



Original Article

Demographic factors associated with within-individual variability of lung function for adults with cystic fibrosis: A UK registry study



Marco Palma ^{*,a}, Ruth H Keogh ^b, Siobhán B Carr ^{c,d}, Rhonda Szczesniak ^{e,f},
David Taylor-Robinson ^g, Angela M Wood ^h, Graciela Muniz-Terrera ^{1,i,j}, Jessica K Barrett ^{1,a}

^a MRC Biostatistics Unit, University of Cambridge, United Kingdom

^b Department of Medical Statistics, London School of Hygiene & Tropical Medicine, United Kingdom

^c Royal Brompton Hospital, part of Guy's and St Thomas' NHS Foundation Trust, United Kingdom

^d National Heart and Lung Institute, Imperial College, London, United Kingdom

^e Divisions of Biostatistics and Epidemiology and Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, United States

^f Department of Pediatrics, University of Cincinnati, United States

^g Department of Public Health, Policy and Systems, University of Liverpool, United Kingdom

^h Cardiovascular Epidemiology Unit, University of Cambridge, United Kingdom

ⁱ Ohio University Heritage College of Osteopathic Medicine, United States

^j University of Edinburgh, United Kingdom

ARTICLE INFO

Keywords:

Cystic fibrosis

Lung function variability

Within-individual variability

Mixed-effects location-scale model (MELSM)

ABSTRACT

Background: Lung function is a key outcome used in the evaluation of disease progression in cystic fibrosis. The variability of individual lung function measurements over time (within-individual variability) has been shown to predict subsequent lung function changes. Nevertheless, the association between within-individual lung function variability and demographic and genetic covariates has not been quantified.

Methods: We performed a longitudinal analysis of data from a cohort of 7099 adults with cystic fibrosis (between 18 and 49 years old) from the UK cystic fibrosis registry, containing annual review data between 1996 and 2020. A mixed-effects location-scale model is used to quantify mean FEV₁ (forced expiratory volume in 1 s) trajectories and FEV₁ within-individual variability as a function of sex, age at annual review, diagnosis after first year of life, homozygous F508 genotype and birth cohort.

Results: Mean FEV₁ decreased with age and lung function variability showed a near-quadratic trend by age. Males showed higher FEV₁ mean and variability than females across the whole age range. Earlier diagnosis and homozygous F508 genotype were also associated with higher FEV₁ mean and variability. Individuals who died during follow-up showed on average higher lung function variability than those who survived.

Conclusions: Key variables known to be linked with mean lung function in cystic fibrosis are also associated with an individual's lung function variability. This work opens new avenues to understand the role played by lung function variability in disease progression and its utility in predicting key outcomes such as mortality.

1. Introduction

The availability of national registries of cystic fibrosis (CF) with longitudinal measurements of health status has led to improved understanding of disease progression and prediction of survival for the CF population. For example, longitudinal information from the UK CF registry has been used to develop dynamic prediction models of survival for people with CF [1,2].

The evolution of lung function over time is a crucial outcome of interest in CF. In Keogh et al. [2], a measure of lung function was identified as the strongest predictor for individual survival. Although previous studies have mostly focused only on mean trajectories, some have also investigated the variability of lung function over time, giving novel insights into disease progression. For example, Morgan et al. [3] provided a working definition of within-individual lung function variability. Four-year follow-up was split into a first two-year window for evaluating

* Corresponding author.

E-mail address: marco.palma@mrc-bsu.cam.ac.uk (M. Palma).

¹ Joint senior authors

lung function variability and a second two-year window for determining the association with lung function decline. This approach was used to evaluate the hypothesis that higher within-individual variability could be linked to stronger subsequent decline in lung capacity in a multi-center observational study of US individuals with CF. The authors proposed to quantify within-individual variability instead of the count of pulmonary exacerbations to better reflect changes in lung capacity, as the latter lack a standardised definition [4]. Heltshe and Szczesniak [5] argued that such an approach does not leverage the full extent of the longitudinal information as well as the correlation between measurements taken on the same individual.

Taylor-Robinson et al. [6] instead evaluated lung function variability in the Danish CF population, splitting it into between-individual, within-individual and measurement error. Their method did not quantify variability for each individual, but identified useful thresholds to distinguish clinically relevant changes from short-range fluctuations and accounted for the long-term correlation between lung function measurement. Those findings were further explored in the US CF Foundation Patient Registry [7], to monitor disease progression at the individual level.

The aim of this work is to quantify long-term variability in lung function in the UK CF population by using the longitudinal trajectory recorded for each individual. We apply the mixed-effects location-scale model (MELSM, [8]) to specify the standard deviation as a function of covariates of interest as well as a random component which is used to account for heterogeneity that is not explained by other factors. In this sense, this study extends the previous knowledge about cystic fibrosis by quantifying the changes in within-individual lung function variability associated with sex, age at annual review, year of birth, diagnosis after first year of life, and homozygous F508del genotype.

2. Materials and methods

2.1. Data source

The dataset comes from the UK Cystic Fibrosis (CF) Registry, collecting anonymised information about CF patients across the country [9]. We used the version available at the time of analysis, which includes records from 1996 through December 2020. The individuals who are clinically stable have annual reviews approximately every 12 months with the care teams in a clinic. The dataset contains data for over 13,000 individuals.

The outcome of interest in the analysis is forced expiratory volume in 1 s (FEV₁), which counts the litres of air exhaled in the first second after maximal inspiration. This outcome was chosen instead of FEV₁ percent predicted (the ratio between the individual FEV₁ and the average FEV₁ in a population of similar sex and age) to provide a more interpretable quantification of within-individual lung function variability in terms of litres rather than percentage points, while highlighting sex differences in mean FEV₁ levels (which are expected). In addition, in the general population FEV₁ values do not vary dramatically over the age range considered.

The covariates used in this analysis are sex, age at each annual review, diagnosis after first year of life, year of birth, homozygous F508 (or F508del) genotype. These covariates are often used in cystic fibrosis studies [2].

2.2. Inclusion criteria

The analysed dataset consisted of all adults between 18 and 49 years old in the CF registry with at least one recorded measurement of FEV₁. Setting age thresholds as inclusion criteria is common in cystic fibrosis studies (e.g. [10,11]): in particular, the older threshold is usually set to exclude cases which are less representative of the general CF population.

In this work, study entry was defined as the date of the first annual review at which the age criteria were met. Individuals were followed up

until death or administrative censoring at the end of December 2020. If an individual had lung transplant before or during the follow-up period, annual reviews after the transplant were excluded. Records with missing FEV₁ or covariates were removed. If multiple annual reviews were recorded in a single calendar year (mostly due to transition to a different CF centre), then only data from the first one were used in the analysis. This situation was observed for a small number of individuals (440, equal to 5.3% of the population in the study).

2.3. Statistical analysis

Linear mixed models (or random effects models) are a standard choice for the analysis of longitudinal data, where multiple observations for the same individuals are collected over time [12]. In this setting, the regression terms are often distinguished between fixed effects (or population-level coefficients) and random effects (or individual-level coefficients). For example, in a simple model with a random intercept and no covariates, there is an overall intercept (fixed effect) representing the population mean and a subject-specific random effect which quantifies the individual departure from the population mean. The random effects for all subjects are assumed to be normally distributed with zero mean and a standard deviation which is estimated from the data. A non-zero standard deviation for the random effect indicates that there is some heterogeneity among the individuals which is not accounted for by the covariates in the model.

The mixed-effects location-scale model (MELSM) is used to quantify within-individual variability in a longitudinal setting [8,13]. It extends standard mixed models by expressing the error variance as a function of covariates and a subject-specific random effect. The detailed formulation of the model is reported in the Supplementary Material. The MELSM is made of three key building blocks: the mean submodel, the variability submodel and the distribution of the random effects.

The mean submodel is similar to a standard mixed model, where the outcome of interest is modelled as a function of known covariates as well as random effects (which capture the correlation of the measurements within each individual and/or each cluster of individuals). In the variability submodel, the residual standard deviation is specified as another function of known covariates as well as a subject-specific random effect. The distribution of the random effects provides a link between the two submodels. The random effects are assumed normally distributed with mean zero; their covariance measures the relationship between the random effects.

In this work, we use MELSM to evaluate changes in the mean and standard deviation of FEV₁ as functions of sex, age at annual review, age at diagnosis, year of birth and F508 genotype. Age-sex interactions are included in both submodels, to show how the mean and variability change over time within each sex. Age at diagnosis is dichotomised into diagnosis before 1 year of age and diagnosis after 1 year. For simplicity, F508 genotype is also transformed into a binary covariate: 2 alleles versus 1, 0, missing or unknown. The association with age is modelled using natural cubic splines with 5 basis functions and knots placed at the quintiles of the covariates. A random intercept is included in both the mean and variability submodels, and also a correlation parameter between the mean and variability random intercepts to account for the dependence between within-individual variability and mean.

In the variability submodel, the estimated coefficients represent the association between the covariates and the variability (measured in units of log standard deviations) of the FEV₁ measurements. To report the association on the standard deviation scale (i.e. the FEV₁ scale), the exponential of the coefficient is computed. This modelling choice returns by default estimates for the standard deviation parameter, which has the same unit of measurement as the mean. By combining the coefficient with the values of the covariates and the subject-specific location and scale random effects, the mean FEV₁ and variability trajectory over time can be computed for each individual in the dataset. The average computed at each age point returns a description of the CF

population mean and variability.

As in Williams et al. [14,15], we fit the model in a Bayesian framework using the R package `brms` [16]. Standard prior distributions were specified (normal distribution for fixed effects, exponential distribution for random effects) with informative prior values. More details are available in the Supplementary Material. The estimation procedure is based on a Markov chain Monte Carlo algorithm with 2400 iterations (of which 1200 warm-up). We provide the posterior estimates for the coefficients and the corresponding 95% posterior credible interval in brackets.

3. Results

3.1. Data description

The total number of individuals in the dataset analysed is 7099 with 65,522 annual reviews. A diagram of inclusion criteria is provided in Figure S.1 in the Supplementary Material.

Table 1 describes the characteristics of the dataset by sex. Females account for less than half of the population in the sample.

The distribution of individuals by number of annual reviews is displayed in Figure S.2 in the Supplementary Material. The maximum number observed is 24, which corresponds to the number of years spanned by the current version of the registry, while the mode is at 5 reviews and the median is 9 reviews. For each individual, the follow-up in years matches approximately the number of annual encounters. Figure S.3 in the Supplementary Material shows both the average levels of FEV₁ for males and females and the sex distribution over the age range observed in the dataset.

3.2. Association between covariates and lung function mean and variability

The estimates of the parameters in both mean and variability submodels of the MELSM are reported **Table 2** (for categorical covariates) and **Fig. 1** (for continuous covariates). The FEV₁ intercept in the mean submodel (common for all individuals) is close to 2 litres, while for the variability submodel is equal to -1.48, which corresponds to a standard deviation of $e^{-1.48} = 0.23$ litres. These represent “baseline” values before including the parameter estimates for the covariates in the model, or equivalently they refer to the case when all the other coefficients are multiplied by zero.

Those diagnosed after the first year from birth seem to show on average higher FEV₁ (by 0.05 litres) and lower FEV₁ variability than those diagnosed before the first year of age after adjusting for other covariates (including the genotype). In particular, the former have approximately $100 \cdot e^{-0.04} = 96.1\%$ of the variability of the latter with

Table 1

Demographic and clinical characteristics of cystic fibrosis individuals included in the analysis. Reported are number (%) for categorical variables and median (interquartile range: 25th percentile and 75th percentile) for continuous variables.

	Females	Males	Total
Number of individuals	3287 (46.4%)	3814 (53.6%)	7099
Median number of annual reviews per individual	8 (5–12)	9 (5–13)	9 (5–13)
Median age at diagnosis in years	0.67 (0.12–4.04)	0.53 (0.12–3.97)	0.58 (0.12–3.99)
Diagnosed within the first year after birth	1807 (55.0%)	2190 (57.4%)	3997 (56.3%)
Homozygous for F508	1589 (48.3%)	1924 (50.5%)	3513 (49.5%)
Number of individuals with one FEV ₁ measure	176 (5.4%)	191 (5.0%)	367 (5.2%)
FEV ₁ (in litres) at first annual review	2.02 (1.41–2.63)	2.9 (1.98–3.7)	2.4 (1.64–3.21)
Number of deaths	1028 (31.3%)	987 (25.9%)	2015 (28.4%)

Table 2

Posterior estimates with 95% CI (credible interval) for the linear fixed parameters and random effects in the model.

Covariates	Estimate (95% CI)
Mean submodel	
Intercept	2.01 (1.99; 2.03)
Diagnosis after 1 year old	0.05 (0.03; 0.07)
Homozygous for F508	-0.05 (-0.06; -0.03)
Variability submodel (log SD)	
Intercept	-1.48 (-1.51; -1.46)
Diagnosis after 1 years old	-0.04 (-0.07; -0.02)
Homozygous for F508	0.06 (0.03; 0.08)
Random effect distribution	
SD for location random effects	1.04 (1.02; 1.06)
SD for scale random effects	0.45 (0.44; 0.46)
Correlation between random effects	0.16 (0.13; 0.20)

the same features. In addition, those homozygous for F508 tend to have lower FEV₁ but slightly higher lung function variability (by a factor of approximately $e^{0.06} = 1.06$) than non-homozygous individuals.

Fig. 1 shows the estimates of the age association for males and females. For the mean submodel, decreasing mean FEV₁ with age is observed across the whole age range. The decrease in FEV₁ appears to be almost linear with a slope of approximately 0.038 litres per year for males and 0.035 litres per year for females. The year of birth shows a non-linear relationship with mean FEV₁ with the maximum reached around the cohort of 1960. Those born in this year show higher FEV₁ on average than people born earlier or after, keeping all the other covariates constant. The minimum is obtained between 1980 and 1985: individuals in this cohort tend to have lower FEV₁ than younger people with the same features.

In the variability submodel, we observe an almost quadratic pattern for both females and males: the variability tends to decrease until approximately 30 years, and then, between the age of 30 and 40, the variability for females seems to remain flat, while for males the variability keeps declining although at a lower rate. For the cohort effect, the variability keeps increasing until the cohort between 1960 and 1965, then it decreases.

Additional heterogeneity across individuals in the lung function mean and variability is captured via the random effects in the model, as indicated by the non-zero standard deviations of the location and scale random effects in **Table 2**. The estimated correlation parameter indicates that those with higher FEV₁ on average tend to show higher within-individual variability, given the other covariates in the model (as shown also in Figure S.6 in the Supplementary Material).

3.3. Average lung function trajectories in the CF population

For each individual in the dataset, two trajectories (one for the mean, one for the standard deviation) are fitted from the model, covering the same age interval as for the observed FEV₁ measurements. As a simple descriptive summary of the CF adult population, the average of all the individual fitted trajectories for mean and variability are reported in solid black lines in **Fig. 2**. These predictions show the combined effects of all the covariates for each individual in the dataset. The population variability for both males and females reaches the minimum at the age of 25, then it increases for older ages. In particular, for males up to 40 years old there is a stronger increase of the variability. Population trajectories stratified by those who died during follow-up and those still alive at the end of 2020 show a higher variability for the former group across almost all the age range considered (**Fig. 2**, bottom plot).

We can also predict the FEV₁ mean and standard deviation trajectories for specific covariate values. When we jointly consider the binary variables for genotype and age at diagnosis (**Fig. 3**), the cluster of late-diagnosed non-homozygous patients is clearly separated from the others, having a higher mean lung function and a lower FEV₁ variability across the whole age range. Additional plots are available in Figure S.4

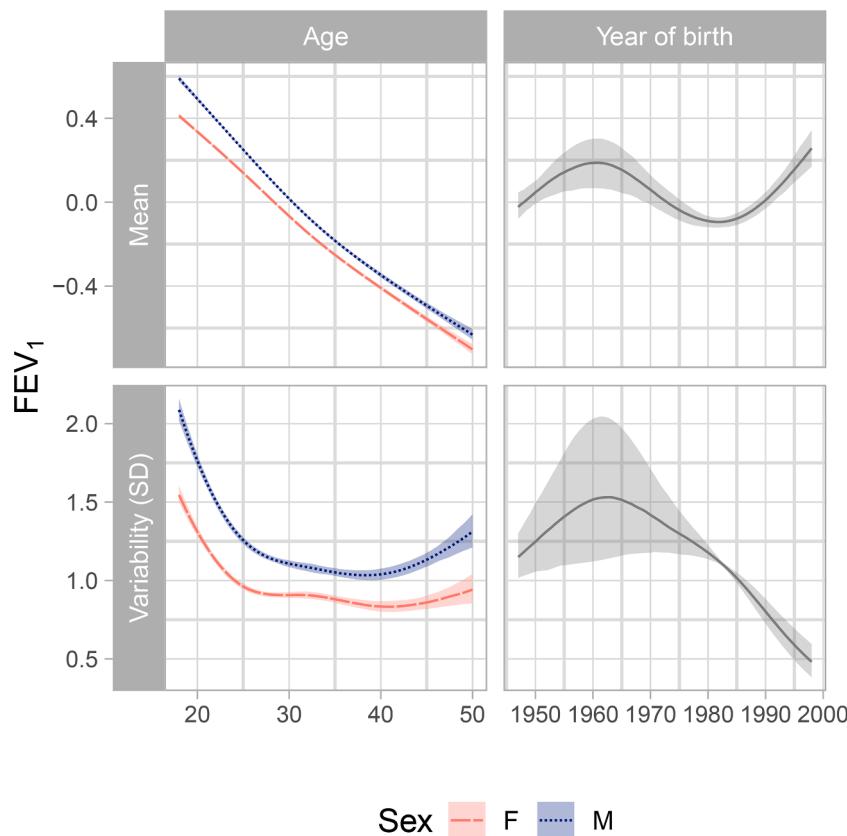


Fig. 1. Posterior estimates of the factor-smooth interaction terms in the model described in the Equations (1) and (2) with the sex main effects added, conditional on the other covariates in the model. Top: association of age and year of birth with the mean of FEV₁. Bottom: association of age and year of birth with the standard deviation of FEV₁.

in the Supplementary Material.

4. Discussion

In this work we investigated long-term (or year-to-year) lung function within-individual variability across adults in the UK CF registry dataset. The mixed-effects location-scale model allows for a flexible model of within-individual variability accounting for its relationship with covariates as well as subject-specific deviations from the population average. The results indicate that both the mean and the variability are highly heterogeneous across individuals, and only a fraction of that heterogeneity could be explained by the factors considered in the study.

As a first main result, we quantified the association of the covariates in the model with both mean FEV₁ and within-individual variability. As age increases, the constant decline in mean lung function accompanies an approximately quadratic association with the variability for males, with minimal variability reached around age 40. The pattern of variability seems to flatten for females between 25 and 33. Further work is needed to determine whether this relates to the lower life expectancy, which is observed in the female UK CF population, and whether it could play a role in survival prediction [17]. For both females and males, FEV₁ variability increases after age 40, indicating higher fluctuations for older ages, despite lower mean FEV₁.

The year of birth is also associated with lung function. In older cohorts we observe increasing lung function mean as well as increasing within-individual variability, whereas individuals born after 1980 show higher mean lung function and at the same time declining variability. The non-monotonic trend for this covariate suggests that there is an interplay between a left-truncation effect (as in older cohorts we observe only those healthier individuals who managed to enter the study) and a cohort effect (capturing for example the improvement of treatments

occurring over time), where the latter becomes the predominant driver in younger cohorts.

The second noteworthy result is that some additional heterogeneity in lung function variability is observed after accounting for the covariates, as indicated by the nonzero standard deviation of the scale random effect. This result shows that the differences between individuals are not only observed in the baseline FEV₁, but also in the extent of the fluctuations around the mean trajectory.

Lastly, this study provides some indication that higher lung function variability could be linked to severity of diseases or more negative outcomes. For those who died during follow-up, a higher lung function variability (as well as lower mean function) was observed compared to those still alive at the end of follow-up. Nevertheless, this analysis does not take into account the age at death (and the length of the individual trajectories) and therefore requires additional verification.

In this direction, further study should be conducted to assess if lung function variability is a predictor of age at death, for example using joint models of longitudinal and survival outcomes accommodating within-individual variability [18]. In addition, other longitudinal outcomes in CF could be explored in the future with this framework. For example, variability in sugar levels could be added as a marker of “pre-diabetes” for individuals with CF as in [19].

We have not included infection as a covariate in the analysis, in line with previous studies of lung function variability. Our measure of variability therefore captures all components of within-individual variation, including treated and untreated exacerbations, treatment received as well as any additional variation due to e.g. CF-related diabetes or other comorbidities [3].

This study has several strengths. To our knowledge, this is the first published study to investigate factors associated with within-individual lung function variability in individuals with CF. The cohort comprises

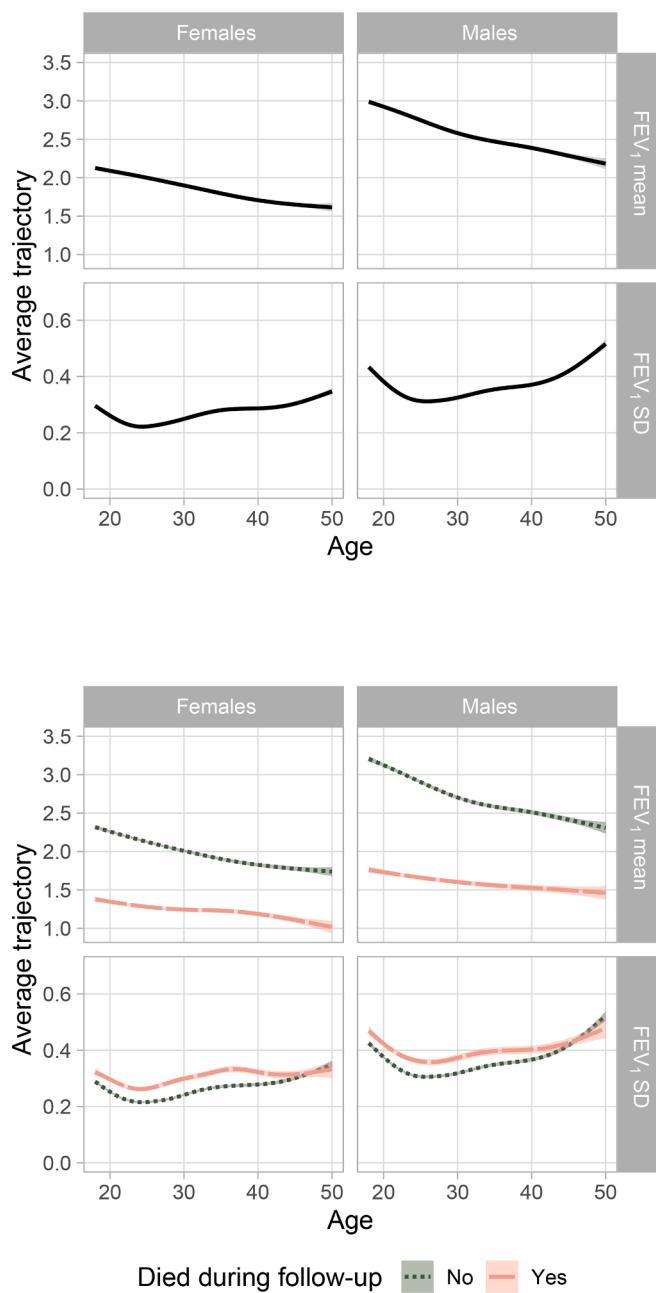


Fig. 2. Posterior predictions of mean and standard deviation of FEV₁ by sex and age. Top: the black solid line is the average prediction across the whole population, enclosed in the 95% prediction interval in gray. Bottom: the lines represent the average trajectory over time of variability over all individuals in the dead (orange dashed) and alive group (green dotted). The dead population includes all individuals whose death occurred before the end of 2020. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

almost all the CF population in the United Kingdom and over 20 years of follow-up. The statistical approach addresses some of the limitations that emerged in the literature about within-individual variability in CF. Using the MELSM for modelling within-individual variability allows all individuals to be included in the analysis without the need to exclude those with insufficient numbers of reviews, for whom the MELSM borrows information from other individuals with similar covariate values. The definition of within-individual variability in this setting is not dependent on the definition of a baseline period. In addition, the model flexibly accommodates nonlinear associations as for the age-sex

interaction and can be used with other datasets.

There are some potential limitations of the approach described in this study. The quantification of within-individual variability depends on the demographic covariates in the mean submodel because it describes variation around the mean trajectory. To use this in a clinical settings, additional studies need to be conducted to find an agreement about which covariates should be included in the model, and possibly to identify causal relationships between covariates and the within-individual variability. The specific choice of the covariates and the age range means that these results cannot be directly extended to populations outside the one considered, such as children, but the same model structure could be used to obtain results for these cohorts. Another limitation is that the model does not clearly disentangle the measurement error from clinically relevant within-individual variability, nor returns a criterion to decide whether a single observed value is “outside” some “normal” interval for an individual. Tackling these issues, along with reducing the computational time, would be useful towards a potential clinical use of this or other metrics of within-individual variability.

We have included in the analysis data from the year 2020, when the start of the COVID-19 pandemic led to missed annual reviews, fewer infections and more stable FEV during lockdown. In addition, the triple combination therapy Kaftrio was rolled out in the UK from September 2020, although not all patients received it initially. Further analysis should be conducted to fully describe the changes induced by these two events.

The findings of this analysis suggest that modelling the within-individual variability could lead to a better characterisation of individual lung function decline in adults with cystic fibrosis and potentially to improved prediction of disease outcomes.

Data and code availability

This work used anonymised data from the UK Cystic Fibrosis Registry, which has research ethics approval (Research Ethics Committee reference number 07/Q0104/2). Use of the data was approved by the Registry Research Committee (data request 426). Data are available following application to the Registry Research Committee (<http://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/apply-for-data-from-the-uk-cf-registry>). The R code is available at https://www.marcopalma3.github.io/CF_WIV/CF_WIV.html.

Source of funding

MP was supported by the MRC grant “Looking beyond the mean: what within-person variability can tell us about dementia, cardiovascular disease and cystic fibrosis” (MR/V020595/1). JKB was supported by MRC Unit Programme MC_UU_00002/5. RHK was funded by UK Research and Innovation (Future Leaders Fellowship MR/S017968/1). RS was supported by the National Heart, Lung and Blood Institute of the National Institutes of Health (R01 HL141286) and Cystic Fibrosis Foundation (Naren19R0 and SZCZES22AB0). GM-T acknowledges the support of the Osteopathic Heritage Foundation through funding for the Osteopathic Heritage Foundation Ralph S. Licklider, D.O., Research Endowment in the Heritage College of Osteopathic Medicine.

For the purpose of open access, the authors have applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

Publication history

An early version of this manuscript is available in medRxiv: <https://doi.org/10.1101/2023.05.12.23289768>.

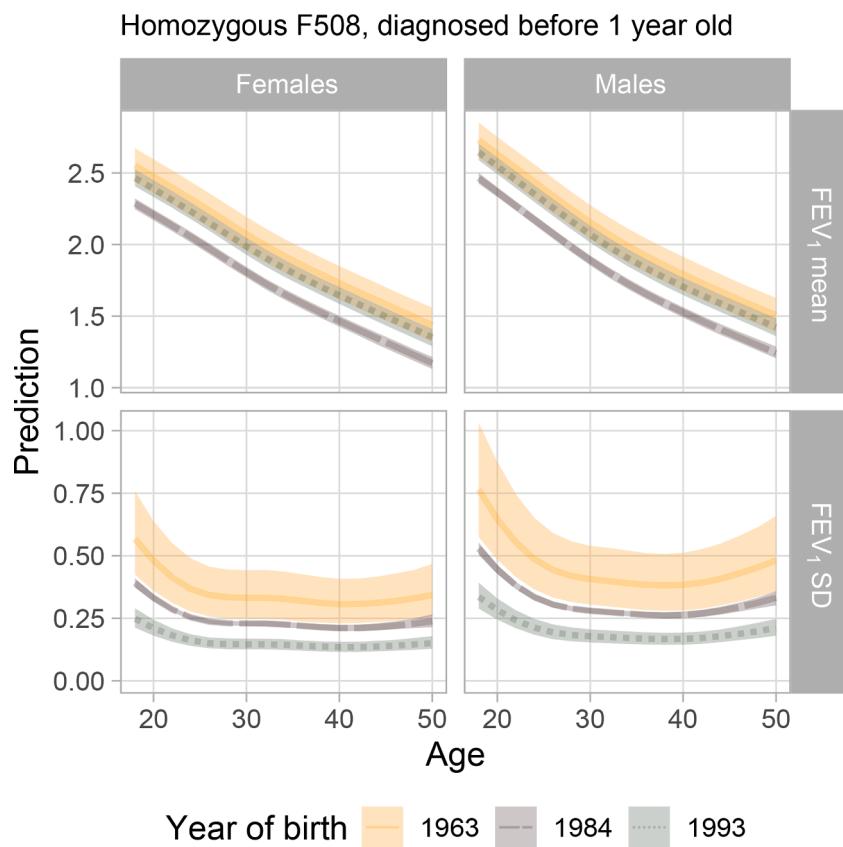


Fig. 3. Posterior predictions of mean and standard deviation of FEV₁ by sex and age, for F508 homozygous/non-homozygous individuals diagnosed before/after year 1. Year 1984 is the median year of birth in the population.

CRediT authorship contribution statement

Marco Palma: Conceptualization, Formal analysis, Visualization, Methodology, Writing – review & editing. **Ruth H Keogh:** Conceptualization, Writing – review & editing. **Siobhán B Carr:** Conceptualization, Writing – review & editing. **Rhonda Szczesniak:** Conceptualization, Writing – review & editing. **David Taylor-Robinson:** Conceptualization, Writing – review & editing. **Angela M Wood:** Conceptualization, Methodology, Writing – review & editing. **Graciela Muniz-Terrera:** Conceptualization, Methodology, Writing – review & editing. **Jessica K Barrett:** Conceptualization, Funding acquisition, Methodology, Supervision, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

JKB has received research funding for unrelated work from F. Hoffmann-La Roche Ltd.

Acknowledgements

We thank the Cystic Fibrosis Epidemiological Network (CF-EpiNet) Strategic Research Centre data group and Elaine Gunn for contributions to data preparation and cleaning. We thank the reviewers for their detailed and insightful feedback.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at [10.1016/j.jcf.2024.05.013](https://doi.org/10.1016/j.jcf.2024.05.013)

References

- [1] Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: a longitudinal study using UK patient registry data. *J Cystic Fibrosis* 2018;17(2):218–27.
- [2] Keogh RH, Seaman SR, Barrett JK, Taylor-Robinson D, Szczesniak R. Dynamic prediction of survival in cystic fibrosis: a landmarking analysis using UK patient registry data. *Epidemiology (Cambridge, Mass)* 2019;30(1):29.
- [3] Morgan WJ, Vandevenant DR, Pasta DJ, Foreman AJ, Wagener JS, Konstan MW, et al. Forced expiratory volume in 1 s variability helps identify patients with cystic fibrosis at risk of greater loss of lung function. *J Pediatr* 2016;169:116–21.
- [4] Stanford GE, Dave K, Simmonds NJ. Pulmonary exacerbations in adults with cystic fibrosis: a grown-up issue in a changing cystic fibrosis landscape. *Chest* 2021;159(1):93–102.
- [5] Heltshe SL, Szczesniak RD. Forced expiratory volume in 1 s variability in cystic fibrosis: has the clinical utility been lost in statistical translation? *J Pediatr* 2016;172:228.
- [6] Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, Diggle P. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. *Thorax* 2012;67(10):860–6.
- [7] Szczesniak RD, Su W, Brokamp C, Keogh RH, Pestian JP, Seid M, Diggle PJ, Clancy JP. Dynamic predictive probabilities to monitor rapid cystic fibrosis disease progression. *Stat Med* 2020;39(6):740–56.
- [8] Hedeker D, Mermelstein RJ, Demirtas H. An application of a mixed-effects location scale model for analysis of ecological momentary assessment (EMA) data. *Biometrics* 2008;64(2).
- [9] Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, MacDougall A, Newsome S, Schlüter DK, Stanjevic S, et al. Data resource profile: the UK cystic fibrosis registry. *Int J Epidemiol* 2018;47(1):9–10e.
- [10] Konstan MW, Wagener JS, Vandevenant DR, Pasta DJ, Yegin A, Rasouliyan L, Morgan WJ. Risk factors for rate of decline in FEV1 in adults with cystic fibrosis. *J Cystic Fibrosis* 2012;11(5):405–11.
- [11] Szczesniak RD, McPhail GL, Duan LL, Macaluso M, Amin RS, Clancy JP. A semiparametric approach to estimate rapid lung function decline in cystic fibrosis. *Ann Epidemiol* 2013;23(12):771–7.
- [12] Fitzmaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis*. John Wiley & Sons; 2012.
- [13] Hedeker D, Mermelstein RJ, Demirtas H. Modeling between-subject and within-subject variances in ecological momentary assessment data using mixed-effects location scale models. *Stat Med* 2012;31(27):3328–36.

- [14] Williams DR, Zimprich DR, Rast P. A Bayesian nonlinear mixed-effects location scale model for learning. *Behav Res Methods* 2019;51(5):1968–86.
- [15] Williams DR, Martin SR, Liu S, Rast P. Bayesian multivariate mixed-effects location scale modeling of longitudinal relations among affective traits, states, and physical activity. *Eur J Psychol Assess* 2021.
- [16] Bürkner P-C. brms: An R package for Bayesian multilevel models using Stan. *J Stat Softw* 2017;80:1–28.
- [17] Taylor-Robinson D, Schlueter DK, Diggle PJ, Barrett JK. Explaining the sex effect on survival in cystic fibrosis: a joint modeling study of UK registry data. *Epidemiology (Cambridge, Mass)* 2020;31(6):872.
- [18] Barrett JK, Huille R, Parker R, Yano Y, Griswold M. Estimating the association between blood pressure variability and cardiovascular disease: an application using the ARIC study. *Stat Med* 2019;38(10):1855–68.
- [19] Brugha R, Wright M, Nolan S, Bridges N, Carr SB. Quantifying fluctuation in glucose levels to identify early changes in glucose homeostasis in cystic fibrosis. *J Cystic Fibrosis* 2018;17(6):791–7.