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ORIGINAL ARTICLE

Longitudinal association between lung function and health-related quality of life in cystic fibrosis

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ABSTRACT

Background Lung function is an important indicator of cystic fibrosis disease status and those with better forced expiratory volume in 1 s (FEV_1)% predicted have tended to report a better health-related quality of life (HRQoL) in cross-sectional studies. The relationship between lung function and HRQoL over time is unknown. This work assesses the natural progression of HRQoL reporting over many years and compares assessments across a whole decade and evaluates the relationship between lung function and HRQoL longitudinally.

Methods Demographic (age, gender), clinical (FEV_1% predicted, body mass index, diabetes, *Burkholderia cepacia* complex, intravenous access device and nutritional status) and HRQoL (Cystic Fibrosis Quality of Life Questionnaire) variables were obtained every 2 years over a 12-year period (seven time points from 1998 to 2010).

Results HRQoL and lung function declined slowly over time and significant decade changes were observed for FEV_1% predicted and the nine domains of the Cystic Fibrosis Quality of Life Questionnaire. The results of random coefficient modelling indicated that, at the population level, decreasing FEV_1% predicted was associated with decreasing HRQoL after adjusting for confounding variables. However, the percentage of patients for whom a decrease in lung function was associated with a decrease in HRQoL differed according to the quality of life domain.

Conclusions HRQoL and FEV_1% predicted decline slowly; nevertheless, a decrease in lung function predicted a decrease in HRQoL over time.

INTRODUCTION

Cystic fibrosis (CF) is the most common lethal autosomal recessive condition in the white population.[1] Improvements in care have led to median survival reaching the late 30s.[2] With increasing age, however, a high proportion of people develop diabetes mellitus and some patients develop a variety of complications including pneumothorax, haemoptysis and osteoporosis. The daily treatment regimen of chest physiotherapy, nutrition, exercise and oral, inhaled and intravenous medication is burdensome, complex and time-consuming. The progressive nature of CF disease and the demanding treatment burden[3 4] have the potential to encroach on daily living and to impact on the person's health-related quality of life (HRQoL). HRQoL measurement allows the inclusion of the patient's perspective in research and clinical practice.[5] The insights that patients have concerning their health and how they report these are important, given that aspects of HRQoL have been shown to be independent predictors of survival.[6]

Forced expiratory volume in 1 s (FEV_1) % predicted is an important indicator of disease status, and those with better lung function tend to report a better HRQoL. The most convincing data come from analyses of known groups undertaken during the evaluation of the CF-specific HRQoL instruments.[7–9] Differences between disease severity groups (mild: FEV_1% predicted ≥70%; moderate: FEV_1% predicted 40–69%; severe: FEV_1% predicted <40%) were observed across many HRQoL domains. Those with mild disease generally reported a better HRQoL than those with severe disease. However, studies have demonstrated weak to moderate correlations between HRQoL and lung function in children and adults,[7–12] with weaker correlations often found in studies employing generic rather than CF-specific scales. Even though FEV_1% predicted was positively associated with HRQoL domains in multivariate analyses, it accounted for only a small proportion of variability in HRQoL scores.[11–14] This cross-sectional work suggests that very large differences in FEV_1% predicted would be required to predict even modest differences in HRQoL scores.

HRQoL instruments are increasingly being used to evaluate the effectiveness of interventions and their use in routine clinical management has been shown to be feasible,[15] but there are scant data as to how HRQoL scores naturally vary over time. A few studies have assessed changes in HRQoL and lung function over 1–2 years. The most salient finding was the stability of HRQoL over this time and its independence from the course of FEV_1% predicted.[15 16] Similarly, data from the US Epidemiologic Study of Cystic Fibrosis showed that, over a 1-year period, changes in both clinical variables and HRQoL were small.[17]

The cross-sectional nature of most studies does not allow the assessment of cause and effect. The initial aim of this work was to provide the first true prospective longitudinal HRQoL data for CF, to assess the natural progression of HRQoL reporting over many years and to compare assessments across a whole decade. A further objective was to evaluate the relationship between HRQoL and lung function longitudinally and to address the question: 'Do HRQoL domains follow the trend of FEV_1% predicted?' Our hypothesis, based on previous work, was that HRQoL is independent of FEV_1% predicted.

METHODS

Subjects and procedure

All patients aged 16 years or older who attended a large Adult Cystic Fibrosis Centre in the UK were

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approached to take part in the study. Demographic, clinical and HRQoL variables were initially obtained during the patient's routine annual CF assessment. The centre followed standard treatment protocols and annual reviews were undertaken as close to the patient's birthday as possible, predominantly when the patient was clinically stable. They were followed-up every 2 years over a 12-year period (seven time points from 1998 to 2010). At each time point patients provided consent for their participation in accordance with ethical committee approval. The Cystic Fibrosis Quality of Life Questionnaire (CFQoL) was mailed out for completion prior to clinic appointments at which demographic and clinical variables were recorded. Not all patients entered the study at time point 1 (T1), but joined the study at later time points (T2–T7).

Measures

At each time point demographic, clinical and HRQoL variables were collected. Age and gender, FEV_1% predicted, body mass index (BMI), whether the person had diabetes, *Burkholderia cepacia* complex or an intravenous access device were recorded. Nutritional status (no oral calorie supplements, prescribed oral calorie supplements or prescribed enteral tube feeds) and lung transplantation were also documented. These variables describe the characteristics of the sample and include known predictors of decline in FEV_1% predicted.[18 19] They have also been shown to relate to HRQoL, but only in cross-sectional studies.[14 15 20–22]

Quality of life was measured using the CFQoL.[9] The CFQoL was developed and validated in the UK and was therefore the most appropriate CF-specific HRQoL measure for this UK sample. The instrument measures nine domains of functioning: Physical functioning, Social functioning, Emotional responses, Treatment issues, Chest symptoms, Body image, Interpersonal relationships, Career concerns and Concerns for the future. The psychometric properties of the instrument are good. Internal reliability of the domains was demonstrated using Cronbach's alpha coefficients (range 0.72–0.92, median 0.89) and item to total domain score correlations. Concurrent validity with three appropriate SF-36 domains (range r=0.64–0.74), known groups validity between different levels of disease severity, sensitivity across transient changes in health (effect size range, d=0.56–1.95) and test-retest reliability (r=0.74–0.96, median 0.91) were found to be robust.[9 10] Each domain has a minimum score of 0% and a maximum score of 100%, with higher scores reflecting a better quality of life.

Statistical analyses

Patient assessments were described by summary statistics. Long-term changes were summarised at time points separated by 10 years; mostly T2 and T7, otherwise T1 and T6. Long-term changes were tested for significance using t tests.

The longitudinal relationships between the nine domains of CFQoL and FEV_1% predicted were explored using regression models with fixed and random coefficients. These models are an established methodology in longitudinal studies[23 24] since they allow the observations on one individual to be explained by an individual regression coefficient which arises from a population of normally distributed coefficients across individuals. For each HRQoL domain, CFQoL=100 × S/N where S was the domain score and N was the maximum score. Maximum scores were: Physical functioning (50), Social functioning (20), Emotional responses (40), Treatment issues (15), Chest symptoms (20), Body image (15), Interpersonal relationships (50), Concerns for the future (30) and Career concerns (20). The relationship between CFQoL domain and FEV_1% predicted was adjusted for the confounding effects of age, gender, BMI, diabetes mellitus and nutritional status by including these variables in the models. Statistical analysis of HRQoL presents challenges because of the well-understood 'ceiling effects' for HRQoL measures which are limited above by 100%[25] and because domain scores are discrete measures only taking values corresponding to whole numbers. There is particular difficulty when the maximum score is low—for example, for Chest symptoms which can take only the values 100%, 95%, 90% etc.

Binomial regression with fixed and random coefficients was chosen as an appropriate analysis because the binomial is a discrete distribution for scores having a predetermined maximum. Binomial regression predicts within the range 0–100% because the covariates predict the logistic transformation of HRQoL, similar to logistic regression analysis. This approach was assessed initially by fitting binomial regression models for individual participants and then exploring the distribution of the coefficients, and the approach was found to be suitable. Models were fitted using the software MLwiN.[26]

The models estimated the means and variances of the random coefficients for FEV_1% predicted, BMI and the intercept. Gender, diabetes mellitus and nutritional status were included as fixed effects. Age was included as a fixed effect because age changes deterministically with time. The random coefficients were tested to check whether each should be retained as random or could be included as fixed.

The normal distribution for the random coefficient for FEV_1% predicted provided evidence of whether HRQoL was related to FEV_1% predicted longitudinally. If the mean of the normal distribution was significantly greater than zero, then the participant population showed overall a positive mean coefficient for the relationship between the CFQoL domain and FEV_1% predicted after adjusting for the confounding variables. A positive coefficient implied that a declining HRQoL domain was associated with declining FEV_1% predicted. The proportion of the participant population exhibiting a positive coefficient was estimated from the fitted normal distribution and 95% CIs were obtained by computer simulation.

Thus, the random coefficients approach permitted an informative answer to the question: 'Do CFQoL domains follow the trend of FEV_1% predicted?' The answer was both a 'yes' or 'no' for the whole cohort, and also an estimate of the proportion of patients with CF for whom the answer was in the affirmative.

RESULTS

Demographic and clinical characteristics of the sample for the seven time points are presented in table 1, together with the clinic total population size at each time point. A total of 234 patients entered the study. The numbers of time points at which patients were assessed are given in table 2. The length of time patients remained in the study (time between first and last assessment) are provided in table 3 together with the number of patients who died during the study period. The median age of death was 28 years (IQR 24–35). Patients with only one time point were still included in the analyses because this improved the estimation of the random intercept and hence contributed to the precision of the longitudinal coefficients.

Changes in FEV_1% predicted and CFQoL domains over a decade

The database contained 91 patients (40 men) with assessments separated by precisely 10 years. Table 4 presents the mean changes for age, clinical variables and CFQoL domains for men

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Table 1 Characteristics of the samples at each time point

Time points	T1	T2	T3	T4	T5	T6	T7
Sample size	**116**	**145**	**105**	**95**	**91**	**107**	**137**
Clinic population size	**220**	**245**	**285**	**286**	**315**	**336**	**355**
Men	45 (39%)	63 (43%)	45 (43%)	39 (41%)	33 (36%)	51 (48%)	61 (44%)
Women	71 (61%)	82 (57%)	60 (57%)	56 (59%)	58 (64%)	56 (52%)	76 (56%)
Age, mean (SD) [Range]	25.1 (6.7) [16–50]	24.7 (7.3) [14–51]	26.3 (7.8) [14–53]	28.6 (7.3) [16–51]	29.7 (8.1) [18–50]	31.6 (7.5) [20–55]	33.7 (7.8) [22–57]
FEV_1%, mean (SD) [Range]	58.5% (24.4) [14.0–133.0%]	59.6% (23.9) [12.0–128.0%]	60.8% (24.4) [16.0–128.0%]	59.6% (22.9) [20.0–113.0%]	57.0% (24.8) [16.0–109.0%]	57.3% (23.9) [14.0–119.0%]	56.9% (23.3) [14.0–114.0%]
Mild disease, N (%)	41 (35%)	55 (38%)	40 (38%)	30 (32%)	30 (33%)	32 (30%)	38 (28%)
Moderate disease, N (%)	42 (36%)	58 (40%)	39 (37%)	44 (46%)	32 (35%)	46 (43%)	63 (46%)
Severe disease, N (%)	33 (29%)	32 (22%)	26 (25%)	21 (22%)	29 (32%)	29 (27%)	36 (26%)
BMI, mean (SD) [Range]	21.4 (3.1) [15.6–30.2]	21.5 (2.9) [16.0–30.1]	21.9 (3.1) [15.1–33.1]	22.0 (2.7) [16.3–29.2]	22.0 (3.2) [13.3–33.7]	21.9 (3.2) [16.8–34.2]	21.3 (3.2) [16.1–33.8]
IV access device	47 (41%)	72 (50%)	50 (48%)	46 (48%)	51 (56%)	66 (62%)	85 (62%)
B cepacia complex	7 (6%)	13 (9%)	10 (10%)	10 (11%)	4 (4%)	10 (9%)	8 (6%)
CF-related diabetes	26 (22%)	49 (34%)	38 (36%)	32 (34%)	36 (40%)	49 (46%)	69 (50%)
Oral nutritional supplements	44 (38%)	45 (31%)	36 (34%)	25 (26%)	30 (33%)	37 (35%)	44 (32%)
Enteral tube feeds	24 (21%)	27 (19%)	10 (10%)	16 (17%)	9 (10%)	16 (15%)	26 (19%)
Post-transplant	11 (9%)	14 (10%)	12 (11%)	17 (18%)	14 (15%)	13 (12%)	18 (13%)

BMI, body mass index; CF, cystic fibrosis; FEV_1%, forced expiratory volume in 1 s; IV, intravenous.

and women over one decade. As a visual example, figures 1 and 2 illustrate the change in FEV_1% predicted and Chest symptoms for men and women, respectively, and for most patients the change is a decline. Significant decade changes were observed for FEV_1% predicted and the nine domains of the CFQoL, but not for BMI (men, p=0.087; women, p=0.305). There were no significant differences between men and women except for BMI (p=0.046), but the actual difference was small and not deemed clinically relevant.

Relationship between FEV_1% predicted and HRQoL over time

Table 5 presents the results of the random coefficient modelling. The FEV_1% predicted variance-covariance estimates were significant for all domains except Body image, and this confirmed that FEV_1% predicted was a random effect for all the domains except possibly for Body image. The FEV_1% predicted coefficient mean was positive and highly significantly different from zero for all domains except Body image. Hence, at the population level, decreasing FEV_1% predicted was associated with decreasing HRQoL even after adjusting for all the other confounding variables in the models.

The statistical analysis assumed patients had a personal coefficient of change in HRQoL with changing FEV_1% predicted. The analysis estimated the mean coefficient of the CF population together with the variability (variance) of the patients' coefficients; the method did not estimate individual patient coefficients and hence could not categorise individuals as those having a positive or negative coefficient. However, because the method estimated the statistical distribution of coefficients, it did allow for the computation of the percentage of patients for whom a decrease in lung function was associated with a decrease in HRQoL, and this percentage differed according to the HRQoL domain. For over 80% of adults, a decrease in lung function predicted a decrease in Chest symptom score. For approximately 70% of patients a decline in lung function predicted a decline in Physical functioning, Social functioning, Treatment issues, Emotional responses and Career concerns. This relationship held true for over 60% of patients for Concerns for the future and Interpersonal relationships. Hence, for all domains except Body image, the majority of patients showed a relationship between declining FEV_1% predicted and declining HRQoL in the longer term, indicating that HRQoL reporting followed the trend of FEV_1% predicted. Approximate CIs for the percentages are given in table 5.

DISCUSSION

This work provides the first longitudinal HRQoL data in CF that follows patients over many years, providing a natural progression of HRQoL reporting over time. Both FEV_1% predicted and HRQoL decline slowly and, contrary to our hypothesis, a decrease in lung function was associated with a decrease in HRQoL. The changes in lung function over a decade were representative of the UK population.[2 18] BMI remained constant, and this is attributed to the exceptional longstanding gastroenterology expertise within this centre.[27] The increase in CF-related diabetes (CFRD) over the decade is likely to reflect

Table 2 Number of times (time points) patients were assessed

Number of assessments	Number of patients
1	54
2	51
3	31
4	32
5	25
6	19
7	22
Total patients	234

Table 3 Number of years between first and last assessment and number of patients who died during the study

Years in study	Number of patients	Number of deaths
<2	54	27
2	22	10
4	24	5
6	14	3
8	18	4
10	38	1
12	64	0
Total patients	234	50

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Table 4 Change over one decade in age, body mass index (BMI), forced expiratory volume in 1 s (FEV_1)% predicted, diabetes mellitus, nutritional supplements, enteral feeding and the nine domains of the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) for 91 patients with cystic fibrosis (CF) in the cohort (40 men and 51 women) with assessments separated by 10 years*

	Start of decade		End of decade		Decade change	
Age (years), mean (SD)						
All	25.1	(7.5)	34.9	(7.6)	9.8	(0.5)
Men	24.5	(7.6)	34.3	(7.7)	9.8	(0.7)
Women	25.5	(7.5)	35.4	(7.5)	9.9	(0.3)
FEV_1%, mean (SD)						
All	61.9	(22.1)	53.1	(22.5)	−8.8	(18.3)
Men	65.9	(20.1)	55.3	(22.2)	−10.6	(13.4)
Women	58.7	(23.2)	51.4	(22.9)	−7.3	(21.4)
BMI, mean (SD)						
All	21.4	(2.8)	21.5	(2.9)	0.1	(1.7)
Men	21.6	(3.0)	22.1	(3.3)	0.5	(1.8)
Women	21.3	(2.7)	21.1	(2.5)	−0.2	(1.7)
Diabetes, n (%)						
All	31	(34)	52	(57)	21	(23)
Men	10	(25)	24	(60)	12	(35)
Women	21	(41)	28	(55)	7	(14)
Nutritional supplements, n (%)						
All	31	(34)	33	(36)	2	(2)
Men	20	(50)	17	(43)	−3	(−7)
Women	11	(22)	16	(31)	5	(9)
Enteral feeding, n (%)						
All	13	(14)	17	(19)	4	(5)
Men	5	(12)	8	(16)	3	(4)
Women	8	(16)	9	(18)	1	(2)
Physical functioning, mean (SD)						
All	86.8	(15.8)	78.8	(21.8)	−8.0	(16.7)
Men	89.3	(14.6)	81.7	(19.2)	−7.6	(13.7)
Women	84.9	(16.6)	76.5	(23.5)	−8.4	(18.9)
Social functioning, mean (SD)						
All	87.6	(16.4)	78.4	(26.2)	−9.2	(21.9)
Men	87.8	(17.6)	81.6	(21.8)	−6.2	(17.7)
Women	87.5	(15.5)	75.8	(29.1)	−11.7	(24.6)
Emotional responses, mean (SD)						
All	80.9	(20.5)	72.6	(23.1)	−8.3	(18.8)
Men	83.8	(21.5)	75.9	(21.4)	−7.9	(19.1)
Women	78.7	(19.6)	69.9	(24.3)	−8.8	(19.0)
Treatment issues, mean (SD)						
All	80.1	(20.6)	66.4	(22.0)	−13.7	(19.9)
Men	80.7	(24.4)	65.8	(21.8)	−14.9	(19.0)
Women	79.6	(17.4)	66.9	(22.4)	−12.7	(20.7)
Chest symptoms, mean (SD)						
All	79.9	(19.8)	70.5	(24.1)	−9.4	(18.9)
Men	81.4	(22.6)	71.6	(23.7)	−9.8	(15.6)
Women	78.7	(17.5)	69.6	(24.7)	−9.1	(22.1)
Body image, mean (SD)						
All	70.1	(23.0)	64.1	(26.1)	−6.0	(15.2)
Men	66.2	(24.2)	59.1	(26.9)	−7.1	(17.4)
Women	73.3	(21.8)	68.0	(25.0)	−5.3	(13.3)
Interpersonal relationships, mean (SD)						
All	64.5	(21.9)	57.7	(25.8)	−6.8	(22.0)
Men	69.0	(22.8)	61.8	(25.5)	−7.2	(22.7)
Women	60.9	(20.7)	54.5	(25.8)	−6.4	(21.6)
Career concerns, mean (SD)						
All	65.5	(26.4)	49.6	(32.5)	−15.9	(23.3)
Men	71.4	(25.4)	55.8	(32.5)	−15.6	(23.4)
Women	61.0	(26.6)	44.7	(31.9)	−16.3	(23.3)
Concerns for the future, mean (SD)						
All	49.4	(25.5)	36.2	(23.4)	−13.2	(21.2)
Men	56.4	(25.1)	42.0	(25.6)	−14.4	(21.1)
Women	43.9	(24.6)	31.7	(20.6)	−12.2	(21.4)

*The 91 patients comprised the 38 patients who had 10 years between first and last observations and 53 of the 64 patients who had 12 years between first and last observations (11 patients in the latter group were omitted because they did not have data separated by precisely 10 years).

the ageing of the cohort since there has been a decrease in CFRD in this centre.[2]

Although HRQoL declined slowly for young adults with CF, it is noteworthy that HRQoL population norms remain constant over a comparative age span.[28] With declining lung function it was not the physical aspects of HRQoL that decreased the most but the psychosocial domains of Career concerns, Concerns for the future and Treatment issues. This may be expected as treatment becomes more burdensome and employment and the future more uncertain with advancing CF disease. Interestingly, Physical functioning and Chest symptoms decreased by 8% and 9.4%, respectively, over a decade, a similar decrease to FEV_1% predicted. However, it would be an erroneous assumption to consider FEV_1% predicted a proxy for the clinical/physical HRQoL domains. HRQoL can provide 'added value' as it can supply information not captured by other outcomes. Indeed, the Physical functioning domain of the CFQoL is an independent predictor of survival[6] and, in a recent trial, only HRQoL provided additional information to lung function from several secondary endpoints.[29] It is also noteworthy that the standard deviations for FEV_1% predicted and the CFQoL domains are large so, although there was a similar percentage decrease at the population level, this was not necessarily true at the individual level.

The cross-sectional data from the literature suggested that large differences in lung function were required to predict differences in HRQoL.[11–14] There was also a lack of association reported over 12–18 month periods.[15–17] This is not surprising since decreases in FEV_1% predicted and HRQoL scores are approximately 1% per year and are highly variable across individuals, as evidenced in figures 1 and 2. It is noteworthy that similar short-term results were reported with the use of different HRQoL instruments.[15–17] Whether HRQoL instruments containing different domains yield similar long-term data

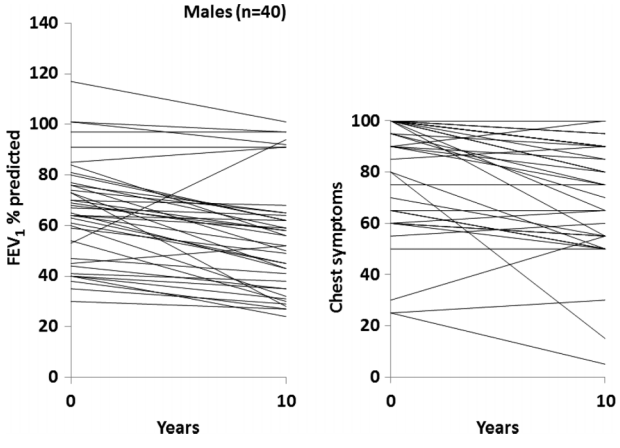

Figure 1 Change over one decade in forced expiratory volume in 1 s (FEV_1)% predicted and Chest symptoms for 40 men in the cohort.

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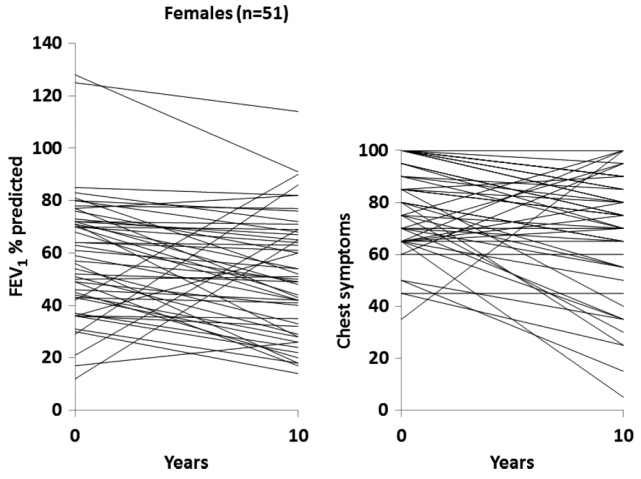

Figure 2 Change over one decade in forced expiratory volume in 1 s (FEV_1)% predicted and Chest symptoms for 51 women in the cohort.

remains to be evaluated. HRQoL changes in response to acute clinical situations are not explicitly considered here (eg, new symptoms or improvements expected with treatments), but knowing the natural rate of change in HRQoL domains provides a benchmark against which changes due to complications or interventions can be compared and should help to inform the clinical relevance of such data.

The decade changes (table 4) were for individuals who survived the decade, but the modelling of the relationship between HRQoL and FEV_1% predicted was carried out using all patients who entered the study. Some of these individuals died or dropped out during the 12 years, but their available data were still included in the analyses. HRQoL reporting followed the decreasing trend of FEV_1% predicted over time. However, the percentage of patients for whom a decrease in lung function was associated with a decrease in HRQoL differed according to the HRQoL domain. For 82% of adults a decrease in lung function was associated with a decrease in their Chest symptom score, whereas this relationship was true for only 58% of people concerning their Body image score. For a significant minority, a decrease in lung function seemed not to be associated with a decrease in HRQoL domains. What differentiates these patients is unknown, but is potentially very important as some individuals had a decrease in lung function but maintained a high level of HRQoL over time, indicating that they were psychologically resilient.[30] Understanding the determinants for sustaining a good HRQoL with advancing disease may help to ensure the best possible HRQoL for people with CF.

There is some evidence in the CF literature that the role of coping and mood may be important. Optimistic coping (focused, determined and optimistic beliefs about the future) and distraction coping (doing things to forget CF) emerged as significant predictors of how adults with CF report their HRQoL. Optimism was consistently associated with a superior quality of life while distraction was consistently associated with a poorer quality of life.[31] Conversely, depressive symptoms were associated with a poorer HRQoL across all CFQ domains.[32] Screening for and treating depression may improve HRQoL, and further robust studies using multivariate modelling are required to assess the impact of mood on HRQoL and clinical status. We await results from the International Depression and Anxiety Epidemiological Study to clarify these relationships.

Table 5 Estimated mean and variance for the random effect of forced expiratory volume in 1 s (FEV_1)% predicted on each domain of Cystic Fibrosis Quality of Life Questionnaire (CFQoL) together with estimated % of patients having a declining CFQoL domain with declining FEV_1% predicted.

Domain	FEV_1% predicted Estimate (SE)	p Value*	% of patients (95% CI)
Physical functioning			
Mean	0.0217 (0.0039)	<0.001	
Variance	0.0014 (0.0003)	<0.001	
			72 (64 to 81)
Social functioning			
Mean	0.0149 (0.0042)	<0.001	
Variance	0.0010 (0.0002)	<0.001	
			68 (58 to 79)
Emotional responses			
Mean	0.0130 (0.0033)	<0.001	
Variance	0.0008 (0.0002)	<0.001	
			68 (59 to 78)
Treatment issues			
Mean	0.0116 (0.0033)	<0.001	
Variance	0.0006 (0.0002)	0.002	
			68 (58 to 82)
Chest symptoms			
Mean	0.0205 (0.0032)	<0.001	
Variance	0.0005 (0.0001)	0.003	
			82 (73 to 91)
Body image			
Mean	0.0019 (0.0082)	0.877	
Variance	0.0001 (0.0001)	0.507	
			58 (39 to 87)
Interpersonal relationships			
Mean	0.0116 (0.0032)	<0.001	
Variance	0.0010 (0.0002)	<0.001	
			64 (57 to 73)
Career concerns			
Mean	0.0164 (0.0032)	<0.001	
Variance	0.0007 (0.0002)	<0.001	
			73 (64 to 84)
Concerns for the future			
Mean	0.0077 (0.0027)	0.044	
Variance	0.0005 (0.0001)	<0.001	
			64 (54 to 73)

*χ^2 test with 1 df for the mean but with 3 df for the variance since the variance was tested jointly with the covariance with the other two random effects in the model.

A limitation of the work is that it was a single-centre study. Nevertheless, this is the first reported longitudinal data set that has enabled the evaluation of population and individual level clinical and HRQoL changes over many years. Additionally, several variables now considered to be important because they increase the rate of decline in FEV_1% predicted were not collected. These included microbiological status (eg, *Pseudomonas aeruginosa*, MRSA and members of the *B cepacia* complex[18 33 34]) and the frequency of pulmonary exacerbations.[35] It is also possible that patients receiving more therapies report different trajectories in HRQoL. When undertaking longitudinal work in a disease that is changing (improving specialist centre care, treatment intensity and survival), it is difficult to predict the factors that will be important a decade later. However, if these variables contributed to an increased rate of decline in FEV_1% predicted, it does not invalidate these models as the focus is on the relationship between HRQoL and FEV_1% predicted. The more FEV_1% predicted declines (for whatever reason), the easier it becomes to detect the relationship between HRQoL and FEV_1% predicted.

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The future entry of HRQoL data into registries is important, although the usefulness and challenges of including HRQoL data in registries (eg, choice of HRQoL tool and domains, time interval, patient burden) requires consideration. Such data could provide evidence to support our conclusion that a decrease in lung function predicts a decrease in HRQoL over time.

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