Longitudinal impact of demographic and clinical variables on Health-Related Quality of Life in Cystic Fibrosis

Janice Abbott[1], Alison M Morton[3], Margaret A Hurley[2], Steven P Conway[3]

[1] School of Psychology and [2] School of Health, University of Central Lancashire, Preston, PR1 2HE, UK

[3]Adult Cystic Fibrosis Unit, St James' Hospital, Leeds, LS9 7TF, UK

Corresponding Author

Professor Janice Abbott

E-mail   jabbott@uclan.ac.uk

Phone +44 (0)1772 893790

ABSTRACT

Objectives: The insights that people with cystic fibrosis have concerning their health are important given that aspects of health-related quality of life (HRQoL) are independent predictors of survival and a decrease in lung function is associated with a decrease in HRQoL over time. Cross-sectional data suggest that key variables, other than lung function, are also associated with HRQoL - although study results are equivocal. This work evaluates the relationship between these key demographic and clinical variables and HRQoL longitudinally.

Design: Longitudinal observational study. Observations were obtained at seven time points: approximately every two years over a twelve year period.

Setting: Large Adult Cystic Fibrosis Centre in the UK.

Participants: 234 participants aged 14-48 years at recruitment.

Outcome measure: Nine domains of HRQoL (Cystic Fibrosis Quality of Life Questionnaire) in relation to demographic (age, gender) and clinical measures (FEV_1% predicted, BMI, cystic fibrosis related diabetes, *B. cepacia complex*, totally implantable vascular access device, nutritional and transplant status).

Results: A total of 770 patient assessments were obtained for 234 patients. The results of random coefficients modelling indicated that demographic and clinical variables were identified as being significant for HRQoL over time. In addition to lung function, transplant status, age, having a totally implantable vascular access device, cystic fibrosis related diabetes, BMI and *B. cepacia complex* impacted on many HRQoL domains longitudinally. Gender was important for the domain of Body image.

Conclusion: Demographic and changes in clinical variables were independently associated with a change in health-related quality of life over time. Compared with these longitudinal data, cross-sectional data are inadequate when evaluating the relationships between HRQoL domains and key demographic and clinical variables, as they fail to recognise the full impact of the CF disease trajectory and its treatments on quality of life.

Strengths and limitations of this study

- This work provides the first longitudinal data that evaluate the association between changes in clinical variables and HRQoL in cystic fibrosis.

- Participants were followed–up every two years over a twelve year period.

- These longitudinal data highlight the inadequacy of cross-sectional data which fail to recognise the full impact of the CF disease trajectory and its treatments on HRQoL.

- This was a single centre study

- Clinical variables that were not evaluated included the frequency of pulmonary exacerbations and microbiological status.

INTRODUCTION

Over the last three decades advances in the care of people with cystic fibrosis (CF) have led to the median age of survival increasing steadily, so that in 2014, median survival had reached 36.6 years in the UK.[1] Greater longevity is at a cost of life-long adherence to a complex and burdensome daily regimen of up to four hours per day,[2,3] which includes chest physiotherapy, daily enzyme replacement therapy, high-fat requirements, exercise and oral, inhaled and intravenous medication. With increasing age, patients may develop complications including CF related diabetes, allergic bronchopulmonary aspergillosis, atypical mycobacteria, osteoporosis and arthropathy. Despite the burdens that the disease and its treatments impose on them, people with CF are psychologically well-adjusted and generally report a good health-related quality of life (HRQoL) on many domains of generic and CF specific measures.[4-9] Understanding the determinants for sustaining a good HRQoL with advancing CF disease may assist in the development of interventions to improve it.

Cross-sectional studies have demonstrated that demographic and clinical variables appear to impact on life quality; with age,[4-5] gender,[5-7] lung transplant status and FEV_1[7-9] most consistently associated with HRQoL. However, while important associations were identified, much of the variation in HRQoL remained unexplained[4,8,10,11] and causal relationships could not be ascertained. Although authors acknowledge that longitudinal work is required to understand these relationships, this is rarely undertaken and assumptions are simply extrapolated from cross-sectional data. Over one or two years there is little change in HRQoL at the population level.[12-14] Recently, two studies have linked HRQoL reporting over many years with clinical outcomes in CF. Patient-reported physical function has been shown to be an independent predictor of survival in CF[15] and recent longitudinal work has demonstrated that, over a decade, both FEV_1% predicted and HRQoL domains declined slowly, with a decrease in lung function being associated with a decrease in HRQoL domains.[16]

In addition to lung function, cross-sectional data suggest that other key demographic and clinical variables are associated with HRQoL. This work aims to evaluate the relationship between these variables and HRQoL longitudinally.

METHODS

Subjects and procedure

All patients who attended a large Adult Cystic Fibrosis Centre in the UK were approached to take part in the study. The Centre followed standard treatment protocols and annual reviews were undertaken as close to the patient's birthday as possible, predominantly when they were clinically stable. The CFQoL[17] was mailed out every two years for completion prior to their clinic visit at which demographic and clinical variables were recorded. People with CF were followed–up, at approximately two yearly intervals, for twelve years. There were seven assessments (time points T1-T7 from 1998 to 2010). At each time point patients provided consent for their participation in accordance with ethical committee approval.

Measures

At each time point demographic, clinical and HRQoL variables were collected. Age, gender, FEV_1% predicted, BMI, and whether the person had cystic fibrosis related diabetes (CFRD), *B. cepacia complex* or a totally implantable vascular access device (TIVAD) were recorded. Nutritional status (no oral calorie supplements, prescribed oral calorie supplements or prescribed enteral tube feeds) and lung transplantation (listed or received transplant) were also documented.

Quality of Life was measured using the Cystic Fibrosis Quality of Life Questionnaire (CFQoL).[17] 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. 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

The modelling was carried out using all patients who entered the study. Not all patients entered the study at time point one (T1), but joined the study at later time points (T2 to T7). Some patients died or dropped out during the twelve years, but their available data were still included in the analyses. Hence, the analyses were not based only on survivors.

Patient characteristics at all the times combined were described by summary statistics. The longitudinal relationships between the nine domains of CFQoL and the eleven variables recording patient characteristics were modelled using regression models with fixed and random coefficients. Random coefficients allowed the observations on an individual patient to be predicted by an individual random coefficient which was assumed to be sampled from a population of normally distributed coefficients across individuals. This type of modelling has been used frequently for longitudinal studies.[18,19] For each CFQoL domain; $CFQoL = 100 \times S/N$ where S was the domain score and N was the maximum domain score. Maximum scores for the domains were: Physical functioning [50], Social functioning [20], Emotional responses [40], Treatment issues [15], Chest symptoms [20], Body image [15], Interpersonal relationships [50], Career concerns [20] and Concerns for the future [30]. Statistical analysis of HRQoL is challenging because of the 'ceiling effects' for all HRQoL scales which have a maximum of 100% [20] and because domain scores (S) are discrete measures that only have values which

correspond to whole numbers; for example with Social functioning N is 20 and so Social functioning can take only the values 100%, 95%, 90% etc.

Therefore, binomial regression with fixed and random coefficients was chosen as a suitable modelling framework because the binomial is a discrete distribution for a score (S) that has a prescribed maximum (N). Binomial regression predicts within the range 0% to 100% because the model predicts the logit transformation of HRQoL (CFQoL on the logit scale), analogous to logistic regression. Models were fitted using the software MLwiN.[21]

The models estimated the means, variances and covariances of the random coefficients for the quantitative covariates $FEV_1\%$ predicted, BMI and the model intercept. The categorical predictors of gender, CFRD, nutritional status (oral supplements and tube feeding), TIVAD, *B. cepacia complex*, and transplant status (listed for or received transplant) were included as fixed effects. Age, although quantitative, was included as a fixed effect because age changes deterministically with time. The random coefficients were tested statistically to determine whether each should be retained as a random coefficient or could be included as fixed. For each CFQoL domain the maximal model was fitted which included all eleven patient variables and a variable was judged as having a significant association with a CFQoL domain if the P-value for the variable in the maximal model was less than 0.1(10% significance). This significance level was chosen because it is conventionally used for retaining terms in a multiple regression analysis with many variables. For the random coefficients the P-value for the coefficient mean was used and for the fixed effects the P-value of the fixed coefficient was used to determine significance. For each variable in the maximal model, the coefficients were used to calculate the typical change in HRQoL (%) from an initial value of HRQoL. The initial HRQoL(%) was transformed to the logit scale, the coefficient was applied and then the result was transformed back to the HRQoL scale. Initial HRQoL in the range 20% to 80% was used and the greatest and smallest changes in HRQoL were recorded.

RESULTS

The intention was to follow individuals every two years but, on occasion, some patients failed to attend annual review or participate in the study, or had died. Therefore, Table 1 presents the number of patients who participated for each total number of study time points (T1-T7) and the consequent number of patient assessments which the clinic visits contributed to the longitudinal data. A total of 770 completed patient assessments were obtained for 234 patients. The median number of completed patient assessments was 3 with interquartile range 2 to 5 assessments.

Table 1 Numbers of patients and patient assessments.

Number of time-points per patient	Number of patients	Number of patient assessments
1	54	54
2	51	102
3	31	93
4	32	128
5	25	125
6	19	114
7	22	154
Total	234	770

The demographic, clinical characteristics and HRQoL measures recorded at all the assessments combined are shown in Table 2. For the categorical variables, the percentage of assessments at which the patients had CFRD, oral supplements etc. are provided. For the quantitative variables such as age, the mean, standard deviation and range are shown.

Table 2 Characteristics of the patient assessments.

	N (%)	Range	Mean (SD)
Total patient assessments	770 (100.0%)		
Female patient	445 (57.8%)		
Oral supplements taken	254 (33.0%)		
Enteral tube feeds taken	122 (15.8%)		
CFRD present	287 (37.3%)		
TIVAD fitted	402 (52.2%)		
B. cepacia complex present	58 (7.5%)		
Listed for transplant	35 (4.5%)		
Received transplant	97 (12.6%)		
Ages (years)		14 - 57	28.5 (8.2)
FEV_1% predicted		12 -133	58.3 (23.8)
BMI		15 - 34	21.8 (3.1)
Physical functioning		2 - 100	83.0 (20.5)
Social functioning		0 - 100	84.7 (21.5)
Emotional responses		8 - 100	78.6 (20.6)
Treatment issues		0 - 100	74.7 (22.5)
Chest symptoms		0 - 100	76.6 (23.2)
Body image		0 - 100	69.8 (24.7)
Interpersonal relationships		2 - 100	64.5 (22.4)
Career concerns		0 - 100	61.7 (29.4)
Concerns for the future		0 - 100	45.0 (25.1)

Longitudinal relationships between HRQoL and demographic and clinical variables

Each model for a domain of HRQoL included all demographic and clinical variables and the model coefficients are shown by variable in Figures 1 and 2. Demographic and clinical variables which were significant at the 10% level were extracted and are presented in Table 3 by HRQoL domain. The coefficients for age and FEV_1% predicted were scaled (5 years increase and 10% decrease respectively) to provide clinically meaning change since HRQoL changes slowly for these variables. In cross-sectional work, predominantly FEV_1% predicted and transplant status were significantly associated with HRQoL[7-9]. Longitudinally, in addition to lung function and transplant status, age, having a TIVAD, CFRD, BMI and *B. cepacia complex* were important for more than half of the HRQoL domains.

Table 3 Variables significant at the 10% level in the multiple regression models together with adjusted coefficients, standard errors and significance levels.

Domain	Coefficient (SE)	P-value	Domain	Coefficient (SE)	P-value
Physical functioning			**Social functioning**		
Age (5y increase)	-0.10 (0.03)	<0.001	Age (5y increase)	-0.11 (0.04)	0.008
BMI (1 unit decrease)	-0.10 (0.04)	0.007	CFRD	-0.28 (0.11)	0.015
TIVAD	-0.34 (0.08)	<0.001	BMI (1 unit decrease)	-0.07 (0.04)	0.078
B. cepacia complex	-0.36 (0.18)	0.053	*B. cepacia complex*	-0.65 (0.25)	0.008
$FEV_1\%$ (10% decrease)	-0.20 (0.04)	<0.001	$FEV_1\%$ (10% decrease)	-0.13 (0.05)	0.004
Listed for transplant	-0.37 (0.11)	<0.001	Listed for transplant	-0.45 (0.15)	0.004
			Received transplant	-0.73 (0.27)	0.007
Emotional responses			**Treatment issues**		
Age (5y increase)	-0.19 (0.03)	<0.001	Age (5y increase)	-0.18 (0.03)	<0.001
CFRD	-0.16 (0.08)	0.032	BMI (1 unit decrease)	-0.09 (0.02)	<0.001
TIVAD	-0.13 (0.07)	0.087	Oral supplements	-0.19 (0.10)	0.068
$FEV_1\%$ (10% decrease)	-0.11 (0.03)	<0.001	TIVAD	-0.36 (0.09)	<0.001
Listed for transplant	-0.35 (0.11)	0.002	*B. cepacia complex*	-0.39 (0.20)	0.045
			$FEV_1\%$ (10% decrease)	-0.06 (0.03)	0.078
			Listed for transplant	-0.35 (0.15)	0.019
			Received transplant	0.67 (0.21)	0.001
Chest symptoms			**Body image**		
Age (5y increase)	-0.07 (0.03)	0.054	Female	0.58 (0.13)	<0.001
CFRD	-0.21 (0.10)	0.027	CFRD	-0.22 (0.09)	0.013
BMI (1 unit decrease)	-0.10 (0.03)	0.001	BMI (1 unit decrease)	-0.15 (0.02)	<0.001
TIVAD	-0.35 (0.09)	<0.001	Enteral tube feeds	-0.24 (0.13)	0.069
B. cepacia complex	-0.48 (0.19)	0.013	TIVAD	-0.30 (0.09)	0.001
$FEV_1\%$ (10% decrease)	0.17 (0.03)	<0.001	*B. cepacia complex*	-0.57 (0.18)	0.002
Listed for transplant	-0.41 (0.13)	0.002	Received transplant	-0.39 (0.17)	0.022
Received transplant	0.79 (0.21)	<0.001			
Interpersonal relationships			**Career concerns**		
Age (5y increase)	-0.08 (0.02)	<0.001	Age (5y increase)	-0.15 (0.03)	<0.001
CFRD	-0.11 (0.06)	0.081	TIVAD	-0.46 (0.08)	<0.001
Oral supplements	0.11 (0.06)	0.081	$FEV_1\%$ (10% decrease)	-0.16 (0.03)	<0.001
TIVAD	-0.16 (0.06)	0.011	Listed for transplant	-0.31 (0.14)	0.019
$FEV_1\%$ (10% decrease)	-0.10 (0.03)	0.001	Received transplant	-0.71 (0.19)	<0.001
Concerns for the future					
Age (5y increase)	-0.19 (0.03)	<0.001			
Female	-0.26 (0.13)	0.057			
BMI (1 unit decrease)	-0.06 (0.02)	0.010			
TIVAD	-0.22 (0.07)	0.001			
Listed for transplant	-0.37 (0.12)	0.002			
Received transplant	0.41 (0.17)	0.015			

The coefficients presented in Table 3 and Figures 1 and 2 apply to the logit scale (as described in the method section). This has the consequence that the actual change in HRQoL depends

on the initial reported value of HRQoL before the change. To aid interpretation, Table 4 shows the typical change in HRQoL domains for initial values in the range of 20%-80%. For age (5 year increase), BMI (1 unit decrease), FEV_1% predicted (10% decrease), oral supplements and enteral tube feeds, small changes, generally less than 5% were predicted. Having CFRD, TIVAD, *B. cepacia complex* and being listed for lung transplant predicted greater decrements across HRQoL domains. The largest changes in HRQoL were associated with having received a lung transplant; large increases in HRQoL occurred for Treatment issues, Chest symptoms, Concerns for the future and Emotional responses. Conversely, receiving a transplant predicted large decreases in Social functioning, Career concerns and Body image.

Table 4 Predicted typical change in domain specific HRQoL (%) from an initial HRQoL in the range 20% to 80%. The change is a decrease unless otherwise indicated by *.

Domain	Age 5y increase	BMI 1 unit decrease	FEV_1% 10% decrease	CFRD	TIVAD
Physical functioning	1.5 – 2.5	1.5 – 2.4	3.0 – 4.9	1.1 – 1.7	4.9 – 8.4
Social functioning	1.7 – 2.8	1.2 – 1.8	2.0 – 3.3	2.2 – 6.9	1.7 – 2.8
Emotional responses	2.8 – 4.6	0.7 – 1.1	1.7 – 2.7	2.5 – 4.1	2.0 – 3.2
Treatment issues	2.8 – 4.6	1.4 – 2.2	0.9 – 1.9	1.8 – 2.9	5.2 – 9.0
Chest symptoms	1.0 – 1.6	1.5 – 2.4	2.6 – 4.2	3.2 – 5.3	5.0 – 8.5
Body image	0.1 – 0.2	2.3 – 3.8	0.1 – 0.2	3.3 – 5.6	4.3 – 7.3
Interpersonal relationships	1.3 – 2.0	0.1 – 0.1	1.6 – 2.6	1.7 – 2.8	2.4 – 3.9
Career concerns	2.2 – 3.6	0.6 – 0.9	2.4 – 3.9	0.8 – 1.2	6.4 – 11.5
Concerns for the future	2.8 – 4.6	0.9 – 1.4	0.6 – 0.9	1.2 – 1.8*	3.3 – 5.5
	Oral supplements	Enteral tube feeds	*B. cepacia complex*	Listed for transplant	Received transplant
Physical functioning	0.9 – 1.4	1.8 – 2.7*	5.1 – 8.8	5.3 – 9.2	4.2 – 7.1
Social functioning	1.5 – 2.3	2.2 – 3.5	8.5 – 16.1§	6.2 – 11.1	9.2 – 18.0
Emotional responses	1.4 – 2.2	0.6 – 1.0	3.6 – 6.0	5.0 – 8.6	5.2 – 7.4*
Treatment issues	2.8 – 4.7	2.3 – 3.7	5.6 – 9.7	5.0 – 8.7	12.9 – 16.6*
Chest symptoms	1.7 – 2.7	1.3 – 2.0*	6.6 – 11.8	5.7 – 10.0	15.4 – 19.4*
Body image	1.1 – 1.7	3.6 – 6.0	7.6 – 14.0	0.7 – 1.1	5.5 – 9.7
Interpersonal relationships	1.8 – 2.8*	2.4 – 3.5*	0.2 – 0.3	1.7 – 2.7	0.2 – 0.3
Career concerns	0.6 – 0.9	1.8 – 3.0	0.7 – 1.0*	4.6 – 7.9	9.0 – 17.5
Concerns for the future	0.0 – 0.1*	2.0 – 3.2	1.9 – 3.2	5.3 – 9.2	7.3 – 10.1*

§Interpretation of table values: With colonisation with *B. cepacia* complex, Social functioning% is expected to decline by between 8.5 and 16.1 points depending on the Social functioning% domain score before colonisation.

DISCUSSION

This is a longitudinal observational study and, as such, it has the advantage over a cross-sectional study of being able to determine temporality. For this reason, it is justifiable to interpret demographic and clinical changes as having impact on HRQoL. Hence, this work has demonstrated that the demands created by the CF disease trajectory and its treatments profoundly impact all aspects of a person's quality of life. Demographic and clinical measures in CF are highly inter-related and the need to separate out the individual effects of these measures on patient HRQoL presents a considerable challenge. The modelling approach taken here has responded well to this challenge and has provided fundamental insight into the way in which changes in these measures impact on HRQoL.

In contrast to previous cross-sectional work, a greater number of demographic and clinical variables were identified as impacting HRQoL over time. This longitudinal work confirms the cross-sectional findings that advancing age, lung function and transplantation are important predictors of outcome across many domains of life quality. Variables which did not consistently emerge as important in cross-sectional regression models have also now been shown to be independent predictors of HRQoL longitudinally. These include BMI, having a totally implantable vascular access device, cystic fibrosis related diabetes and *B. cepacia complex.*

We have recently reported data that assessed the natural progression of HRQoL reporting in cystic fibrosis over many years.[16] Patient-reported HRQOL declines slowly over time at approximately 1% per year. Over a decade, population score decline was different for each CFQoL domain (Physical function -8.0, Social function -9.2, Emotional response -8.3, Treatment issues -13.7, Chest symptoms -9.4, Body image -6.0, Interpersonal relationships -6.8, Career concerns-15.9, Future concerns -13.2). Knowing the natural rate of change in HRQoL domains provides a benchmark against which changes due to CF complications or interventions can be compared and should help to inform the clinical relevance of HRQoL changes.

Previous work demonstrated that both $FEV_1\%$ predicted and HRQoL declined slowly, however, a decrease in lung function was associated with a decrease in HRQoL over time.[16] $FEV_1\%$ predicted was significantly associated with all domains of HRQoL except Body image and these analyses have substantially supported that finding. Previously, it was reported that $FEV_1\%$ declines on average by 8.8% and that Physical functioning declines on average by 8.0% for survivors over one decade. This accords with the results shown here which indicate that a decade increase in age alone was associated with a 3.0 to 5.0% decline in Physical functioning. Additionally an 8.8% decline in $FEV_1\%$ was associated with a 2.6 to 4.3% decline in physical functioning producing a total decline of between 5.6 to 9.3% in physical functioning; any small differences being due to the increased risk of change in clinical condition such as the onset of CFRD.

An improvement in HRQoL is a compelling argument for lung transplantation.[22,23] Those in need of transplantation report restrictions on most aspect of their HRQoL.[24,25] Generally, CF lung transplant recipients have been reported to have good outcomes with high levels of life quality in some HRQoL domains.[26-28] However, longitudinal data comparing pre and post transplantation is lacking. The current modelling estimated the effect of undergoing a lung transplant on HRQoL by evaluating the change between the mean pre and post transplantation values. As expected, being listed for transplant predicted a profoundly negative impact on HRQoL. However, following transplantation only the domains of Treatment issues, Chest symptoms, Emotional functioning and Concerns for the future were radically improved. Transplant was associated with continuing poor HRQoL for Physical functioning, and a considerable further deterioration in Social functioning, Career concerns and perceived Body image. This highlights the importance of monitoring HRQoL over time.

Cross-sectional work highlighted a complex relationship between BMI, Body image and gender.[4] These longitudinal data have clarified this matter. Females typically report a better body image than males[4-7,29] and this association was confirmed from these longitudinal data. The model coefficient for gender for Body image was 0.58 (p<0.001) showing that females

had a significantly higher Body image than males over time. However, the model coefficient for Body image for a one unit decrease in BMI was -0.154 for males and females combined (-0.159 for males and -0.162 for females separately), so although females have a higher level of Body image, a decrease of one unit BMI results in the same decrease in perceived Body image for both males and females. Previous work had indicated that both males and females receiving nutritional interventions generally desired to be heavier, although females still only desired a BMI of 19.[29] When BMI falls below what is desired, Body image HRQoL decreases for both genders. There was little negative impact on HRQoL as a result of nutritional interventions over time (oral nutritional supplements and enteral tube feeding), suggesting that the interventions to maintain BMI were successful. The single exception to this was the association between enteral tube feeds and Body image.

Totally implantable vascular access devices (TIVADs) have emerged as an effective means for intermittent venous access for therapeutic infusions[30] nevertheless; having an access device predicted a poorer HRQoL for virtually all HRQoL domains over time. The reasons for this are unclear and we did not collect data on complication rates or the nature of complications. TIVADs provide the opportunity and social benefits of home intravenous therapy but Body image issues and the interference with daily activities (e.g. car seatbelts, engaging in sport)[31] remain a continuing concern.

CFRD is considered to be a condition in its own right. It is associated with a decrease in Social functioning, Chest symptoms, Body image and Emotional responses; although it is surprising that it does not predict a greater decline across HRQoL domains longitudinally. While it does not lessen the impact CFRD has on HRQoL, it is noteworthy that diabetes in people with CF has been shown to have a less negative impact on HRQoL than in those with Type 1 diabetes mellitus (T1DM). Both groups experienced hypoglycaemia, but loss of consciousness or needing help was more common in T1DM patients and symptoms suggestive of hypoglycaemia were less of a problem for CFRD patients in terms of severity, with T1DM patients having more neuroglycopenic symptoms.[32]

B. cepacia complex had an immense negative impact on Social functioning and Body image, together with a considerable decline in Chest symptoms, Treatment issues and Physical functioning. This may be anticipated as during the collection of these data patients with *B.* cepacia complex were segregated at clinic, on wards and at scientific meetings.[33] People with CF are aware of the associated increase in morbidity and mortality and the knowledge of colonisation with the bacteria brings further uncertainty about the future. Hence, one minor limitation of this study is that it commenced prior to the routine clinical classification of genomovar status, although this alone cannot predict clinical outcome in any individual patient.[34]

Further limitations are that this was a single Centre study and several important variables were not evaluated, including the frequency of pulmonary exacerbations[35] and microbiological status (Pseudomonas aeruginosa*, B.* cepacia complex*,* genomovar classification, Allergic Broncho Pulmonary Aspergillosis). The longitudinal data analysis showed that many more demographical and clinical variables were associated with HRQoL than in cross-sectional work. This was achieved by estimating coefficients that measured the different average level of HRQoL between all data recorded before and all data recorded after a change in a clinical variable. A limitation of this analysis was that it did not estimate HRQoL in relation to the time since the change occurred. So, for example, transplantation may have resulted in a relatively large decrease in a HRQoL domain for the first few years followed by recovery in the HRQoL subsequently. A more sophisticated analysis would be required to determine any such pattern.

The long-term determinants of life quality are becoming clearer and repeated HRQoL assessments should be able to provide useful information concerning the individual's adaptation to the disease and be used to improve the care delivered to patients. HRQoL measurement in CF remains largely a research endeavour, although monitoring HRQoL in routine clinical care has been shown to be feasible.[12] Web-based completion of HRQoL scales may allow screening and the detection of problems, the monitoring of patient's difficulties over

time, and improving clinician – patient communication by addressing these issues during a clinical consultation. Additionally, the input of these data into registries should enable robust evaluations of HRQoL over time and allow further evaluation of patient-reported outcomes in predicting morbidity and survival. The challenge for the future is to use the available information when designing and interpreting the results of studies, and to develop and evaluate psychological interventions that could improve HRQoL, or mitigate the effects of interventions known to impact adversely on HRQoL, for people with CF.

Contributors

JA: conception and design, analysis and interpretation of data, drafting, revising and final approval of the article. AMM: conception and design, acquisition of data, critical revision and final approval of the article. MAH: analysis and interpretation of data, drafting, revising and final approval of the article. SPC: conception and design, interpretation of data, critical revision and final approval of the article.

Competing Interests

None. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval

Ethics approval was obtained from Leeds research ethics committee and the University of Central Lancashire Ethics Committee.

**Data sharing statement**

No additional data are available

REFERENCES

1.   UK Cystic Fibrosis Registry. Annual Data Report 2013. Cystic Fibrosis Trust 2014.

2.   Sawicki GS, Sellers DE, Robinson WM. High Treatment Burden in Adults with Cystic Fibrosis: Challenges to Disease Self-Management. *J Cyst Fibros* 2009;8:91-96.

3.   Sawicki GS, Tiddens H. Managing treatment complexity in cystic fibrosis: challenges and opportunities. *Pediatr Pulmonol* 2012;47:523-33

4.   Gee L, Abbott J, Hart A, *et al*. Associations between clinical variables and quality of life in adults with cystic fibrosis. *J Cyst Fibros* 2005;4:59-66.

5.   Schmitz TG, Henrich G, Goldbeck L. Quality of life with cystic fibrosis – aspects of age and gender. *Klinische Padiatrie* 2006;218:7-12.

6.   Arrington-Sanders R, Yi MS, Tsevat J, Wilmott RW, Mrus JM, Britto MT.   Gender differences in health-related quality of life of adolescents with cystic fibrosis. *Health and Quality of Life Outcome* 2006;4:5. http://www.hqlo.com/content/4/1/5

7.   Gee L, Abbott J, Conway SP, *et al*. Quality of life in cystic fibrosis: the impact of gender, general health perceptions and disease severity. *J Cyst Fibros* 2003;2:206-213.

8.   Wahl AK, Rustoen T, Hanestad BR, *et al*. Living with cystic fibrosis: Impact on global quality of life. *Heart and Lung* 2005;34:324-331.

9.   Quittner A, Buu A, Messer M, *et al*. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005;128:2347-2354.

10.   Staab D, Wenninger K, Gerbert N, *et al*. Quality of life in patients with cystic fibrosis and their parents; what is important besides disease severity. *Thorax* 1998;53:727-731.

11.   Bradley J, McAlister O, Elborn S. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis. *Eur Respir J* 2001;17:712-715.

12.   Goldbeck L, Zerrer S, Schmitz TG. Monitoring quality of life in outpatients with cystic fibrosis: Feasibility and longitudinal results *J Cyst Fibros* 2007;6:171-178.

13.   Sawicki GS, Rasouliyan L, McMullen AH, *et al.*   Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. *Pediatr Pulmonol* 2011;46:36-44.

14.   Dill EJ, Dawson R, Sellers DE, *et al.* Longitudinal trends in health-related quality of life in adults with cystic fibrosis. *Chest.* 2013 Sep;144(3):981-989.

15.   Abbott J, Hart A, Morton AM, *et al.* Can health-related quality of life predict survival in adults with cystic fibrosis. *Am J Resp Crit Care Med* 2009;179:54-58.

16.   Abbott J, Hurley MA, Morton AM, *et al.* Longitudinal Association between Lung Function and Health-Related Quality of Life in Cystic Fibrosis. *Thorax* 2013;68:149–154.

17.   Gee L, Abbott J, Conway S, *et al.* Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. *Thorax* 2000;55:946-954.

18.   Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis., 2nd Edition 2011 Wiley Series in probability, New Jersey.

19.   Kreft I, De Leeuw, J. Introducing multilevel modelling. 1998 Sage Publications, London.

20.   Walters SJ. Quality of Life Outcomes in Clinical Trials and Health Care Evaluation: A practical guide to health care interpretation. 2009, Wiley, Chichester.

21.   Rasbash J, Charlton C, Browne WJ, *et al.*   MLwiN Version 2.1. Centre for Multilevel Modelling, 2009 University of Bristol.

22.   Spahr JE, Love RB, Francois M, *et al* Lung transplantation for cystic fibrosis: Current concepts and one center's experience. *J Cyst Fibros* 2007;6:334-350.

23.   Quattrucci S, Rolla M, Cimino G, *et al.* Lung transplant for cystic fibrosis : 6-year follow-up. *J Cyst Fibros* 2005;4:107-114.

24.   Feltrim MIZ, Rozanski A, Borges ACS, *et al.* The quality of life of patients on the lung transplantation waiting list. *Transplantation proceedings* 2008;40:819-821.

25.   Taylor JL, Smith PJ, Babyak MA *et al.* Coping and quality of life in patients awaiting lung transplantation. *J Psychsom Res* 2008;64:71-79.

26.   Kugler C, Fischer S, Gottlieb J *et al*. Health-related quality of life in two hundred-eighty lung transplant recipients. *J Heart Lung Transplant* 2005;24:2262-2268.

27.   Smeritschnig B, Jaksch P, Kocher A, *et al*. Quality of life after lung transplantation: a cross-sectional study. *Heart Lung Transplant* 2005;24:474-480.

28.   Ullrich G, Jaensch H, Niedermeyer J. Quality of life in young adults after lung transplantation: Only a matter of improved performance? *Transplant Med* 2004;16:202-202.

29.   Abbott J, Conway S, Etherington C, *et al*. Nutritional status, perceived body image and eating behaviours in adults with cystic fibrosis. *Clinical Nutrition* 2007;26:91-99.

30.   A-Rahman AKM, Spencer D. Totally implantable vascular access devices for cystic fibrosis. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004111. DOI: 10.1002/14651858.CD004111.

31.   Rodgers HC, Liddle K, Nixon SJ, *et al*. Totally implantable venous access devices in cystic fibrosis: complications and patients' opinions. *Eur Respir J* 1998;12:217–220

32.   Tierney S, Deaton C, Webb K, *et al*. Living with cystic fibrosis-related diabetes or type 1 diabetes mellitus: a comparative study exploring health-related quality of life and patients' reported experiences of hypoglycaemia. *Chronic Illness* 2008;4:278-288

33.   Duff AJA. Psychological consequences of segregation resulting from chronic Burkholderia cepacia infection in adults with cystic fibrosis. *Thorax* 2002;57:756-758.

34.   Lowton, K. Gabe J. Cystic fibrosis adults' perception and management of the risk of infection with Burkholderia cepacia complex. *Health, Risk and Society* 2006;8:395-415.

35.   Bradley JM, Blume SW, Balp MM, *et al*. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *Eur Respir J* 2013;41:571-577.

Figure 1. Coefficients from the multilevel models for six demographic and clinical variables. The limits show plus and minus one standard error. Coefficients are not significant (blue bars), significant at the 10% level (yellow bars) and significant at the 5% level (red bars).
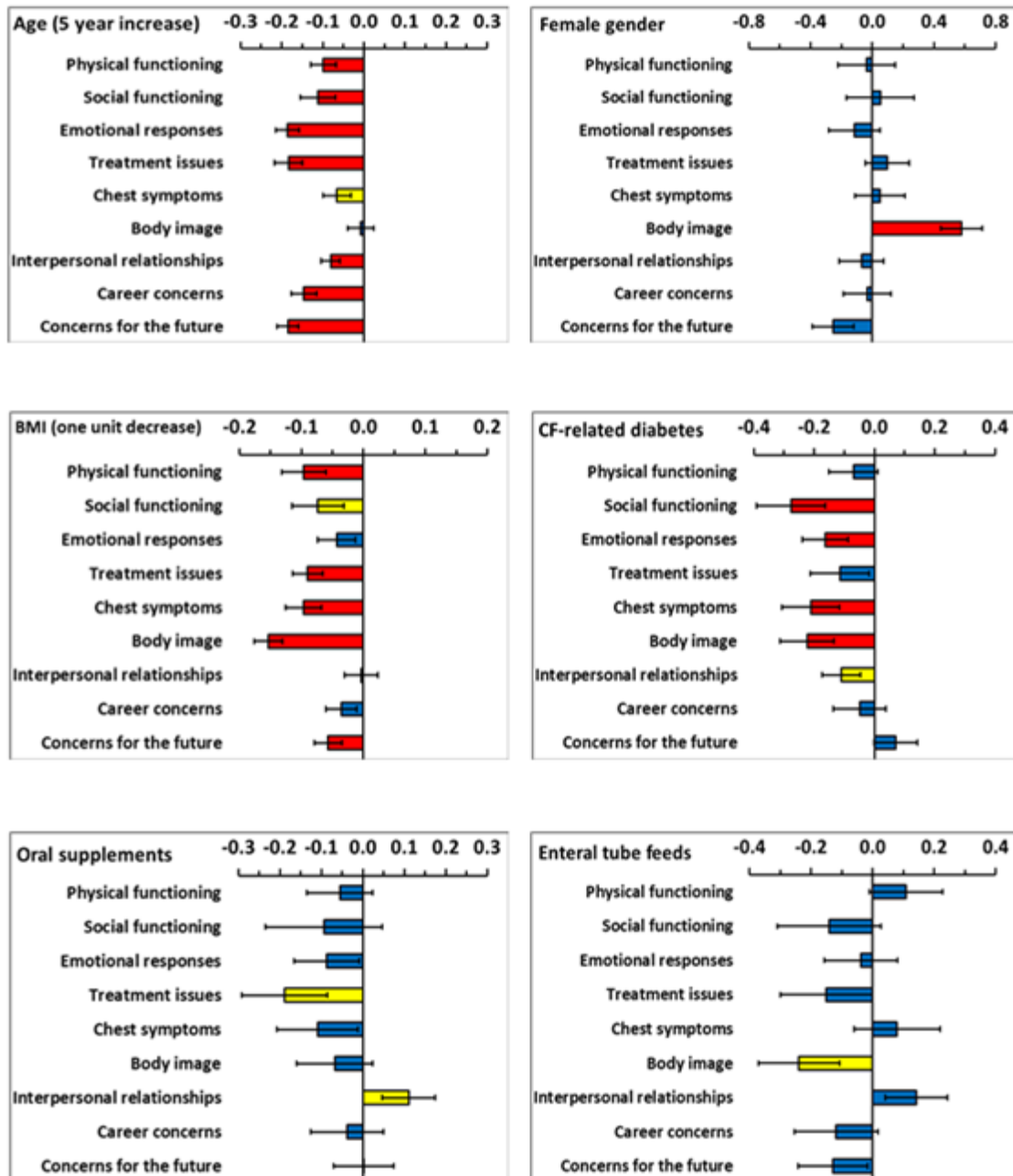
Figure 2. Coefficients from the multilevel models for five demographic and clinical variables. The limits show plus and minus one standard error. Coefficients are not significant (blue bars), significant at the 10% level (yellow bars) and significant at the 5% level (red bars).