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Caley, L orcid.org/0000-0001-8957-1018, Smith, L orcid.org/0000-0002-4280-6323, White, H et al. (1 more author) (2020) Average rate of lung function decline in adults with cystic fibrosis in the United Kingdom: Data from the UK CF registry. *Journal of Cystic Fibrosis*. ISSN 1569-1993

<https://doi.org/10.1016/j.jcf.2020.04.008>

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Average Rate of Lung Function Decline in Adults with Cystic Fibrosis in the United Kingdom: Data from the UK CF Registry

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Abstract

Background: Rate of change in lung function is used as a measure of disease progression and a predictor of mortality in individuals with cystic fibrosis (CF). The aim of this study was to determine the national rate of decline in percent predicted Forced Expiratory Volume in 1 second (ppFEV₁) in adults in the UK accounting for age, sex and pancreatic status.

Methods: Data on ppFEV₁ for adults with CF, excluding those post lung transplantation, was extracted from the UK CF registry between 2015 and 2017. Multilevel modelling was conducted to calculate the annual rate of change in ppFEV₁ accounting for age, sex and pancreatic status.

Results: Overall annual ppFEV₁ decline was -1.52% (95% CI: -1.66 to -1.38%) and -0.55% (95% CI: -0.86 to -0.23%) in pancreatic insufficient (PI) and sufficient (PS) adults respectively. In PI individuals, females had a greater rate of decline in ppFEV₁. There were differences between age groups. The fastest rate of decline was observed in the 18-28 years group, declining -1.76% (95% CI: -2.06 to -1.46) and -1.61% (95% CI: -1.91 to -1.31) per year in females and males respectively. The pattern between the sexes and age categories was more inconsistent in the PS group.

Conclusions: The average annual rates of decline in lung function in adults with CF in the UK are similar to reports from other large international cohorts. Pancreatic status has a marked impact on average rate of decline. Younger adults, especially females, have a faster rate of decline and need close monitoring.

Key words: CF; rate of decline; lung function

Highlights

- ppFEV₁ declines annually by -1.5% in CF pancreatic insufficient adults in the UK
- People with pancreatic sufficiency have a slower rate of decline in ppFEV₁
- Younger adults, especially females, have a higher rate of decline

1. Background

Cystic Fibrosis (CF) is characterised by recurrent lower respiratory tract infections, airway inflammation and progressive respiratory failure. Despite significant improvements in survival, lung disease remains the major cause of morbidity and mortality. Early interventions to minimise pulmonary exacerbations and preserve lung health remains an essential part of treatment[1].

Percent predicted forced expiratory volume in one second (ppFEV₁) is routinely used in clinical practice to monitor disease progression. Other tools such as lung clearance index, high resolution computed tomography and magnetic resonance imaging are more sensitive at identifying early ventilation changes and structural lung damage[2]. However, these techniques are rarely used in routine clinical practice as they can be expensive and less practicable. Percent predicted FEV₁ is routinely used globally to monitor clinical stability, assess treatment outcomes, stratify disease stage and as a comparator of care between units and national registries[3-5].

ppFEV₁ remains a robust measurement of lung function with variability and rate of decline associated with adherence, clinical outcome and the need for lung transplantation [6-8]. It is also a key outcome measure in clinical trials and has been used to assess the impact of cystic fibrosis transmembrane conductance regulator (CFTR) modulators in individuals with CF[9]. Values are also used to classify lung disease stage into mild, moderate and severe using arbitrary figures of >80%, 40-79% and <40% respectively[5].

There are limitations to using raw ppFEV₁ values and arbitrary cuts-offs to classify lung disease stage. It may be that the rate of decline is more relevant and a better predictor of clinical deterioration[10]. Currently, the average rate of decline of FEV₁ for adults with CF in the United Kingdom (UK) has not been reported, nor has the relative rate of decline in those with pancreatic insufficiency versus sufficiency. Comparing individual's actual and expected rate of decline in ppFEV₁ could be a better approach to assess clinical status and provide personalised feedback.

National registries tend to use best or baseline annual ppFEV₁ when comparing centre outcome data. This can lead to misinterpretations on performance, especially in those centres where survival is high and individuals with CF have a low but stable lung function[11]. The aim of

this study was to determine the current rate of decline of ppFEV₁ in adults with CF in the UK, accounting for age, sex and pancreatic status.

2. Methods

Study population and data extraction

Annual data for ppFEV₁, age, sex and pancreatic status for individuals with CF attending specialist care centres in the UK was extracted from the National CF Registry, which holds data for over 99% of the UK CF population[12]. The registry has National Health Service approval (07/Q0104/2 UK Cystic Fibrosis Registry, AB/AM04/1) for collection of data and its use for anonymised research. Requests for data was reviewed and approved by the UK CF Registry Research Steering Committee.

Data for 2015- 2017 was extracted and received in March 2019[13]. The Global Lung Function Initiative reference system was employed to calculate ppFEV₁[14]. The taking of pancreatic supplements was used as a proxy marker for exocrine pancreatic insufficiency (EPI), as this was the closest measure recorded annually in the registry. Individuals with CF at least 18 years old were included if they had no lung transplant and were not outliers, defined as a rate of change of ppFEV₁ >150%.

Anonymous data were received as a Microsoft Excel document which was exported to Microsoft Access (2013) to connect an individual's ppFEV₁ for each consecutive year and clinical data, outlined above.

Statistical analysis

Values for ppFEV₁ were reported as mean (standard deviation) and the difference in ppFEV₁ between pancreatic sufficient and insufficient adults with CF was compared using a t-test.

Annual ppFEV₁ measures for each individual were recorded over a three-year period therefore, multilevel models were used to account for repeated measures[15]. This methodology also allows the inclusion of uneven number of measurements between individuals[15]. .

For all models, ppFEV₁ was the dependent variable and year of measurement as the main exposure of interest to assess ppFEV₁ decline over time. Models were considered separately for different clinical groups: this included two stratifying by pancreatic status while adjusting

for age and sex and then 16 further groups for each combination of age category (18-28, 29-39, 40-50 and 51+ years), sex and pancreatic status. This further analysis stratified by age and sex allowed for the assessment of more subtle changes in lung function by sex and over discrete age ranges.

For all of the clinical groups (described above), four models were compared and the best fitting model selected. The first three models were: 1) baseline model with year as fixed effect, 2) random intercept and 3) random intercept and random slope model. The variance components structure was selection for all of these. The fourth model tested was the random intercept and slope model with an unstructured covariance structure. The best fitting model was selected based on which had the statistically significantly lower chi-squared statistic for the Schwarz's Bayesian Information Criterion (BIC). The BIC was employed as this data set has a large sample size and few parameters. For all the models, the repeated covariance type was set as first-order regressive, AR(1), well suited to repeated measures over time. Maximum likelihood estimation was selected. Analysis was conducted using SPSS Version 21 (Chicago, Illinois).

3. Results

Demographic Data

Data for 5554 adults with CF were included in the dataset. Nine individuals were excluded from analysis as their rate of change in ppFEV₁ exceeded 150%. In total, 3024 (54.5%) were male and 2521 (45.5%) female. The mean age was 31.5 years, standard deviation (SD) 11.1 years. The majority of individuals were taking pancreatic supplements n=4617 (83.3%) with only 918 (16.5%) classed as pancreatic sufficient (PS). Pancreatic status was unknown in 10 (0.2%) cases, and data was excluded from further analysis due to the low number.

ppFEV₁ in overall sample and impact of pancreatic supplement status

In the total, mean ppFEV₁ was similar across the three years, being 64.0 (23.5), 63.6 (23.5) and 63.5 (23.9) in 2015, 2016 and 2017 respectively, with large standard deviations apparent (Table 1). The mean ppFEV₁ was lower in individuals taking pancreatic supplements. There was also a statistically significant difference in ppFEV₁ between pancreatic insufficient (PI) and sufficient individuals ($p<0.01$). For example, in 2017 mean (SD) ppFEV₁ was 61.3 (23.4) in PI compared to 74.8(23.4) in PS individuals with CF respectively (Table 1).

Table 1 Descriptive statistics on ppFEV₁ overall and by pancreatic supplements status in CF adults who have not had a lung transplant in 2015, 2016 and 2017

	Pancreatic Supplements	Number	Mean	Standard Deviation
ppFEV₁ 2015	Overall	4719	63.96	23.51
	Yes	3999	62.16	23.04
	No	717	73.98	23.53
	Not Known	3	68.33	39.43
ppFEV₁ 2016	Overall	4828	63.60	23.53
	Yes	4083	61.68	22.94
	No	742	74.11	23.96
	Not Known	3	77.67	12.90
ppFEV₁ 2017	Overall	5026	63.49	23.92
	Yes	4218	61.33	23.38
	No	803	74.79	23.43
	Not Known	5	68.2	39.16

Adults with CF who reported taking pancreatic supplemented differed significantly in ppFEV₁ from those who did not (two-tail t-test, P<0.01)

Rate of Change in ppFEV₁ by age category, sex and pancreatic status

The differences in the mean rate of decline in ppFEV₁ by age categories and sex in those taking pancreatic supplements and those not are shown in Figures 1 and 2. Adjusting for age and sex, the average decline in ppFEV₁ was -1.52% a year in those taking pancreatic supplements (95% confidence interval [CI]: -1.66 to -1.38) and -0.55% for those not taking pancreatic supplements (95% CI: -0.86 to -0.23%), Table 2 and 3.

To better characterise the influence of age on rate of change in ppFEV₁, 16 separate models were developed for each combination of age category (18-28, 29-39, 40-50, 51+ years), sex and pancreatic supplement status. For those taking pancreatic supplements, the rate of decline was higher in females across all four age categories (Figure 1). Females also consistently had a lower mean ppFEV₁ value in those taking pancreatic supplements. For those not taking pancreatic supplements, females had a lower mean ppFEV₁ than males in all age categories apart from those aged 51+ years. The rate of ppFEV₁ decline was also higher than men in all but the 29-39 age category.

The decline in ppFEV₁ varied across age categories; the greatest decline occurred in those taking pancreatic supplements aged 18-29 years old (Table 2). In males, there was a trend that the rate of decline decreased with increasing age, whilst in females, rate of decline decreased with increasing age up until the age of 51+ years old, where it increased (Table 2).

The pattern was different for those not taking pancreatic supplements (Table 3, Figure 2). While for females the biggest rate of decline in ppFEV₁ per year was seen between the ages of 18-28 years, for males those aged 29-39 years saw the largest decrease. The rate of decline was less steep as age increased for females. For males, rate of decline increased up to the age of 29-39 years old but by age 51+ years there was a mean annual increase in ppFEV₁ which varied greatly (95% CI: -0.23 to 1.95).

Figure 1: Mean ppFEV₁ in Males and Females Adults with CF taking Pancreatic Supplements by age category

Figure 2: Mean ppFEV₁ in Males and Females Adults with CF not taking Pancreatic Supplements by age category

Table 2 Rate of Decline in ppFEV₁ predicted in One Year in Adults with CF taking Pancreatic Supplements by age category and sex

		N	Mean FEV ₁ % in 2015	95% Confidence intervals	Mean annual change in ppFEV ₁	95% Confidence intervals
Overall¹		4617	56.54	53.60 to 59.49	-1.52	-1.66 to -1.38
18-28 years	Females¹	1124	66.18	64.85 to 67.52	-1.76	-2.06 to -1.46
	Males¹	1287	68.35	67.11 to 69.58	-1.61	-1.91 to -1.31
29-39 years	Females¹	608	57.66	55.88 to 59.45	-1.49	-1.85 to -1.13
	Males¹	851	59.52	58.00 to 61.04	-1.31	-1.60 to -1.02
40-50 years	Females²	217	55.63	52.57 to 58.69	-1.42	-1.98 to -0.87
	Males²	301	57.15	54.63 to 59.67	-1.15	-1.59 to -0.71
51+ years	Females²	81	54.61	49.81 to 59.40	-1.61	-2.64 to -0.58
	Males²	148	56.40	52.26 to 60.54	-1.06	-1.66 to -0.46

- 1- Random intercept and slope model
2- Random intercept model

Table 3 Rate of Decline in ppFEV₁ predicted in One Year in Adults with CF Not taking Pancreatic Supplements by age category and sex

		N	Mean FEV₁% in 2015	95% Confidence intervals	Mean annual change in ppFEV₁	95% Confidence intervals
Overall¹		918	64.83	61.10 to 68.56	-0.55	-0.86 to -0.23
18-28 years	Females¹	171	80.67	77.41 to 83.93	-1.01	-1.84 to -0.19
	Males¹	119	86.04	82.47 to 89.62	-0.53	-1.39 to 0.33
29-39 years	Females¹	133	75.64	71.70 to 79.57	-0.74	-1.47 to -0.02
	Males¹	125	82.16	78.22 to 86.09	-0.86	-1.96 to 0.23
40-50 years	Females¹	94	66.24	61.85 to 70.64	-0.79	-1.60 to 0.01
	Males¹	109	78.34	73.78 to 82.89	-0.13	-1.01 to 0.75
51+ years	Females¹	92	63.28	58.44 to 68.11	-0.51	-1.45 to 0.43
	Males¹	75	58.56	52.30 to 64.83	0.86	-0.23 to 1.95

1- Random intercept model

4. Conclusions

Analysis of the UK CF registry data from 2015-2017 shows that the overall annual rate of decline in ppFEV₁ for all PI adults is -1.52% and -0.55% for those with PS. The findings provide new insight into the rate of lung function decline according to pancreatic status.

In adults with PI, this reported rate of annual decline, is similar to previous findings of a small single centre study carried out in the UK between 1995 to 2004, which described an annual rate of decline of -1.53% in a young adult cohort aged 18-22 years old[16]. Further studies have reported results within the context of different age groups which precludes direct comparison with our own findings. In a larger North American study the reported rates of decline in ppFEV₁ per year were -1.92% in 18-24 years old and -1.45% in those ≥ 25 years[17]. In similar analysis of the same cohort but including unstable young adults resulted in a higher rate of decline of -2.68% in the 18- 22 year old cohort[18]. A more recent study using CF Registry data from 1993-2010 evaluated the change in lung function over time according to age of diagnosis and described an annual rate of change of -1.42%/year for ages 6–11, -2.04% for ages 12–17 and -1.13% for ages 18–65 years[19]. A predictive algorithm developed to improve the detection of clinical deterioration did define a cut-off rate of decline in ppFEV₁ as -1.5% /year, a value concordant with this study[20].

The rate of lung function decline calculated in the present study compared to those outlined above has occurred despite significant improvements in standards of care and survival[21]. For instance, even from 2015 to 2017, the median age of death has increased from 28 to 31 in the UK[4]; attributable to factors such as earlier diagnosis, associated with new-born screening, pro-active multidisciplinary care and improved treatments[21]. Additionally, milder forms of CF are being better detected and are increasingly being included in registry

data[21]. These changes make it difficult to directly compare these findings to historical datasets.

There are also inter-country variations in genotypes, environmental exposure, health economies and access to healthcare and medications, all of which are likely to impact both ppFEV₁ and rate of decline [21]. For example, in the USA, Canada and UK the median ppFEV₁ is 61%, 64% and 63% for those aged 30 years respectively, with the latter two countries having a higher median ppFEV₁ and universal access to healthcare[4, 22, 23]. The concordance in ppFEV₁ rate of decline between this and other studies, in spite of these inter-country differences, not only lends support for the validity of this finding, it also reinforces the value of employing rate of decline as a complementary, but distinct, measure to ppFEV₁ alone.

It is noteworthy that many of the studies reporting on rate of ppFEV₁ decline are in developed countries with access to highly developed, multidisciplinary CF services. In developing countries and those with limited health resources, ppFEV₁ and survival can be significantly lower and further studies using international registries, such as the European CF registry, will provide comparative data to monitor health inequalities and support best practice. The concept that national registry data is a valuable source for comparative effectiveness research is supported[24].

Many studies[16-19] do not discriminate cohorts according to pancreatic status. This is despite significant differences between both groups in terms of CFTR mutations and clinical outcomes. Indeed, PI individuals were found to have three times the annual rate of decline in lung function when compared to those who were PS. This underlies the need to differentiate between these two groups when comparing ppFEV₁ and the rate of decline in clinical trials and interventional studies.

In this study we also focused on pancreatic status in the context of age and sex. While there is conflicting data on the impact of sex on rate of lung function decline[11, 17, 18], we found that females generally did worse. This may reflect differences in multiple factors including

hormones, anatomy and lifestyle[25]. Age was also an important factor, with younger adults having a higher rate of decline in lung function; findings that have been replicated elsewhere[17]. Survivorship effects may have influenced these findings; those with a more severe disease may have died younger and the older age categories represent milder forms of CF[16, 17]. Young adulthood is also recognised as a particularly vulnerable time for individuals with CF with its complex associations with lifestyle changes and adherence challenges[26]. Presenting decline in ppFEV₁ by age category and sex provides additional insight into the subtle changes in outcomes and employing these values allow a more direct, accurate and relevant comparison of data between registries[14, 21]. Children and adolescences' change in ppFEV₁ will likely be driven by factors specific to their developmental stage, such as rapid growth[14]. Therefore, inspection of their rate of decline is also warranted but fell outside this study's scope which focused on adults; a growing segment of the CF population.

The importance of monitoring rate of decline in lung function as well as variability in FEV₁ has been highlighted in previous studies[10, 27, 28]. It can help identify poor adherence and those in need of more aggressive monitoring and treatment[10, 27]. Reducing the clinical impact of pulmonary exacerbations remains essential[1]. New complex algorithms linked to national registries could provide individuals with CF comparative data as part of a self-monitoring tool to personalise and contextualise lung function. Furthermore, rate of change in ppFEV₁ will be an important measure of treatment response following the introduction of new agents, such as CFTR modulator therapy.

One of the study's strengths was that data from a large national registry was used, allowing for a large sample size and the inclusion of individuals who may not otherwise enrol in research. However, limitations of the model are acknowledged. There are many factors which were not

accounted for in this study which can impact lung function. These include rapid reduction in body mass index[18], *Pseudomonas aeruginosa* and other bacterial and fungal infections[18, 19], socioeconomic status[29] and CF-related diabetes[30]. Rate of decline is non-linear, if a longer time period than three years were to be used then a more complex non-linear model may be required[31]. Other studies have been more stringent and included graphs with vectors derived from mixed model linear regression analysis[17], Gaussain process model[32] and smoothed posterior estimates from a longitudinal sub-model[31]. Additionally, only a single annual measurement for ppFEV₁ was available and significant variability throughout the year is unaccounted for. Finally, survivorship effects could have influenced the findings between the age categories[16, 17]. Consequently, these results need to be interpreted with due caution.

To our knowledge this is the first study reporting the rate of lung function decline in pancreatic insufficient and sufficient adults with CF in the UK. Younger adults, especially females, are at greater risk of increased lung function decline and need close monitoring. Further studies evaluating tools which compare an individual's actual and predicted rate of decline in ppFEV₁ could prove useful in triggering early intervention and avoiding clinical deterioration.

323 **Acknowledgments**

324 We would like to thank William Peckham for his support with designing the Access
325 Database.

326 **Competing Interests Statement**

327 None declared

328 **Funding Source**

329 LC's role is funded by the Cystic Fibrosis Trust [SRC 012]

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