Risk factors for forced expiratory volume in 1 s decline in European patients with cystic fibrosis: data from the European Cystic Fibrosis Society Patient Registry

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Shareable abstract (@ERSpublications)
Longitudinal data in people with CF show a different FEV_1 evolution in patients with class III mutation, the only group on effective modulators. Similar FEV_1 evolution in middle- and high-income countries underlines opportunities for low-income countries. https://bit.ly/3YgIOIo

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Abstract

Aim To examine the trajectory of forced expiratory volume in 1 s (FEV_1) using data from the European Cystic Fibrosis Society patient registry (ECFPR) collected from 2008 to 2016, *i.e.* the era before highly effective modulator therapy (HEMT). We evaluated risk factors for FEV_1 decline.

Methods The study population included patients with a confirmed diagnosis of cystic fibrosis recorded in the ECFPR (2008–2016). The evolution of FEV_1 % predicted (%FEV_1) with age, and the yearly change in %FEV_1 were evaluated. Risk factors considered were cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation class, gender, age at diagnosis, neonatal screening, meconium ileus, sweat chloride concentration at diagnosis and country's income level.

Results We used 199 604 FEV_1 recordings from 38 734 patients. The fastest decline was seen during puberty and in patients diagnosed before the age of 10 years. Males had a higher %FEV_1, but a higher yearly %FEV_1 loss between the ages of 15 and 25 years. We showed stabilisation and even improvement in %FEV_1 over age in adults with a class III *CFTR* mutation, but a steady decline in patients homozygous for F508del or with both mutations of classes I/II. A faster decline in %FEV_1 was found in patients from low-income countries compared to a similar %FEV_1 evolution in patients from middle- and high-income countries.

Conclusions These longitudinal FEV_1 data reflect the reality of cystic fibrosis across Europe in the era pre-HEMT, and can serve as baseline for comparison with the post-HEMT era. The similar evolution in middle- and high-income countries underlines opportunities for low-income countries.

Introduction

Lung function decline has been consistently associated with numerous markers of disease progression among people with cystic fibrosis (CF). Low forced expiratory volume in 1 s (FEV_1) sets patients at increased risk of pulmonary exacerbation, hospitalisation and chronic *Pseudomonas aeruginosa* infection [1]. Patient registries and large-scale epidemiological cohort studies are instrumental in understanding the disease's natural history and identifying risk factors for clinical outcomes. Much of the epidemiological

evidence for FEV_1-specific associations has been derived from CF patient registries, which collect clinical data on lung function and other markers of disease. The CF community has been systematically collecting longitudinal data for these purposes. The recent advances in analytical methodologies have enabled a better understanding of the mechanisms behind disease progression [1].

The European Cystic Fibrosis Society patient registry (ECFSPR) has been collecting data on people with CF annually from national registries and individual CF centres in Europe and neighbouring countries. The ECFSPR has already provided a valuable estimation of the number of people with CF in Europe in the first decade of the 21st century [2]. From 2008 to 2016, 43 786 CF patients from 26 countries reported data in the ECFSPR. This is a time period before highly effective modulator therapy (HEMT) was introduced for the majority of patients with CF. Ivacaftor was licensed by the European Medicines Agency (EMA) in 2012 for use in patients with a class III mutation, whereas the combination of ivacafor with tezacaftor and elexacaftor was only approved in 2020.

The aim of this study was to examine FEV_1 progression over time among people with CF in Europe and to evaluate potential risk factors for FEV_1 decline, such as cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation class, gender, age at diagnosis, neonatal screening, meconium ileus, sweat chloride concentration at the time of diagnosis and country's income level.

Findings from the current study reflect the reality of CF across Europe, and due to their international nature, they offer a unique basis for comparison and discussion. In addition, given the huge number of data and the wide variability in lung disease and potential risk factors, they can highlight the major factors associated with FEV_1. The results might help improve clinical care by indicating where there is a need to implement the recommended standards of care across European countries. Finally, these longitudinal FEV_1 data reflect the reality of CF across Europe in the pre-HEMT era, and can serve as a baseline for comparison with the post-HEMT era.

Methods

The European Cystic Fibrosis Society patient registry

The ECFSPR collects data on people with CF annually from national registries and individual CF centres in Europe and neighbouring countries [3, 4]. The percentage of the total number of people with CF reported to the ECFSPR (self-reported coverage) varies between the participating countries and between years of follow-up; this information is presented in the ECFSPR annual reports (www.ecfs.eu/projects/ecfs-patient-registry/annual-reports). For a detailed description of this registry and its contents, refer to www.ecfs.eu/ecfspr.

Study population (dataset)

The study population included patients with a confirmed diagnosis of CF, who had at least one spirometry (FEV_1) measurement in the ECFSPR from 2008 to 2016. Patients who underwent solid organ transplantation were included in the $\%FEV_1$ analysis until the year of their transplant. Patients who died during the study period are included until the year of death. Measurements before the age of 6 years and after 50 years were excluded from $\%FEV_1$ analysis, as spirometry may not be sufficiently reliable in children aged <6 years, and the number of measurements after 50 years was too low.

Definition of FEV_1

The ECFSPR collects the best FEV_1 value measured over the year and the corresponding height and weight of the patient [3, 4]. All FEV_1 values in litres were transformed into percent predicted using the Global Lung Function Initiative reference values [5].

Age at diagnosis groups and age at follow-up

Age was calculated as the time between the date of birth and the date of the FEV_1 value measured during that registry year. To define diagnosis in infants, the first decade of life, adolescents and adults, the following "age at diagnosis" groups were considered: <1, 1–10, 11–18 and >18 years.

Risk factors for the yearly change of $\%FEV_1$

These comprised type of *CFTR* mutation, gender, age at diagnosis, neonatal screening, meconium ileus at birth, sweat chloride concentration reported at the time of diagnosis and country's income status.

Country's income status groups

Countries were stratified into three income status groups based on tertiles of gross national income per capita, obtained from World Bank tables [6]. Bulgaria, Hungary, Lithuania, Republic of North Macedonia,

Republic of Moldova, Romania, Russian Federation, Serbia, Turkey and Ukraine were assigned to the low-income group; Czech Republic, Greece, Israel, Italy, Latvia, Portugal, Slovakia, Slovenia and Spain were assigned to the middle-income group; and Austria, Belgium, Denmark, France, Germany, Ireland, Luxemburg, the Netherlands, Sweden, Switzerland and the United Kingdom were assigned to the high-income group.

Mutation groups

Patients were divided into the following mutation groups known to influence disease severity. 1) Both class I/II; 2) both F508del; 3) at least one mutation of class III; 4) at least one mutation of class IV; 5) at least one mutation of class V; 6) one of class I or II, other mutation in class unknown, or mutation unknown [7, 8, 9].

Statistical analysis

A linear mixed model was used to evaluate the evolution of $\%FEV_1$, quantify the yearly change and verify if the FEV_1 progression depended on risk factors by including interaction terms in the model. In addition, nonlinear evolution of FEV_1 as a function of age was allowed in the model using restricted cubic splines. The approach is similar to the model proposed by Szczesniak *et al*. [10], except that they did not include slope as a random effect.

Restricted cubic splines with five knots (at percentiles 5, 27.5, 50, 72.5 and 95) were used [11] to allow nonlinearity in the relation between age and $\%FEV_1$. This approach allows deviations from linearity to be captured in a flexible way. The yearly change in FEV_1 (%) was calculated as the derivative of the function used to model age. The delta rule was used to calculate the 95% confidence interval for the yearly change [10].

It was evaluated whether each of the potential risk factors (gender, socioeconomic status of country, age, neonatal screening, sweat chloride concentration at time of diagnosis, meconium ileus at birth and mutation type) moderated the rate of $\%FEV_1$ change, by including interactions with age in the model. To have a uniform approach in analysis and reporting of results, the continuous moderators age at diagnosis and sweat chloride concentration have been categorised. The patients were divided into four groups according to age at diagnosis: <1, 1–10, 11–18 and >18 years, as specified earlier. The patients were divided into four groups for sweat test value based on the quantiles (<Q1, Q1–median, median–Q3 and >Q3, *i.e.* <80, 80–97, 98–109 and $\geqslant$110 $mmol \cdot L^{-1}$).

Results were reported from models for each moderator separately (univariable model) and a multivariable model containing all specified potential moderators. Models were based on all available cases. Differences between subjects with and without complete moderator information were evaluated. Given the large number of missing values for sweat chloride concentration, a multivariable model without sweat test value as moderator was considered additionally. Subgroup analyses (univariable models) were also performed in each mutation group separately. A detailed description of the methodology can be found in the supplementary material.

Software

All analyses were performed using SAS software (version 9.4 of the SAS System for Windows; SAS Institute, Cary, NC, USA).

Results

Study population

During the study period 2008–2016, 43 786 patients aged $\geqslant$6 years had data reported in the ECFSPR; 5052 subjects were excluded from the analysis (supplementary figure S1). 15 582 and 29 254 patients were included in the multivariable analysis with and without the parameter sweat chloride concentration at diagnosis, respectively. Clinical and demographic characteristics of the study population (univariable and multivariable model) are shown in table 1.

Rate of FEV_1 decline

199 604 FEV_1 recordings from 38 734 patients were analysed to describe the evolution of FEV_1 % predicted over age ($\%FEV_1$) and the yearly change of $\%FEV_1$ (figure 1, table 2). At every age there was a decline in mean FEV_1 % predicted, with the highest rate of decline found during puberty (figure 1).

TABLE 1 Clinical and demographic characteristics of the study population (study population and population included in the multivariable model)

	Baseline analysis	Multivariable model
Male	23 096/43 786 (52.75)	8120/15 582 (52.11)
Socioeconomic status of country		
High-income group	29 918/43 786 (68.33)	9781/15 582 (62.77)
Middle-income group	10 042/43 786 (22.93)	4336/15 582 (27.83)
Low-income group	3826/43 786 (8.74)	1465/15 582 (9.40)
Age at diagnosis, months	42 023 4.86±10.49 0.0–86.0	15 582 3.0±7.06 0.0–49.0
Age at diagnosis		
0 years	23 744/42 023 (56.50)	9731/15 582 (62.45)
1–10 years	12 160/42 023 (28.94)	4400/15 582 (28.24)
11–18 years	2413/42 023 (5.74)	732/15 582 (4.70)
>18 years	3706/42 023 (8.82)	719/15 582 (4.61)
BMI (first year in the ECFSPR)	38 533 −0.43±1.18 −1.07–0.36	NA NA NA
Neonatal screening		
Not performed	28 476/35 460 (80.30)	11 074/15 582 (71.07)
Performed, result positive	4668/35 460 (13.16)	2987/15 582 (19.17)
Performed, result negative	242/35 460 (0.68)	175/15 582 (1.12)
Performed, result unknown	2074/35 460 (5.85)	1346/15 582 (8.64)
Meconium ileus at birth		
No	35 548/40816 (87.09)	13 926/15 582 (89.37)
Yes, operated	2791/40 816 (6.84)	893/15 582 (5.73)
Yes, not operated	869/40 816 (2.13)	306/15 582 (1.96)
Yes, don't know if operated	1608/40 816 (3.94)	457/15 582 (2.93)
Chloride value, mmol·L^{-1} (sweat test)	22 747 93.95±25.53 97.00 (80.0–110.0) 1.0–170.0	15 582 95.9±24.58 99.0 (83.0–110.0) 1.0–170.0
Mutation		
Both class I/II	9053/43 786 (20.68)	3830/15 582 (24.58)
Both F508del	17 133/43 786 (39.13)	6311/15 582 (40.50)
At least one of class III	1393/43 786 (3.18)	562/15 582 (3.61)
At least one of class IV	3006/43 786 (6.87)	1152/15 582 (7.39)
At least one of class V	2501/43 786 (5.71)	987/15 582 (6.33)
One of class I/II, other mutation in class unknown or both mutations unknown or genetic test not performed	10 520/43 786 (24.03)	2740/15 582 (17.58)

Data are presented as number of subjects with specific characteristics/total number of subjects with information on the variable (%), n, mean±SD, range or median (interquartile range). BMI: body mass index; ECFSPR: European Cystic Fibrosis Society patient registry; NA: not applicable.

Effect of moderators on FEV_1 evolution

Mutation groups

The most substantial and quite comparable FEV_1 decline was found in the mutation groups "both class I/II" and "both F508del" (figure 2, supplementary table S1). The multivariable model confirmed the results from the univariable analysis (table 3). A different mean course was seen in people with CF with a class III mutation, with $\%FEV_1$ improving from age 20 years to 25 years onwards.

Gender

A significant, but slight, difference in the evolution of FEV_1 between males and females was found. Males showed, on average, a higher $\%FEV_1$ (figure 3), especially when pre-pubertal and in later adulthood, but they had a higher rate of decline during puberty and even more so during young adulthood. A comparable pattern was observed in analyses performed separately in each mutation group (data not shown). Moreover, a similar difference in evolution between males and females was seen in the multivariable model (table 3).

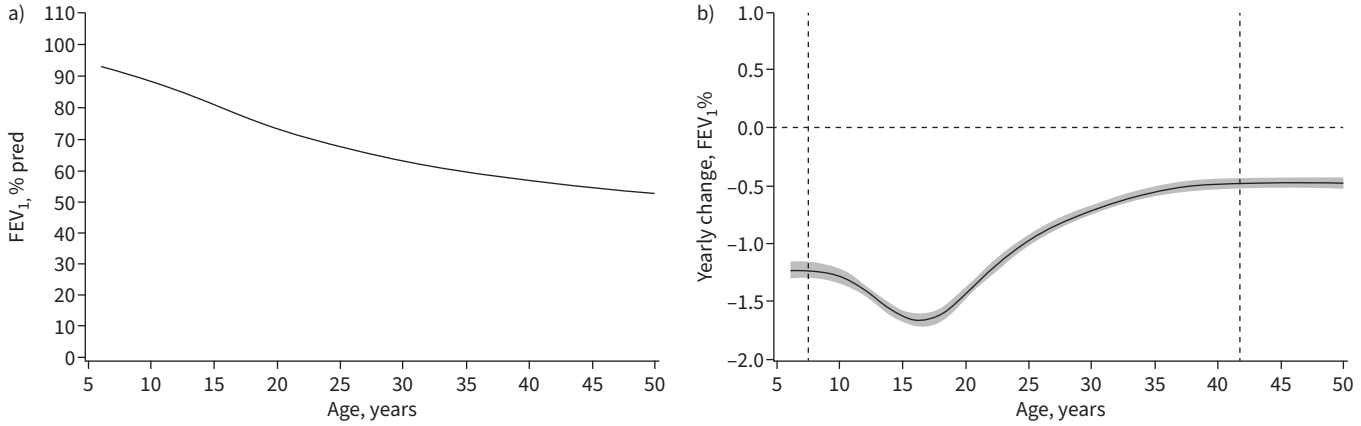

FIGURE 1 a) Overall evolution of forced expiratory volume in 1 s (FEV_1); b) yearly changes in FEV_1. Data are presented as mean (95% CI). Note that the yearly rate of change is constant before 7.40 and after 41.88 years (dashed vertical lines), since by using restricted cubic splines, the relationship is assumed to be linear in the outer intervals (defined by quantiles 0.05 and 0.95, respectively).

Country's income status

A much worse FEV_1 decline was found in the group of countries with low income compared to the middle- and high-income groups who follow a similar evolution. In the univariable analysis, the middle-income group has slightly higher $\%FEV_1$ values (figure 4a), but this difference disappears in the multivariable model (figure 4b, table 3). The same separation of low *versus* middle- and high-income countries is seen in the subgroups of both mutations class I/II (supplementary figure S2a), and in patients with both mutations F508del (supplementary figure S2b).

Age at diagnosis

A small, but significantly lower, mean $\%FEV_1$ and a higher rate of decline was found in groups with age ⩽10 years at diagnosis (<1 years and 1–10 years) compared to those with age 11–18 years at diagnosis in the univariable model ($p<0.001$) (table 3). The group with diagnosis at age >18 years had higher $\%FEV_1$ values and showed less decline than those with earlier diagnoses (figure 5a, table 3).

However, this pattern was less clear when evaluating the effect of age at diagnosis in each mutation group separately. Within the groups of patients diagnosed at <1 years and between 1 and 10 years (approximately), 73% and 60% had both class I/II or both F508del mutation, respectively. For the groups diagnosed between 11 and 18 years and >18 years, these percentages were 25% and 9%, respectively (supplementary table S2). A subanalysis of the group of patients diagnosed at <1 year and between 1 and 10 years indicated that the difference between the mutation groups was still present (supplementary figure S3).

TABLE 2 Forced expiratory volume in 1 s (FEV_1) % predicted and yearly rate of FEV_1 % pred change at specific ages

Age, years	Patients,[#] n	Mean (95% CI)	Rate (95% CI)
6	6908	93.03 (92.09–93.98)	−1.23 (−1.30– −1.16)
10	7486	88.05 (87.14–88.97)	−1.29 (−1.35– −1.23)
15	7465	80.80 (79.88–81.72)	−1.64 (−1.69– −1.58)
20	6756	72.78 (71.84–73.71)	−1.43 (−1.47– −1.39)
30	3966	62.65 (61.68–63.61)	−0.72 (−0.75– −0.69)
35	2700	59.46 (58.49–60.44)	−0.56 (−0.60– −0.53)
40	1853	56.87 (55.85–57.88)	−0.49 (−0.54– −0.44)
45	1247	54.45 (53.35–55.54)	−0.48 (−0.53– −0.43)
50		52.03 (50.81–53.26)	−0.48 (−0.53– −0.43)

[#]: number of subjects in each category (*e.g.* number of subjects at 6 years refers to number of subjects in age category 6–7 years.

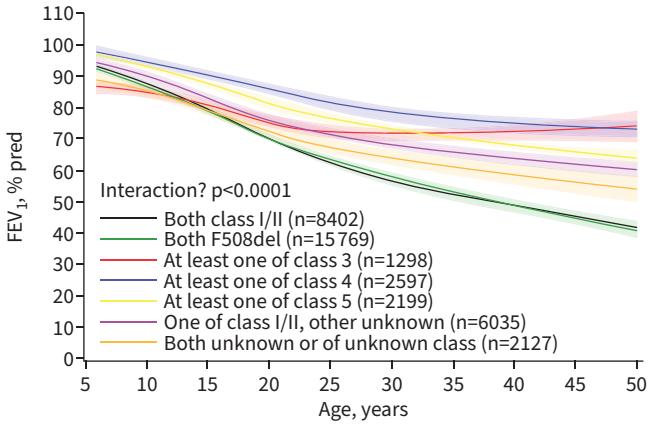

FIGURE 2 Evolution of forced expiratory volume in 1 s (FEV_1) as a function of mutation group (univariable model, only considering effect of mutation).

In the multivariable model, the differences in mean FEV_1 were attenuated compared to the univariable result (after correction for the other variables, the $\%FEV_1$ was lower in the diagnosis at age >18 years group compared to the univariable results). However, the differences in decline still had the same order of magnitude as in the univariable analysis (figure 5b, table 3).

Neonatal screening

Up to the age of 30 years, there was a small, but significantly more negative yearly change of $\%FEV_1$ when neonatal screening was not performed *versus* "result positive" (table 3, supplementary figure S4).

Meconium ileus

In the univariable analysis, patients with meconium ileus had lower $\%FEV_1$ values and showed a stronger decline (supplementary figure S5a). No difference was found in the yearly change within the mutation groups "both class I/II" and "both F508del" (supplementary figure S6a and b). In the multivariable model, there was neither evidence for a difference in decline as a function of meconium ileus nor a difference in mean $\%FEV_1$ value (supplementary figure S5b).

Sweat chloride concentration

In the univariable analysis, higher $\%FEV_1$ values and a lower rate of decline were found in the lowest quartile group for sweat chloride concentration (<Q1) (supplementary figure S7a). However, this difference disappeared in most subanalyses according to mutation groups. For example, there was no/hardly any difference in FEV_1 according to sweat chloride concentration in mutation groups "both class I/II" and "both F508del" groups, probably also due to the low number of subjects with sweat chloride values <Q1 (supplementary figure S8a and b). In the multivariable model, there remained a significant difference in the mean $\%FEV_1$ value between the four groups, *i.e.* the lower the sweat test value, the higher the mean $\%FEV_1$. Only the comparison of Q4 *versus* Q3 was not significant (supplementary figure S7b, table 3). However, there was no evidence for a difference in decline in the multivariable model as a function of sweat chloride concentration.

Discussion

Longitudinal analysis of FEV_1 change over age among CF patients in Europe over 9 years from 2008 to 2016 was performed, that is, the era before HEMT for the majority of patients with CF. Our study showed a vastly different FEV_1 evolution in patients with a class III mutation, the only class with effective modulator treatment during the data collection. Ivacaftor was licensed by the EMA in 2012 for use in patients with a class III mutation, whereas the combination of ivacafor with tezacaftor and elexacaftor was only approved in 2020. A similar evolution in FEV_1 in middle- and high-income countries and a much worse course of FEV_1 with age in countries with low socioeconomic status was found. Finally, we confirmed several known risk factors for worse $\%FEV_1$ outcome such as female sex, diagnosis prior to the age of 10 years, and both mutations class I/II or F508del.

TABLE 3 Results of the multivariable model analysis

	Interaction effect[#]		Main effect[¶]		
	Degrees of freedom	p-value	Difference±SE	Degrees of freedom	p-value
Males *versus* females	4	**<0.0001**	2.32±0.54	1	**<0.0001**
Country-status	8	**<0.0001**		2	**<0.0001**
Middle *versus* low	4	**<0.0001**	9.61±0.76	1	**<0.0001**
High *versus* low	4	**<0.0001**	8.15±0.73	1	**<0.0001**
High *versus* middle	4	**<0.0001**	−1.47±0.60	1	**<0.0001**
Neonatal screening	12	0.0055		3	**<0.0001**
Not done *versus* result positive	4	**0.0024**	−3.93±0.65	1	**<0.0001**
Not done *versus* result negative	4	0.0931	−5.41±1.18	1	**<0.0001**
Not done *versus* result unknown	4	0.0593	−3.07±0.72	1	**<0.0001**
Result positive *versus* result negative	4	0.5407	−1.48±1.19	1	0.2925
Result positive *versus* result unknown	4	0.4819	0.86±0.76	1	0.1381
Result negative *versus* result unknown	4	0.2139	2.34±1.21	1	0.1111
No ileus meconium *versus* ileus meconium	4	0.7555	0.54±0.69	1	0.2640
Sweat values	12	0.0937		3	**<0.0001**
Q1 *versus* Q2	4	0.4581	0.95±0.67	1	**0.0339**
Q1 *versus* Q3	4	0.1870	2.14±0.67	1	**<0.0001**
Q1 *versus* Q4	4	0.0792	2.24±0.67	1	**<0.0001**
Q2 *versus* Q3	4	0.1143	1.19±0.64	1	**0.0034**
Q2 *versus* Q4	4	0.3122	1.29±0.63	1	**0.0013**
Q3 *versus* Q4	4	0.1179	0.11±0.63	1	0.7922
Mutation	20	**<0.0001**		5	**<0.0001**
Both class I/II *versus* both F508del	4	0.5984	−0.18±0.61	1	0.6199
Both class I/II *versus* at least one class III	4	**<0.0001**	−2.44±0.91	1	**0.0029**
Both class I/II *versus* at least one class IV	4	**<0.0001**	−6.05±0.82	1	**<0.0001**
Both class I/II *versus* at least one class V	4	**<0.0001**	−5.10±0.85	1	**<0.0001**
Both class I/II *versus* one of class I/II, other unknown	4	**<0.0001**	−3.07±0.68	1	**<0.0001**
Both F508del *versus* at least one class III	4	**<0.0001**	−2.25±0.89	1	**0.0045**
Both F508del *versus* at least one class IV	4	**<0.0001**	−5.87±0.80	1	**<0.0001**
Both F508del *versus* at least one class V	4	**<0.0001**	−4.92±0.84	1	**<0.0001**
Both F508del *versus* one of class I/II, other unknown	4	**<0.0001**	-2.89±0.66	1	**<0.0001**
At least one class III *versus* at least one class IV	4	0.1260	-3.61±0.98	1	**0.0002**
At least one class III *versus* at least one class V	4	**0.0077**	-2.66±1.00	1	**0.0080**
At least one class III *versus* one of class I/II, other unknown	4	**0.0002**	-0.64±0.92	1	0.4520
At least one class IV *versus* at least one class V	4	0.1625	0.95±0.92	1	0.2577
At least one class IV *versus* one of class I/II, other unknown	4	**0.0045**	2.98±0.82	1	**<0.0001**
At least one class V *versus* one of class I/II, other unknown	4	0.9029	2.03±0.85	1	**0.0053**
Age at diagnosis	11[+]	<0.0001		3	**<0.0001**
<1 year *versus* 1–10 years	4	**0.0004**	−0.99±0.61	1	**0.0089**
<1 year *versus* 11–18 years	4	**<0.0001**	−1.82±0.92	1	**0.0331**
<1 year *versus* >18 years	4	**<0.0001**	−11.3±1.11	1	**<0.0001**
1–10 years *versus* 11–18 years	4	**0.0011**	−0.84±0.92	1	0.3257
1–10 years *versus* >18 years	4	**<0.0001**	−10.3±1.11	1	**<0.0001**
11–18 years *versus* >18 years	4	0.1509	−9.50±1.19	1	**<0.0001**

p-values and estimates for the main effects and p-values for the interaction effects are given. To interpret the effect of each factor on the decline of forced expiratory volume in 1 s (FEV_1), refer to the relevant figure. Q: quartile. [#]: *i.e.* does the rate of change depend on gender, age at diagnosis, *etc.*; [¶]: *i.e.* does the mean FEV_1 (averaged over the age range) depends on gender, age at diagnosis, *etc.*; [+]: the interaction effect of age at diagnosis contained 11 instead of 12 degrees of freedom, due to overparametrisation of the model.

This study has great strengths. First, we performed a longitudinal analysis of FEV_1 change over age among people with CF in Europe (ECFSPR) over 9 years, in the era before HEMT. The ECFSPR is the world's largest CF database, with information on >52 000 subjects from 40 countries in Europe [2, 12]. This is the most extensive dataset (according to our knowledge) analysing longitudinal FEV_1 data among patients with CF.

Several studies have analysed longitudinal data from CF registries, but they are not as extensive as ours [13–17]. In addition, the heterogeneous European CF population showed a wide variability for some baseline factors potentially associated with FEV_1, and hence is ideally suited for evaluation.

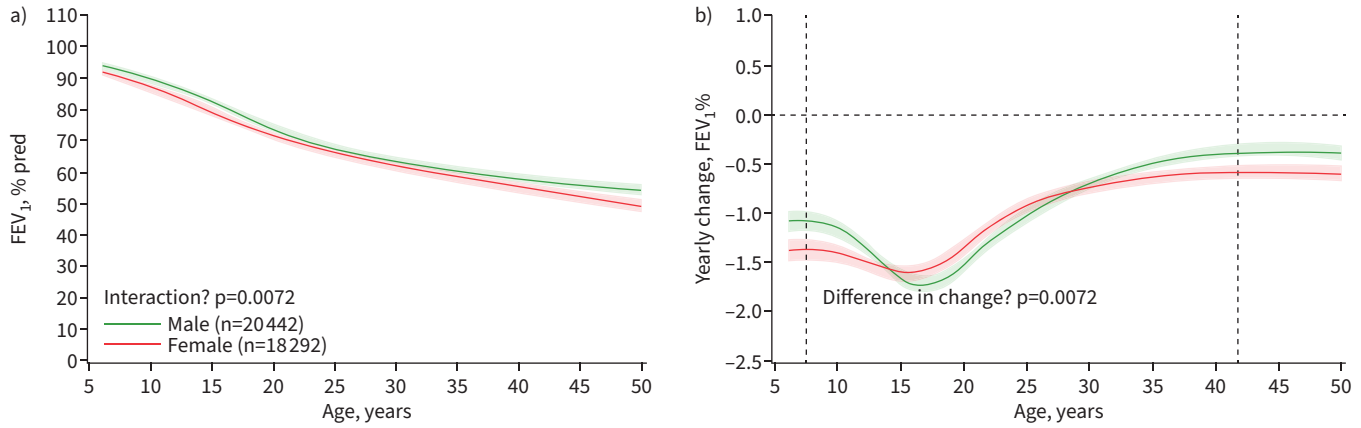

FIGURE 3 a) Evolution and b) yearly rate of change of forced expiratory volume in 1 s (FEV_1) as a function of gender (univariable model, only considering effect of gender). Note that a test for an interaction equals a test for a difference in change. Vertical dashed lines represent 5th and 95th percentiles.

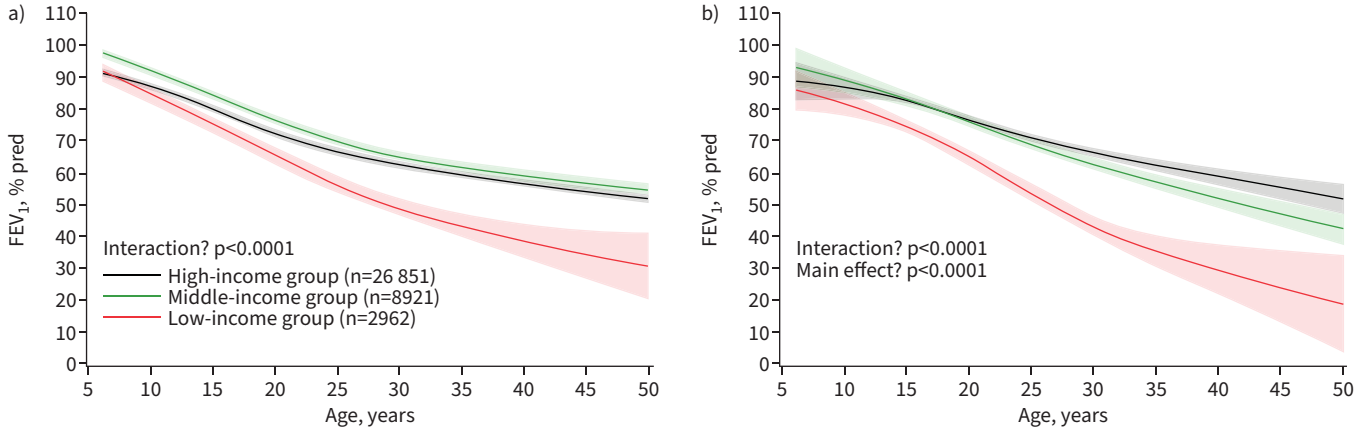

FIGURE 4 Evolution of forced expiratory volume in 1 s (FEV_1) as a function of the country's socioeconomic status: a) univariable and b) multivariable model.

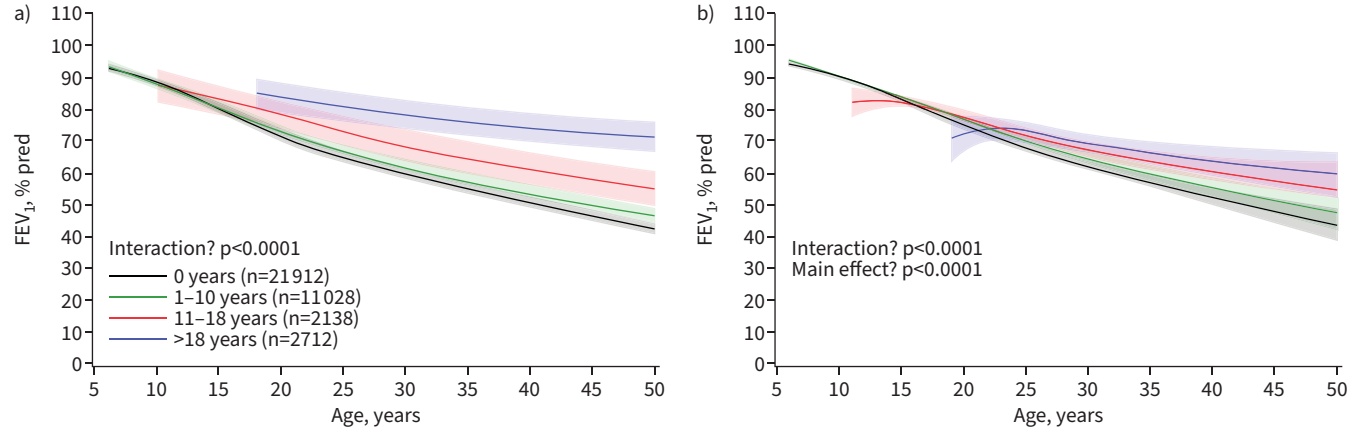

FIGURE 5 Evolution of forced expiratory volume in 1 s (FEV_1) as a function of age at diagnosis: result from a) univariable and b) multivariable model.

Furthermore, we used the appropriate methodology to evaluate CF lung function decline. Decline in FEV_1 is the strongest predictor of mortality in people with CF [14, 15], but recent epidemiological studies point out that FEV_1 progression is not constant (linear) over age [1]. Szczesniak *et al*. [15] substantiated the growing body of evidence that CF lung function decline is nonlinear. Our study underpins this and used appropriate methodology to evaluate this outcome. Using splines enabled us to obtain a smooth longitudinal evolution of FEV_1 without imposing a simplified relationship (such as linear or quadratic), either for the mean evolution nor for the rates of change. Furthermore, given the importance of appropriate modelling of the variance and the correlation of the FEV_1 values, serial correlation and correlated random intercepts and slopes were included in the statistical model. Finally, using multivariable analysis enabled us to point out the major fixed determinants of FEV_1 decline among people with CF.

Many risk factors influence the progression of CF lung disease and early mortality [16, 17], but their relative impact over time has been uncertain. Previous studies have typically focused on a limited number of intrinsic (*e.g.* meconium ileus [18], genotype [19, 20]) or extrinsic (*e.g.* pulmonary exacerbations) [21] risk factors. Our study evaluated a battery of fixed risk factors, *i.e.* gender, age at diagnosis, neonatal screening, sweat test value, meconium ileus, mutation type and economic status of the country in the era before HEMT.

FEV_1 progression with age

Our study showed a rapid lung function decline during adolescence and early adulthood, which is a frequent observation in the clinical course of CF, mainly attributed to low medication adherence during puberty [15]. In a retrospective study using the United States Cystic Fibrosis Foundation Patient Registry data, Szczesniak *et al*. [10] found that individuals experienced the most rapid decline at a median of 16.3 years, and the average maximal FEV_1 loss was 2.0% pred per year. Higher risk of decreases in lung function during adolescence was also reported by Liou *et al*. [22] and by Welsh *et al*. [23].

In our study, as in other studies [24], FEV_1 seems to be better maintained in the advanced age groups (figure 1). This is potentially a survivor effect: patients with the most severe lung disease are not included in cross-sectional studies because they died or underwent a lung transplant, leaving an increased proportion of "less severely ill" patients in the eldest age groups.

Mutation groups

Our study showed the most substantial decline in FEV_1 in mutation groups "both class I/II" and "both F508del" (both groups being comparable). A better outcome in people with CF and at least one class IV or V mutation has been reported [9, 25]. However, we describe a different evolution in people with CF with a class III mutation: from adulthood onwards, mean lung function increased. This distinct FEV_1 course in this subgroup reflects the benefit from treatment with the CFTR modulator ivacaftor licensed by the EMA since July 2012. De Boeck and Zolin [7], using ECFSPR data from the years 2008–2010, did not find differences in year-to-year change in FEV_1 between patients with a stop-codon mutation, homozygous for F508del or at least one class III mutation. However, they confirmed the less severe disease in patients with class IV and V mutations, reflected by a higher median age and a lower proportion of subjects with severe FEV_1 impairment [7]. The substantial benefit from the CFTR modulator ivacaftor [26–28] was also reported by Kawala *et al*. [29], who analysed retrospective data from the Canadian CF Registry and showed that FEV_1 increased significantly by 5.7% pred ($p<0.001$) after initiation of ivacaftor. Moreover, Volkova *et al*. [30], using data from national United States and United Kingdom registries, showed that relative to comparators, ivacaftor-treated patients had better-preserved lung function. However, we are the first to demonstrate reversal of the downward slope of FEV_1 over age in this longitudinal analysis of patients with a class III mutation.

Gender

Several studies have identified a "gender gap", with less morbidity and mortality in males [31]. Our study showed a significant difference in evolution between males and females, and males having a higher $\%FEV_1$ on average. This same difference in evolution between males and females remained in the multivariable model. We also showed a more rapid decline of FEV_1 in males during puberty and even more during young adulthood than females. This could be attributed to reduced treatment adherence among males over puberty.

The CF gender gap in mortality/survival has been described before, and the majority of data indicate that it still exists in the modern era of aggressive treatment of CF lung disease [32]. Sweezey [32] emphasised the increasing evidence suggesting a role for the effects of gender, particularly the female sex hormone

oestrogen, on infection, inflammation and transepithelial ion transport, all significant determinants of CF lung disease.

Country's income status

Socioeconomic status is another perspective worth considering affecting the progression of lung disease, with several reports indicating that a low socioeconomic status is associated with significantly poorer outcomes in CF [2], and is shown to affect survival among people with CF [13, 33, 34, 35].

Our study showed the most substantial decline in FEV_1 with age in countries in the low-income group. Middle- and high-income groups followed a similar evolution, with the middle-income group having slightly higher $\%FEV_1$ values. The "unexpected" higher values in the middle-income group were due to the higher prevalence of "both class I/II" and "both F508del" in the higher income group, and were therefore cancelled out in the multivariable model.

Mehta *et al*. [2] showed that there were fewer children and young adults with CF than expected in non-European Union countries. This finding is reinforced by the increased chance of patients surviving to the age of 40 years in European Union countries, even if they have the severe Phe508del mutation [2]. In contrast, Schechter *et al*. [34] showed that children with CF in the United States who could not afford health insurance were reported to have a more significant risk of death, poorer pulmonary function, poorer nutrition and were more likely to require hospitalisation for pulmonary exacerbation when compared to CF patients with health insurance. In another study, Schechter *et al*. [35] showed that CF health outcomes are correlated with the socioeconomic status spectrum.

Age at diagnosis, newborn screening, meconium ileus and sweat chloride concentration

Our study showed a small but significant difference in mean $\%FEV_1$ and rate of decline between groups with age at diagnosis at age $\leqslant$10 years. The group with a diagnosis aged >18 years had higher $\%FEV_1$ values and showed less decline than groups with earlier diagnoses. However, this pattern was attenuated when evaluating the effect of age at diagnosis in each mutation group separately (supplementary table S1). Adult diagnosis of CF is typically considered a milder form of the disease [36]. Keating *et al*. [36] showed that lung function declines more slowly in adults diagnosed with CF. Nick *et al*. [31] showed that people with CF diagnosed in childhood and who survive to the age of 40 years have more severe *CFTR* genotypes and phenotypes than adult-diagnosed patients.

Moreover, our study showed a significant difference in the yearly change between the two groups "newborn screening not done" *versus* "result positive". There is clear evidence supporting newborn screening for CF. Early diagnosis allows the early management to improve clinical outcomes [37, 38].

Patients with meconium ileus had lower $\%FEV_1$ values and showed a more robust decline, but there was neither evidence for a difference in decline as a function of meconium ileus nor for a difference in mean $\%FEV_1$ value in the multivariable model. The latter coincides with the absence of a difference in the yearly change within the mutation groups "both class I/II" and "both F508del". Johnson *et al*. [39] also showed that babies presenting with meconium ileus had no worse long-term outcomes than those presenting symptomatically later in infancy.

Our study showed higher $\%FEV_1$ values and a lower rate of decline in the group with the lowest values in the sweat test (supplementary figure S6a). However, this difference disappeared in most analyses performed separately in the mutation groups. In addition, Davis *et al*. [40] showed that sweat chloride concentration did not correlate with the severity index, either in the population as a whole or in the population of patients with alleles associated with pancreatic sufficiency, thought to have some residual CFTR function. These data suggested that sweat chloride concentration *per se* does not necessarily predict a milder pulmonary course in people with CF.

Limitations

Our study has some limitations that should be considered, including potential survivor bias. This is a common problem in datasets of this type [41]. In addition, disease registries may have problems with adherence to the definitions proposed, data quality process, missing data (such as many missing values for sweat chloride concentration in the ECFSPR), data entry errors and differences between countries with varied socioeconomic status [42]. In recent years, the ECFSPR introduced a data quality control project to check and overcome these limitations. Moreover, in 2018, the EMA qualified the ECFSPR as a resource for collecting CF-specific data for pharmacoepidemiology studies [43]. However, given longitudinal

observations over a mean of 9 years and analysing such a big dataset, it is unlikely that any other possible Type II errors occurred for clinically significant determinants of lung disease.

Finally, this was an observational study based on registry data, so confounding factors that were not measured in the registry are possible. Moreover, patient variables that change over time, such as allergic bronchopulmonary aspergillosis, CF-related diabetes, and liver disease were not analysed in the study. Therefore, our ability to assess the impact of extrinsic factors known to affect disease progression is limited.

Conclusions and clinical implications of the study

In this retrospective study using longitudinal data from a large dataset from the heterogeneous European CF population in the ECFSPR, we found that individuals with CF experienced the most rapid decline during puberty, with males showing a more potent drop during puberty and even more so during young adulthood. Furthermore, we showed that key predictors of the early FEV_1 decline included both mutation classes I/II and F508del. However, we described a different evolution in people with CF with a class III mutation, as from adulthood onwards, mean lung function increased. This was attributed to HEMT. Finally, our study showed a similar evolution in middle- and high-income countries, underlining opportunities for low-income countries.

Our study is the first to objectively analyse lung disease trajectory in an extensive European CF population dataset. Finding predictors and/or treatments associated with a slower rate of FEV_1 decline remains a significant clinical objective within epidemiologic and comparative effectiveness, especially in the era of new therapies in CF, with the establishment of CFTR modulators. This study has the potential to be the last in line of publications defining CF disease prior to CFTR modulator therapies, except for class III mutation group, as results already have shown. This is of great importance for objective validation of CFTR modulator effects on a population scale, or even evaluating the risk factors for low FEV_1 in people with CF on CFTR modulator therapy.

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