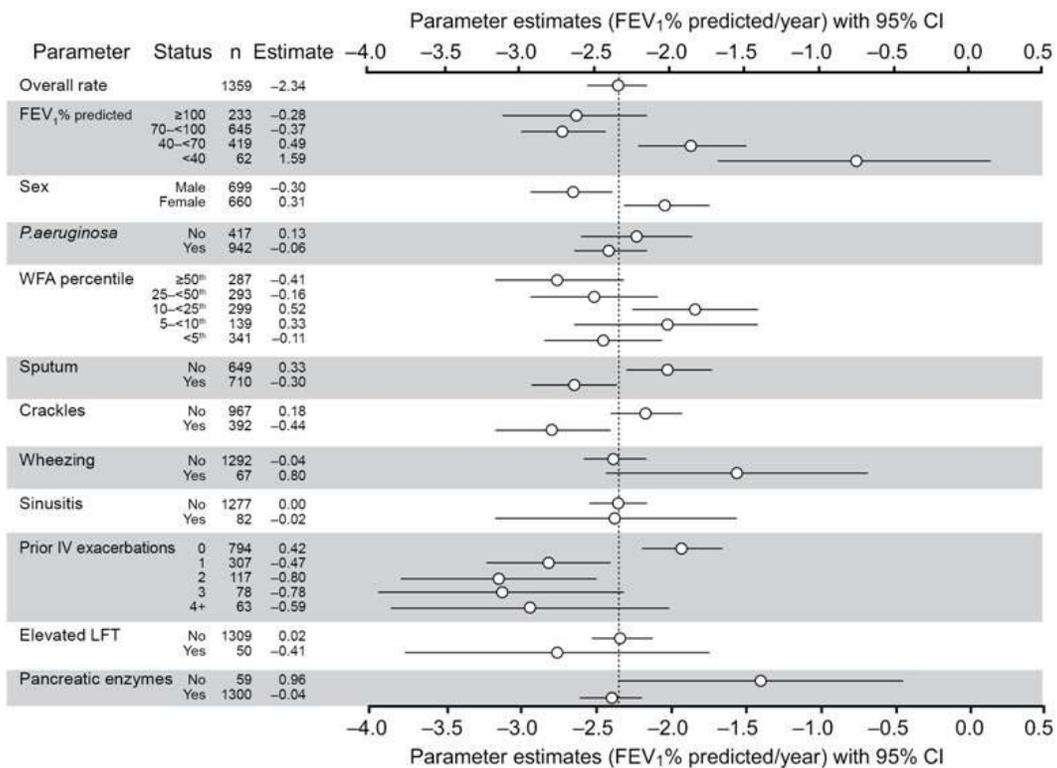


Fig. 4. Distribution of lung function in adolescents with cystic fibrosis (CF) by age and geographical location. Stacked bars show the proportions of adolescents with CF of a given age group within different lung function ranges (as FEV₁% predicted) by geographical region. Aus 2009, patients followed in the Australian CF Registry in 2009; EU 2009, patients followed in the European CF Society Registry in 2009 from Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Moldova, Portugal, Serbia, Slovenia, Spain, Sweden, Switzerland and The Netherlands; UK 2010, patients followed in the United Kingdom CF Registry in 2010; US 2010, patients followed in the US CF Foundation Patient Registry in 2010.

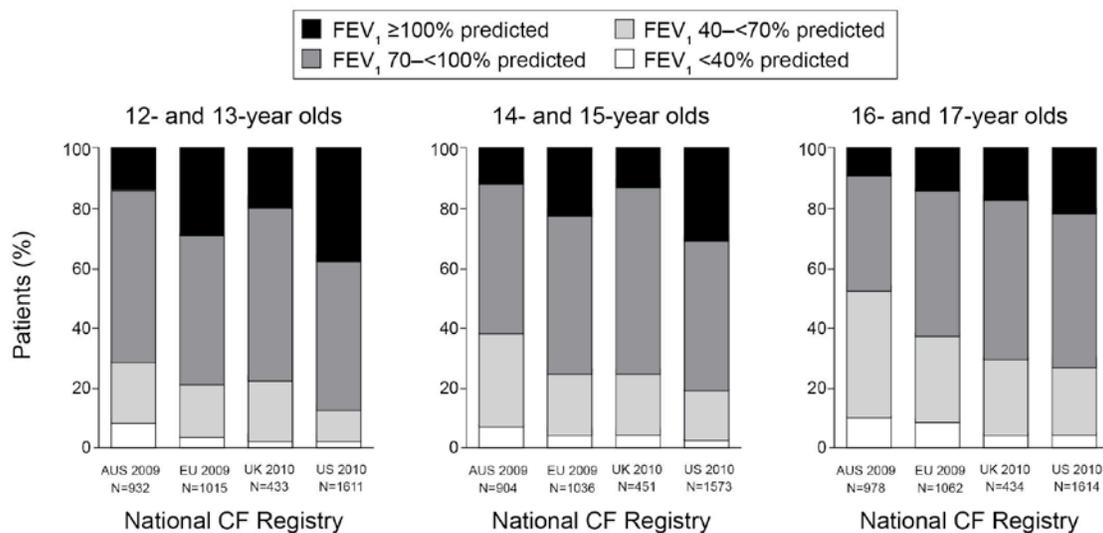


Fig. 5. Changes in FEV₁ distribution among adolescents in the US Cystic Fibrosis Foundation Patient Registry, 1995–2010. Left panel: FEV₁% predicted distributions among 12- and 13-year-old patients. Right panel: FEV₁% predicted distributions among 16- and 17-year-old patients. Lines represent simple linear regressions of proportions of patients in each FEV₁ category versus time, for which correlation coefficients (R^2) and p -values are provided.

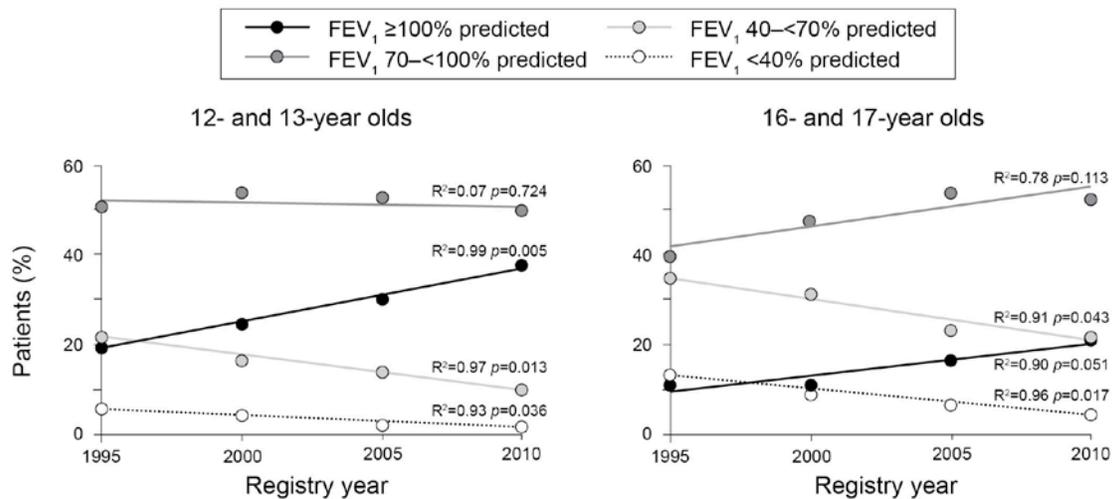


Fig. 6. Prescriptions of inhaled antibiotics, inhaled corticosteroids, and dornase alfa among patients aged 13–17 years followed in the Epidemiologic Study of Cystic Fibrosis Registry for the years 1995, 2000 and 2005 [42].

