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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 ($ppFEV_1$) in adults in the UK accounting for age, sex and pancreatic status.

Methods: Data on $ppFEV_1$ 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 $ppFEV_1$ accounting for age, sex and pancreatic status.

Results: Overall annual $ppFEV_1$ 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 $ppFEV_1$. 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

- $ppFEV_1$ declines annually by -1.5% in CF pancreatic insufficient adults in the UK
- People with pancreatic sufficiency have a slower rate of decline in $ppFEV_1$
- 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 ($ppFEV_1$) 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 FEV_1 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].

$ppFEV_1$ 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 $ppFEV_1$ 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 FEV_1 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 $ppFEV_1$ could be a better approach to assess clinical status and provide personalised feedback.

National registries tend to use best or baseline annual $ppFEV_1$ 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 $ppFEV_1$ in adults with CF in the UK, accounting for age, sex and pancreatic status.

2. Methods

Study population and data extraction

Annual data for $ppFEV_1$, 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 $ppFEV_1$[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 $ppFEV_1$ >150%.

Anonymous data were received as a Microsoft Excel document which was exported to Microsoft Access (2013) to connect an individual's $ppFEV_1$ for each consecutive year and clinical data, outlined above.

Statistical analysis

Values for $ppFEV_1$ were reported as mean (standard deviation) and the difference in $ppFEV_1$ between pancreatic sufficient and insufficient adults with CF was compared using a t-test.

Annual $ppFEV_1$ 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, $ppFEV_1$ was the dependent variable and year of measurement as the main exposure of interest to assess $ppFEV_1$ 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 $ppFEV_1$ 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.

$ppFEV_1$ in overall sample and impact of pancreatic supplement status

In the total, mean $ppFEV_1$ 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 $ppFEV_1$ was lower in individuals taking pancreatic supplements. There was also a statistically significantly difference in $ppFEV_1$ between pancreatic insufficient (PI) and sufficient individuals ($p<0.01$). For example, in 2017 mean (SD) $ppFEV_1$ 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 $ppFEV_1$ 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
$ppFEV_1$ 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
$ppFEV_1$ 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
$ppFEV_1$ 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 $ppFEV_1$ from those who did not (two-tail t-test, $P<0.01$)

Rate of Change in $ppFEV_1$ by age category, sex and pancreatic status

The differences in the mean rate of decline in $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1$, 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 $ppFEV_1$ value in those taking pancreatic supplements. For those not taking pancreatic supplements, females had a lower mean $ppFEV_1$ than males in all age categories apart from those aged 51+ years. The rate of $ppFEV_1$ decline was also higher than men in all but the 29-39 age category.

The decline in $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1$ which varied greatly (95% CI: -0.23 to 1.95).

Figure 1: Mean ppFEV$_1$ in Males and Females Adults with CF taking Pancreatic Supplements by age category

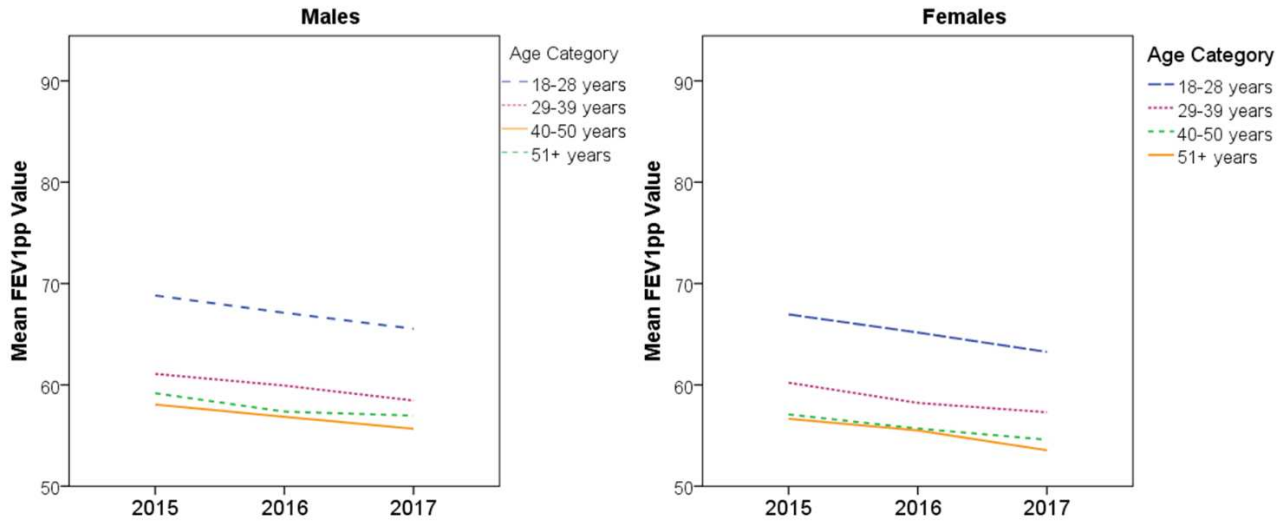

Figure 2: Mean ppFEV$_1$ in Males and Females Adults with CF not taking Pancreatic Supplements by age category

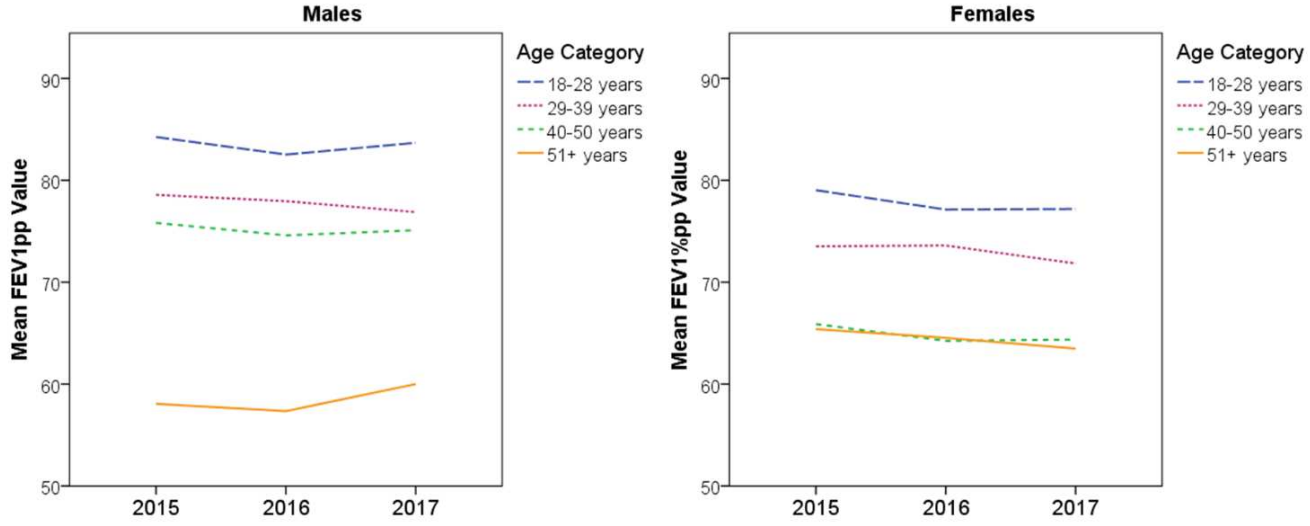

Table 2 Rate of Decline in ppFEV$_1$ predicted in One Year in Adults with CF taking Pancreatic Supplements by and age category and sex

		N	Mean FEV$_1$% in 2015	95% Confidence intervals	Mean annual change in ppFEV$_1$	95% Confidence intervals
Overall[1]		4617	56.54	53.60 to 59.49	-1.52	-1.66 to -1.38
18-28 years	**Females**[1]	1124	66.18	64.85 to 67.52	-1.76	-2.06 to -1.46
	Males[1]	1287	68.35	67.11 to 69.58	-1.61	-1.91 to -1.31
29-39 years	**Females**[1]	608	57.66	55.88 to 59.45	-1.49	-1.85 to -1.13
	Males[1]	851	59.52	58.00 to 61.04	-1.31	-1.60 to -1.02
40-50 years	**Females**[2]	217	55.63	52.57 to 58.69	-1.42	-1.98 to -0.87
	Males[2]	301	57.15	54.63 to 59.67	-1.15	-1.59 to -0.71
51+ years	**Females**[2]	81	54.61	49.81 to 59.40	-1.61	-2.64 to -0.58
	Males[2]	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

222 **Table 3** Rate of Decline in ppFEV$_1$ predicted in One Year in Adults with CF Not taking
223 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
Overall[1]		918	64.83	61.10 to 68.56	-0.55	-0.86 to -0.23
18-28 years	**Females**[1]	171	80.67	77.41 to 83.93	-1.01	-1.84 to -0.19
	Males[1]	119	86.04	82.47 to 89.62	-0.53	-1.39 to 0.33
29-39 years	**Females**[1]	133	75.64	71.70 to 79.57	-0.74	-1.47 to -0.02
	Males[1]	125	82.16	78.22 to 86.09	-0.86	-1.96 to 0.23
40-50 years	**Females**[1]	94	66.24	61.85 to 70.64	-0.79	-1.60 to 0.01
	Males[1]	109	78.34	73.78 to 82.89	-0.13	-1.01 to 0.75
51+ years	**Females**[1]	92	63.28	58.44 to 68.11	-0.51	-1.45 to 0.43
	Males[1]	75	58.56	52.30 to 64.83	0.86	-0.23 to 1.95

224 1- Random intercept model
225

4. Conclusions

Analysis of the UK CF registry data from 2015-2017 shows that the overall annual rate of decline in $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1$ 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

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

254 There are also inter-country variations in genotypes, environmental exposure, health
255 economies and access to healthcare and medications, all of which are likely to impact both
256 $ppFEV_1$ and rate of decline [21]. For example, in the USA, Canada and UK the median $ppFEV_1$
257 is 61%, 64% and 63% for those aged 30 years respectively, with the latter two countries having
258 a higher median $ppFEV_1$ and universal access to healthcare[4, 22, 23]. The concordance in
259 $ppFEV_1$ rate of decline between this and other studies, in spite of these inter-country
260 differences, not only lends support for the validity of this finding, it also reinforces the value
261 of employing rate of decline as a complementary, but distinct, measure to $ppFEV_1$ alone.
262
263 It is noteworthy that many of the studies reporting on rate of $ppFEV_1$ decline are in developed
264 countries with access to highly developed, multidisciplinary CF services. In developing
265 countries and those with limited health resources, $ppFEV_1$ and survival can be significantly
266 lower and further studies using international registries, such as the European CF registry, will
267 provide comparative data to monitor health inequalities and support best practice. The concept
268 that national registry data is a valuable source for comparative effectiveness research is
269 supported[24].
270
271 Many studies[16-19] do not discriminate cohorts according to pancreatic status. This is despite
272 significant differences between both groups in terms of CFTR mutations and clinical outcomes.
273 Indeed, PI individuals were found to have three times the annual rate of decline in lung function
274 when compared to those who were PS. This underlies the need to differentiate between these
275 two groups when comparing $ppFEV_1$ and the rate of decline in clinical trials and interventional
276 studies.
277
278 In this study we also focused on pancreatic status in the context of age and sex. While there is
279 conflicting data on the impact of sex on rate of lung function decline[11, 17, 18], we found that
280 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 $ppFEV_1$ 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 $ppFEV_1$ 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 FEV_1 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 $ppFEV_1$ 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

306 accounted for in this study which can impact lung function. These include rapid reduction in
307 body mass index[18], *Pseudomonas aeruginosa* and other bacterial and fungal infections[18,
308 19], socioeconomic status[29] and CF-related diabetes[30]. Rate of decline is non-linear, if a
309 longer time period than three years were to be used then a more complex non-linear model may
310 be required[31]. Other studies have been more stringent and included graphs with vectors
311 derived from mixed model linear regression analysis[17], Gaussain process model[32] and
312 smoothed posterior estimates from a longitudinal sub-model[31]. Additionally, only a single
313 annual measurement for $ppFEV_1$ was available and significant variability throughout the year
314 is unaccounted for. Finally, survivorship effects could have influenced the findings between
315 the age categories[16, 17]. Consequently, these results need to be interpreted with due caution.

316 To our knowledge this is the first study reporting the rate of lung function decline in pancreatic
317 insufficient and sufficient adults with CF in the UK. Younger adults, especially females, are at
318 greater risk of increased lung function decline and need close monitoring. Further studies
319 evaluating tools which compare an individual's actual and predicted rate of decline in $ppFEV_1$
320 could prove useful in triggering early intervention and avoiding clinical deterioration.
321
322

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Competing Interests Statement

None declared

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