A Systematic Review of Factors Associated with Health-Related Quality of Life in Adolescents and Adults with Cystic Fibrosis

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Abstract

Rationale: As the life expectancy for individuals with cystic fibrosis (CF) continues to improve, an emphasis on optimizing health-related quality of life (HRQoL) has become increasingly important. The Cystic Fibrosis Questionnaire-Revised (CFQ-R 14+) is the most widely accepted method to quantify HRQoL in this patient population.

Objectives: Our objective was to systematically review the literature to identify sociodemographic and clinical factors associated with HRQoL among adolescents and adults with CF.

Methods: Five major literature databases were searched (MEDLINE, EMBASE, CENTRAL, CINAHL, psychINFO) to identify studies published from January 1989 to April 2014 (n = 1,921). We included all full-text studies that: (*1*) focused on individuals 14 years of age or older, and (*2*) examined the relationship between sociodemographic (age, sex, body-mass index [BMI], socioeconomic status, and employment) and clinical (FEV_1 % predicted, pulmonary exacerbation, comorbidities) factors with the CFQ-R 14+. Effect estimates and levels of statistical significance in the association between sociodemographic and clinical factors with each of the 12 CFQ-R 14+ domains were analyzed, if examined in at least two studies.

Measurements and Main Results: Twenty-eight articles met our inclusion/exclusion criteria, but 5 studies were excluded at the data synthesis stage, leaving 23 articles for analysis. In relation to the CFQ-R 14+, 10 candidate factors were examined in at least two studies. The five most commonly studied factors were FEV_1 % predicted (57.1% of 28 studies), sex (32.1%), BMI (28.6%), age (17.6%), and pulmonary exacerbations (13%). In studies incorporating multivariable methods, FEV_1 % predicted was positively associated with all CFQ-R 14+ domains with the exception of Digestion, Social Functioning, and Emotional Functioning. Male subjects reported higher Physical Functioning and lower Body Image scores than female subjects, BMI was positively correlated with Body Image and Weight, and age was negatively correlated with Treatment Burden. Pulmonary exacerbations were negatively associated with multiple domains, including Respiratory Symptoms, Physical, and Role Functioning.

Conclusions: Although several factors have been found to be associated with the CFQ-R in adolescents and adults with CF, FEV_1 % predicted and pulmonary exacerbations have the broadest impact on HRQoL. Further research is required to investigate the impact of age-related comorbidities, psychosocial factors, and treatment-related factors on HRQoL in adolescents/adults with cystic fibrosis.

Keywords: review; quality of life; cystic fibrosis

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In the past four decades, the median age of survival has nearly doubled for individuals living with cystic fibrosis (CF) (1). This has resulted in a tremendous growth in the proportion of individuals living into adulthood (1). As survival age increases, living with CF has become increasingly complex as chronic CF-related conditions such as diabetes, kidney disease, bone and joint disease, depression, and sinus disease rise in prevalence (2). With ongoing improvements in pulmonary and

nutritional outcomes, the impact of treatment burden and extrapulmonary conditions such as diabetes on health-related quality of life (HRQoL) are likely to grow in importance.

The two most common CF-specific HRQoL instruments are the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and Cystic Fibrosis Quality of Life questionnaire (CFQoL). Both questionnaires are considered valid HRQoL instruments, measure multiple dimensions (e.g., physical, social, and emotional functioning), and have demonstrated adequate reliability, internal validity and clinical sensitivity (3–5). However, the CFQ-R is the most widely used HRQoL instrument in CF-related research, and its Respiratory domain has been approved by the U.S. Food and Drug Administration (FDA) for use as an endpoint in clinical trials (6).

As individuals with CF live longer, it is important to identify sociodemographic and clinical factors associated with HRQoL in this aging cohort. Equipped with this knowledge, CF clinicians can focus their efforts on prioritizing and optimizing the management of factors that impact most on HRQoL. The objective of this study was to systematically review the literature to identify sociodemographic and clinical factors associated with HRQoL in adolescents and adults, as measured by the CFQ-R 14+.

Table 1. Description of *a priori* chosen sociodemographic and clinical factors potentially associated with health-related quality of life in adults with cystic fibrosis

Category	Factors
Sociodemographic	Age, sex, race
	Household or personal income, education, employment, marital status
Clinical (including comorbidities)	Age of CF diagnosis, genotype, transplant status
	FEV_1, FVC
	BMI, weight, nutritional status
	Shwachman score
	Use and frequency of nebulized, oral, or inhaled medications
	Exacerbation status, frequency of exacerbation, use of intravenous antibiotics, hospitalization at time of questionnaire completion
	Positive sputum culture for *Pseudomonas aeruginosa*, *Burkholderia cepacia*, or *Aspergillus fumigatus*
	Pneumothorax, hemoptysis, supplemental oxygen use, use of home ventilation
	CF-related diabetes (impaired glucose intolerance, dysglycemia, diabetes requiring insulin treatment, diabetes with microvascular complications)
	Liver disease with or without portal hypertension
	Chronic rhinosinusitis, nasal polyposis, allergic fungal sinusitis
	Gastroesophageal reflux disorder
	Pancreatic insufficiency with or without enzyme treatment
	Distal intestinal obstruction syndrome
	Depression, use of antidepressants, anxiety disorder, mood disorder, stress, self-esteem, body satisfaction, acceptance, symptom burden, illness perception
	Osteopenia, osteoporosis
	Renal stones, chronic renal failure, chronic kidney disease
	CF-related arthropathy
	Chronic pain
	Insomnia, sleep apnea, daytime sleepiness, sleep quality

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis.

Methods

Study Population

The patient population of interest was defined as adolescents and adults (≥14 yr old) who were diagnosed with CF based on a positive sweat chloride test and/or positive CF genotyping. Observational studies investigating the association between sociodemographic and clinical factors with HRQoL measured by the CFQ-R 14+ were included in this study (4). Studies using the predecessor of the CFQ-R 14+, the Cystic Fibrosis Questionnaire for adolescents and adults (CFQ 14+) were also included. A list of all *a priori* chosen candidate factors has been outlined in Table 1. These factors were chosen after discussion with CF clinical experts with the purpose of establishing a comprehensive list of variables that were both clinically meaningful and could influence HRQoL (e.g., sociodemographic, clinical, comorbidities). A detailed description of the considerations used regarding the CFQ-R 14+ is provided in the online supplement.

Search Strategy

Our search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (7). A search was conducted of articles published in the English language between January 1, 1989 and April 1, 2014 using MEDLINE, EMBASE, CENTRAL, CINAHL, and psychINFO. A detailed description of the search strategy for each literature database is provided in the supplemental Methods and Table E1 on the online supplement.

Data Collection Process

Once eligible articles for full-text review were identified, a standardized data collection form was established according to PRISMA, Meta-analysis of Observational Studies in Epidemiology (MOOSE), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group (7–10). This included an evaluation of study and patient characteristics, a description of the patient population from which the study sample was recruited, sociodemographic factors and clinical characteristics of the subjects included, description of statistical methods, magnitude of observed effects, and an assessment of study quality and potential risk of bias (Table E2). As described by the GRADE Working Group, all articles were

initially considered as "low" quality (7–10). Articles were considered as "moderate" quality if they had used multivariable methods to account for potentially confounding factors and/or were national, epidemiological studies. Studies were considered "very low" quality if potentially deleterious bias was suspected in recruitment and/or analysis.

Synthesis of Results

To synthesize results extracted from studies, candidate factors that were examined in at least two studies were analyzed. To accommodate the heterogeneity in reporting of results, the standardized data collection form included details pertaining to the appropriate statistical tests required to quantify the association between candidate factors with CFQ-R 14+ domain scores. A detailed description of the methodology used to synthesize results extracted from studies included in the final collection is provided in the online supplement. To consolidate our findings, we calculated the proportion of studies reporting significant findings (i.e., P value < 0.05) for each candidate factor on each of the 12 CFQ-R 14+ domains.

Results

Study Selection

The study selection was a total of 2,677 potentially relevant abstracts and articles. After removing duplicates (n = 756), a total of 1,921 abstracts were reviewed for eligibility. A total of 199 articles were eligible for full-text review. After full-text review, 28 articles met the inclusion and exclusion criteria as illustrated in Figure 1 (4, 11–36). No additional articles were found from screening the reference lists of these 28 articles.

Summary of Risk of Bias, Study Design, and Subject Characteristics

According to the GRADE system of Quality of Evidence, 36% of studies were moderate quality, 57% were low quality, and 7% were very low quality. The characteristics of included studies are described in Table 2, and the composition of study participants is detailed in Table E3. The mean age of subjects in the included articles was 26 (median, 26) years, and the mean FEV_1 % predicted of participants was 64% (median, 63%).

Nine of 28 (32.1%) studies examined the effect of a single factor on CFQ-R 14+ domain scores, and the remainder examined multiple factors (Table 2). FEV_1 % predicted was the most frequently studied factor, being evaluated in 16 of 28 of articles. Sex (32.1%), body mass index (BMI, 28.6%), and age (17.9%) were the next most frequently studied factors. Twenty-one of 28 articles investigated all 12 domains of the CFQ-R 14+. For data analysis, a total of 23 studies were included, as the candidate factors were investigated in at least two studies.

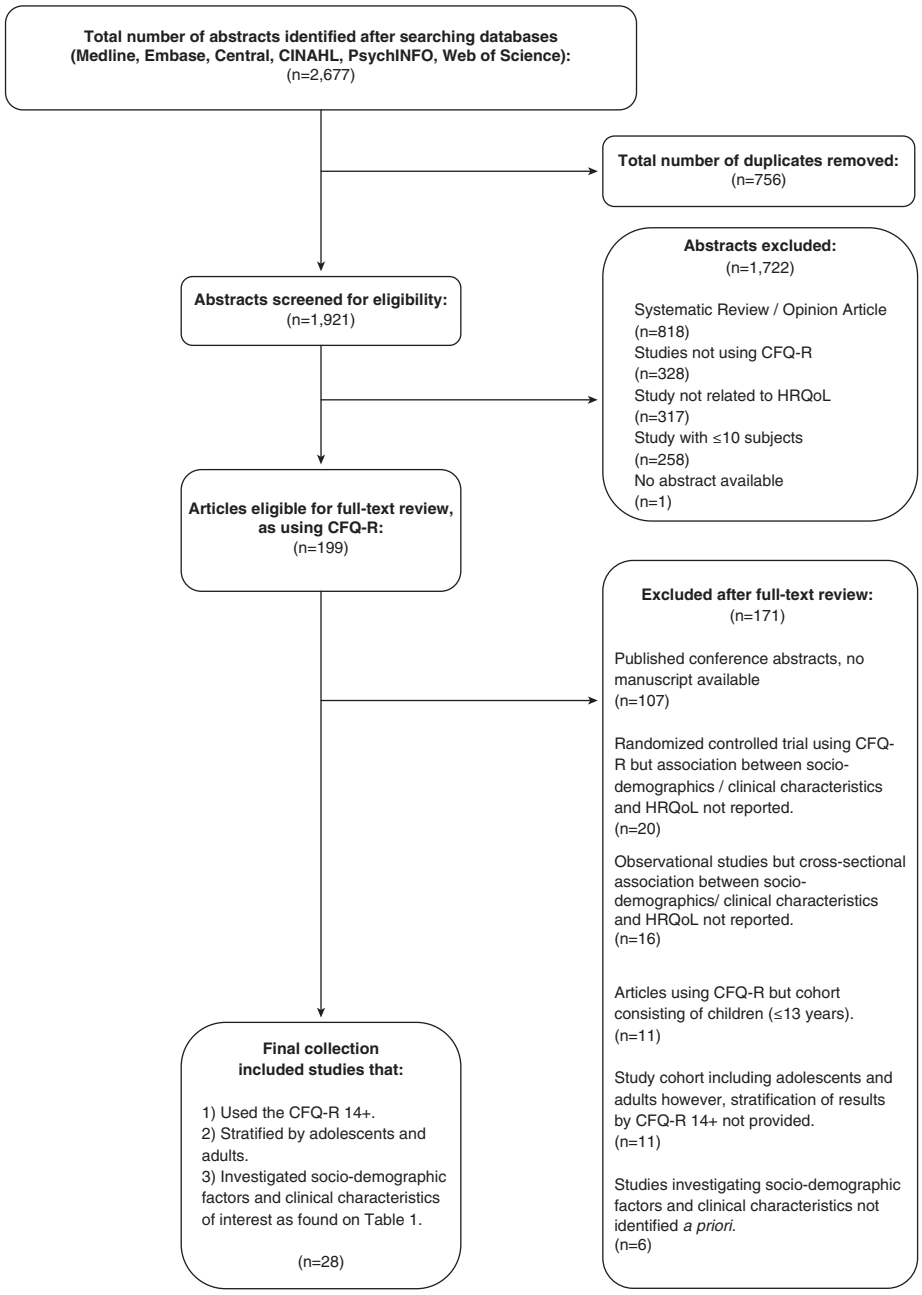

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram depicting search results and eligible articles. CFQ-R = Cystic Fibrosis Questionnaire-Revised; HRQoL = health-related quality of life.

Sociodemographic Factors

Age. In bivariable analysis, older age was significantly associated with worse Physical Functioning (correlation coefficient, −0.52) (3, 15, 33), Emotional Functioning (correlation coefficients, −0.23 to −0.28)

Table 2. Characteristics of the 28 articles meeting the inclusion/exclusion criteria of identifying sociodemographic and clinical factors potentially associated with health-related quality of life in adults with cystic fibrosis

Study	Year	Single or Multicenter	Countries	No. (%) Subjects ⩾ 14 yr of Age*	Sociodemographic/ Clinical Factor Studied	GRADE Study Quality
Quittner *et al.* (11)	2000	M	United States	10 (33)	Sex, FEV_1 %	Low
Henry *et al.* (12)	2003	S	France	124 (59)	Shwachman score, FVC	Low
Wenninger (13)	2003	M	Germany	103 (100)	BMI, FEV_1 %	Low
Wenninger *et al.* (14)	2003	S	Germany	72 (100)	BMI, FEV_1 %	Low
Klijn *et al.* (15)	2004	S	Netherlands	84 (100)	Age, sex, BMI, FEV_1 %	Low
Dobbin *et al.* (16)	2005	S	Australia	22 (100)	Exacerbation status	Low
Quittner *et al.* (3)	2005	M	United States	206 (100)	Age, BMI, FEV_1 %	Low
Riekert *et al.* (17)	2007	S	United States	76 (100)	Depression, FEV_1 %	Moderate
Bregnballe *et al.* (18)	2008	M	Denmark	180 (100)	BMI, FEV_1 %	Very low
Havermans *et al.* (19)	2008	S	Belgium	57 (100)	Depression, FEV_1 %	Low
Sawicki *et al.* (20)	2008	M	United States	303 (100)	Symptom burden (CF-specific psychological, gastrointestinal, respiratory)	Moderate
Dunnink *et al.* (21)	2009	S	Netherlands	27 (100)	Sex	Low
Havermans *et al.* (22)	2009	S	Belgium	57 (100)	BMI, FEV_1 %, employment, *Pseudomonas aeruginosa* infection	Low
Sawicki *et al.* (23)	2009	M	United States	204 (100)	Age, sex, FEV_1 %	Low
Quittner *et al.* (24)	2010	M	United States	3,030 (46)	Socioeconomic status	Moderate
Casier *et al.* (25)	2011	M	Belgium	40 (100)	Sex, FEV_1 %	Moderate
Cohen *et al.* (26)	2011	S	Brazil	24 (32)	FEV_1 %	Low
Hayes *et al.* (27)	2011	S	United States	83 (100)	Overall pain, chest pain, back pain, abdominal pain	Low
Sawicki *et al.* (28)	2011	M	United States	199 (100)	Age, sex, BMI, FEV_1 %, exacerbation status, symptom burden (CF-specific psychological, gastrointestinal, respiratory)	Moderate
Ashish *et al.* (29)	2012	S	UK	157 (100)	*Pseudomonas aeruginosa* infection	Moderate
Bouka *et al.* (30)	2012	S	Germany	55 (100)	Daytime sleepiness, sleep quality	Moderate
Quittner *et al.* (4)	2012	M	United States	4,679 (64)	Sex, BMI, FEV_1 %, exacerbation status	Moderate
Bradley *et al.* (31)	2013	M	UK Ireland	94 (100)	Exacerbation status	Very low
Dill *et al.* (32)	2013	M	United States	303 (100)	Age, sex, FEV_1 %, exacerbation status	Moderate
Platten *et al.* (33)	2013	M†	UK	74 (100)	Age, sex, FEV_1 %	Low
Sawicki *et al.* (34)	2013	M	United States Canada	4,228 (58)	Treatment complexity	Moderate
Targett *et al.* (35)	2014	M	UK	254 (100)	Employment	Low
Wojewodka *et al.* (36)	2014	S	Canada	52 (100)	Exacerbation status	Low

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; M = multicenter; S = single center.

*Proportion of subjects among the entire study sample who were ⩾ 14 years of age.

†Subjects recruited from online discussion boards and social media websites. We have categorized this as multicenter because it is unclear if these subjects received care from a single center.

(3, 33), Respiratory Symptoms (correlation coefficient, −0.19) (3), and Health Perceptions (correlation coefficient, −0.22) (3) in all studies investigating these domains (Table 3).

Of the statistically significant bivariable associations, only Physical Functioning remained associated with age after adjustment in multivariable analysis. Two additional studies examined the relationship between age and CFQ-R 14+ domains using multivariable methods (28, 32). Sawicki and colleagues found that age was only associated with the domain Treatment Burden after adjustment for sex, BMI, maximum FEV_1 % predicted, frequency of pulmonary exacerbations, and sputum culture positive for *Burkholderia cepacia* and/or *Pseudomonas aeruginosa* (28). Dill and colleagues found that age was associated with Physical Functioning, Social Functioning, and Treatment Burden after adjustment for sex, weight, education, FEV_1 % predicted, pancreatic insufficiency, frequency of exacerbations, and the probability of participants being sampled from the eligible population (32). In both studies using multivariable methods, Treatment Burden was consistently associated with age, but the association with Physical Functioning and Social Functioning was inconsistent.

Table 3. Summary of findings from studies using bivariable methods to examine associations between candidate factors and domains of the Cystic Fibrosis Questionnaire-Revised 14+

Candidate Factors (Investigated in ⩾2 Studies)	CFQ-R 14+ Domains											
	Physical Functioning	Vitality	Emotional Functioning	Social Functioning	Role Functioning	Eating Disturbances	Body Image	Treatment Burden	Health Perceptions	Respiratory Symptoms	Digestion	Weight
Age												
Significant association	2 of 3	2 of 2	2 of 3	1 of 3	1 of 3	1 of 2	1 of 2	1 of 3	2 of 2	2 of 2	0 of 2	0 of 2
Correlation coefficient	−0.52	−0.10 to −0.26	−0.23 to −0.28	−0.30	−0.26	−0.17	NP	NP	−0.22	−0.19	NS	NS
Sex												
Significant association	2 of 6	1 of 5	4 of 6	3 of 6	1 of 6	1 of 4	3 of 4	2 of 5	1 of 4	2 of 4	1 of 4	1 of 4
Mean differences (males − females)	8.4 to 15.0	4.9	2.7 to 18.8	3.2 to 14.7	4.7	2.0	−7.2 to 12.1	2.9 to 6.6	2.3	4.3 to 12.0	1.3	−13.9
Employment												
Significant association	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1
Mean difference (work − not work)	30.4	16.7	19.8	15.6	26.1	11.6	9.0	13.0	25.3	18.3	8.6	13.7
Lung function												
Significant association	13 of 13	4 of 11	5 of 13	6 of 13	8 of 13	6 of 11	8 of 11	5 of 12	9 of 11	7 of 11	0 of 11	6 of 11
Correlation coefficient	0.27 to 0.76	0.26 to 0.33	0.23 to 0.54	0.25 to 0.52	0.25 to 0.45	0.23 to 0.33	0.29 to 0.56	0.26 to 0.39	0.34 to 0.66	0.36 to 0.47	NS	0.27 to 0.41
BMI												
Significant association	1 of 7	1 of 7	1 of 7	1 of 7	1 of 7	5 of 7	6 of 7	1 of 7	4 of 7	1 of 7	0 of 7	6 of 7
Correlation coefficient	NP	−0.24	NP	0.24	NP	0.16 to 0.44	0.28 to 0.54	NP	0.14 to 0.30	NP	NS	0.43 to 0.47
PEx												
Significant association	2 of 2	1 of 2	2 of 2	1 of 2	2 of 2	1 of 2	2 of 2	1 of 2	2 of 2	1 of 2	1 of 2	2 of 2
Mean differences (presence − absence)	−16.1 to −17.2	−11.9	−6.0 to −12.7	−6.7	−11.3 to −12.5	−7.1	−7.7 to −21.6	−6.6	−14.2 to −5.9	−16.5	−1.6	−11.3 to −28.6
Frequency of PEx												
Significant association	1 of 1	1 of 1	0 of 1	0 of 1	1 of 1	0 of 1	0 of 1	0 of 1	1 of 1	1 of 1	0 of 1	0 of 1
Correlation coefficient	−0.35	−0.25	NS	NS	−0.32	NS	NS	NS	−0.30	−0.27	NS	NS
PA infection												
Significant association	1 of 1	1 of 1	1 of 1	0 of 1	1 of 1	0 of 1	1 of 1	1 of 1	1 of 1	1 of 1	0 of 1	1 of 1
Mean difference (LES − none)	NP	NP	NP	NS	NP	NS	NP	NP	NP	NP	NS	NP
Depression (BDI)												
Significant association	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1	1 of 1
Correlation coefficient	−0.67	−0.72	−0.74	−0.68	−0.55	−0.53	−0.43	−0.51	−0.62	−0.68	−0.59	−0.21
Symptom burden (MSAS-Psych)												
Significant association	None	None	1 of 1	None	None	None	None	None	None	1 of 1	1 of 1	0 of 1
Correlation coefficient	NS	NS	−0.69	NS	NS	NS	NS	NS	NS	−0.28	−0.32	NS
Symptom burden (MSAS-GI)												
Significant association	None	None	1 of 1	None	None	None	None	None	None	1 of 1	1 of 1	1 of 1
Correlation coefficient	NS	NS	−0.35	NS	NS	NS	NS	NS	NS	−0.31	−0.19	−0.49
Symptom burden (MSAS-Resp)												
Significant association	None	None	1 of 1	None	None	None	None	None	None	1 of 1	1 of 1	0 of 1
Correlation coefficient	NS	NS	−0.56	NS	NS	NS	NS	NS	NS	−0.60	−0.32	NS

Definition of abbreviations: BDI = Beck Depression Inventory; BMI = body-mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; GI = gastrointestinal; LES = Liverpool Epidemic Strain; MSAS = Memorial Symptom Assessment Scale; NP = not provided; NS = not significant; PA = *Pseudomonas aeruginosa*; PEx = pulmonary exacerbation; Psych = psychological; Resp = respiratory.

Sex. In bivariable analysis, female subjects reported significantly higher scores on the Body Image domain than male subjects in three of four studies (4, 11, 15). However, female subjects scored significantly lower on the domains of Emotional Functioning in four of six studies (4, 15, 25, 33), Social Functioning in three of six studies (4, 25, 33), Respiratory Symptoms in two of four studies (4, 21), and Physical Functioning in two of six studies (Table 3) (4, 25).

Two studies examined the relationship between sex and CFQ-R 14+ domains using multivariable analysis (28, 32). Sex was significantly associated with Body Image and Physical Functioning in both studies. Sawicki and colleagues found that female subjects scored significantly higher on the Body Image domain and lower on Physical Functioning than male subjects, after adjustment for age, maximum FEV_1 % predicted, BMI, frequency of pulmonary exacerbations, and positive sputum culture for *B. cepacia* and/or *P. aeruginosa* (28). Dill and colleagues also found that female subjects scored significantly higher on the Body Image domain and lower on Physical Functioning than male counterparts, after adjustment for age, weight, education, FEV_1 % predicted, pancreatic insufficiency, frequency of exacerbations, and sampling method (32).

Employment. Employment, defined as current participation in part- or full-time employment or school, was associated with higher scores on all CFQ-R 14+ domains in bivariable analysis (35). When studied using multivariable methods, Havermans and colleagues found that employment remained associated with Physical Functioning, Social Functioning, and Role Functioning, after adjustment for BMI, FEV_1 % predicted, use of caloric supplements, CF-related diabetes (CFRD), and presence or absence of a central venous implantable device (22).

Clinical Factors

Lung function. In bivariable analysis, FEV_1 % predicted was significantly associated with 11 of 12 domains of the CFQ-R 14+. FEV_1 % predicted was consistently associated with Physical Functioning (13 of 13 studies, (correlation coefficients, 0.27 to 0.76) (3, 4, 11, 13–15, 17–19, 22–26, 33), Health Perception (9 of 11 studies, correlation coefficients, 0.34 to 0.66) (3, 4, 13–15, 17–19, 22), Respiratory Symptoms (7 of 11 studies, correlation coefficients, 0.36 to 0.47) (3, 4, 13, 15, 17, 18, 26), and Treatment Burden (5 of 12 studies, correlation coefficients, 0.26 to 0.39) (4, 13, 15, 17, 18) (Table 3). FEV_1 % predicted was not associated with Digestion in any of the 11 studies having evaluated this domain (3, 4, 11, 13–15, 17–19, 22, 26).

Of the significant bivariable associations, 9 of 11 domains were still significant in at least one of the two studies using multivariable methods (28, 32). However, Emotional Functioning and Social Functioning were no longer associated with FEV_1 % predicted after adjustment. Both studies using multivariable analysis found that FEV_1 % predicted was associated with Physical Functioning and Treatment Burden. Sawicki and colleagues adjusted for age, sex, BMI, frequency of pulmonary exacerbations, and sputum culture positive for *B. cepacia* and/or *P. aeruginosa* (28). Dill and colleagues adjusted for age, sex, weight, education, pancreatic insufficiency, frequency of exacerbations and the probability of participants being sampled from the eligible population (32).

BMI. In bivariable analysis, BMI was consistently associated with the Body Image (correlation coefficients, 0.28 to 0.54) and Weight (correlation coefficients, 0.43 to 0.47) domains in 6 of 7 studies (3, 4, 13, 15, 17, 22). BMI was also associated with Eating Disturbances (5 of 7 studies, correlation coefficients, 0.16 to 0.44) (3, 13, 15, 18, 22), Health Perceptions (4 of 7 studies, correlation coefficients, 0.14 to 0.30) (3, 13, 14, 18) and Vitality (1 of 7 studies, correlation coefficient, −0.24) (14).

Compared with bivariable findings, only the domains of Body Image, Weight, and Vitality remained significantly associated with BMI after adjustment for age, sex, FEV_1 % predicted, frequency of pulmonary exacerbations, and sputum culture positive for *B. cepacia* and/or *P. aeruginosa* (15).

Pulmonary exacerbations. In bivariable analysis, Quittner and colleagues found that pulmonary exacerbations were associated with significantly lower scores on all CFQ-R 14+ domains (effect sizes, −0.09 to −0.83) (4). Wojewodka and colleagues also compared the presence or absence of pulmonary exacerbation on CFQ-R 14+ scores and found significant differences in Physical Functioning, Emotional Functioning, Role Functioning, Body Image, Health Perceptions, and Weight, but effect estimates were not reported (36).

Compared with bivariable findings, Dobbin and colleagues found that scores for individuals experiencing a pulmonary exacerbation were significantly lower on 5 of 12 domains (Respiratory Symptoms, Physical Functioning, Vitality, Role Functioning, and Health Perceptions), after adjustment for age and sex (16).

Frequency of pulmonary exacerbations. In bivariable analysis, Quittner and colleagues found that increased frequency of pulmonary exacerbations was associated with lower scores on the domains of Physical Functioning (correlation coefficient, −0.35), Vitality (correlation coefficient, −0.25), Role Functioning (correlation coefficient, −0.32), Health Perceptions (correlation coefficient, −0.30), and Respiratory Symptoms (correlation coefficient, −0.27) (7). All other domains were not significantly correlated with frequency of pulmonary exacerbations (7).

All domains significantly associated with frequency of pulmonary exacerbations in bivariable analysis were also supported in studies using multivariable methods. Sawicki and colleagues found that frequency of pulmonary exacerbations was associated with Role Functioning, Eating Disturbances, Body Image, Respiratory Symptoms, and Weight, after adjustment for age, sex, BMI, FEV_1 % predicted, and sputum culture positive for *B. cepacia* and/or *P. aeruginosa* (14). Dill and colleagues also found that frequency of pulmonary exacerbations was associated with all CFQ-R 14+ domains except for Digestion, after adjustment for age, sex, weight, education, FEV_1 % predicted, pancreatic insufficiency, and sampling method (32). Consistent associations in multivariable analysis were found regarding Respiratory Symptoms, Role Functioning, Body Image, Eating Disturbances, and Weight.

Pseudomonas aeruginosa *infection.* In bivariable analysis, Ashish and colleagues found that individuals harboring the Liverpool Epidemic Strain (LES) of *P. aeruginosa* reported significantly lower scores for Physical Functioning, Emotional Functioning, Role Functioning, Body Image, and Weight, and higher scores for Respiratory Symptoms and Treatment Burden compared with individuals with non-LES *P. aeruginosa* infection (29).

However, individuals infected with non-LES *P. aeruginosa* reported significantly lower scores only on the Body Image domain, compared with individuals without any *P. aeruginosa* infection (29). Among individuals infected with *P. aeruginosa*, those with LES reported significantly worse scores on all domains except Body Image and Weight. A secondary analysis using propensity scores found that individuals with LES *P. aeruginosa* reported significantly lower scores for Physical Functioning, Treatment Burden, Health Perceptions, and Respiratory Symptoms domains, when compared with those infected with non-LES *P. aeruginosa* (29).

In multivariable analysis, Sawicki and colleagues compared CFQ-R 14+ domain scores between individuals with or without *P. aeruginosa* infection, regardless of strain (28). No significant associations were found for any domains of the CFQ-R 14+ and *P. aeruginosa* infection (28).

Depression. Depression was assessed using the Beck Depression Inventory. Scores were considered continuous, and correlation was investigated with each CFQ-R 14+ domain. Riekert and colleagues found that greater depressive symptoms were associated with worse scores on all domains of the CFQ-R 14+ (correlation coefficients, −0.21 to −0.74) (17). All associations remained significant despite stratification by lung function, except the Weight domain (correlation coefficients, −0.44 to −0.85) (17).

In a second study, Havermans and colleagues used the Hospital Anxiety and Depression Scale to quantify depression (19). Individuals scoring greater than 8 were considered depressed. The authors found that depression was significantly associated with Emotional Functioning, Eating Disturbances, and Body Image, despite adjustment for lung function (25).

Symptom burden. Symptom burden was measured using the Memorial Symptom Assessment Scale (MSAS), to assess the severity, frequency, and distress caused by psychological, gastrointestinal, and respiratory symptoms (13, 26). Symptom burden was categorized into three CF-specific groups: psychological (MSAS-CF-PSYCH), gastrointestinal symptoms (MSAS-CF-GI), and respiratory symptoms (MSAS-CF-RESP). In bivariable analysis, Sawicki and colleagues found that all symptom burden groups were associated with Emotional Functioning, Respiratory Symptoms, Digestion, and Weight (correlation coefficients, −0.11 to −0.69) (26).

In multivariable analysis, Sawicki and colleagues found that MSAS-PSYCH was associated with Vitality, Emotional Functioning, Social Functioning, Role Functioning, Eating Disturbances, Body Image, and Weight, after adjustment for several sociodemographic and clinical factors (28). MSAS-CF-GI was associated with Role Functioning, Eating Disturbances, Body Image, and Weight (13). MSAS-CF-RESP was associated with all CFQ-R 14+ domains, except Eating Disturbances and Body Image (13).

Discussion

As the life expectancy for individuals with CF increases, the prevalence of extrapulmonary comorbidities continues to rise. This has shifted the concern of CF care providers to achieving a balance between maintaining lung function and nutritional status and preventing/managing age- and disease-related chronic conditions such as diabetes. With many potentially competing diagnoses and treatments, the emphasis on optimizing HRQoL has become increasingly important. The primary purpose of this systematic review was to identify sociodemographic and clinical factors associated with the CFQ-R 14+ in adolescents and adults so that clinicians can prioritize issues that have the most significant impact on HRQoL.

All articles included in this review were observational, the majority of which were of low quality (57%). Few studies (36%) used multivariable methods to adjust for potentially confounding variables or were national epidemiological studies. In total, 10 sociodemographic/clinical factors were found to be associated with domains of the CFQ-R 14+ and were examined in at least two studies. FEV_1 % predicted has been the most widely studied factor to date and consistently associated with multiple domains of the CFQ-R except Digestion, Social Functioning, and Emotional Functioning. The consistent absence of a significant correlation between FEV_1 % predicted and Digestion strongly suggests divergent validity for the included studies. As expected, lower BMI was associated with worse Body Image and less Vitality. Pulmonary exacerbations were consistently associated with Respiratory Symptoms, Physical Functioning, Vitality, Body Image, Eating Disturbances, Weight, and Role Functioning, the latter most likely attributed to the adverse impact these events and their treatments have on work or school absenteeism and productivity (37).

A sex gap in survival has been reported in international CF registries, with female patients demonstrating a survival disadvantage (38–40). There remains no confirmed explanation for the observed disparity in health outcomes for female patients with CF despite multiple mechanisms being postulated (41–43). In studies using multivariable methods included in this systematic review (28, 32), female subjects consistently reported lower scores on the domain of Physical Functioning and higher scores with respect to Body Image. Both of these important observations might provide potential insights into the sex survival gap. A previous study using the CFQoL questionnaire has linked Physical Functioning to reduced survival in CF (44). Therefore, reduced Physical Functioning might be in the causal pathway for the worse health outcomes observed for female patients with CF or at least be a marker of more advanced disease independent of traditional markers of disease severity. Future studies are required to determine if interventions such as exercise training targeted at improving Physical Functioning in female patients can improve health outcomes and reduce the survival gap. The higher scores for Body Image reported by female subjects are contrary to expectations, but a prior study using the CFQoL questionnaire has also demonstrated better HRQoL on this domain for female subjects relative to male subjects with CF (45).

A potential explanation for this based on a study by Abbott and colleagues is that male patients with CF desire to be heavier and more muscular and are thus less content with their body image, whereas female patients desire to be thinner (due to cultural stereotypes) and are often content with their lower body weight (46). Malnutrition has been epidemiologically linked to worse survival in CF (41, 47). As both male and female patients with CF tend to be undernourished compared with the general population (39), efforts to optimize weight and nutritional status are less likely to be

successful in underweight adolescent/adult female patients compared with male patients, as they are more likely to be satisfied with their lean body habitus and thus less likely to feel compelled to gain weight.

Older age was consistently associated with greater Treatment Burden scores even after adjusting for lung function, chronic *P. aeruginosa* and *B. cepacia* infection status, and pulmonary exacerbations (28, 32). This finding suggests that therapies related to the treatment of other extrapulmonary comorbidities (e.g., CFRD, osteoporosis, depression) that rise in prevalence with age (2) increase treatment burden and complexity over a lifetime. Studies have demonstrated that adults with CF administer an average of seven therapies per day and spend an average of 2 hours per day performing airway clearance techniques and treatments (23). CF care providers must remain sensitive to the impact of adding additional treatments over a lifetime, as this may adversely affect HRQoL and treatment adherence (48, 49).

This systematic review had several potential limitations. First, the data synthesis criteria (i.e., candidate factors examined in at least two studies) might have introduced selection bias with overlooking of factors associated with CFQ-R based on single studies. For example, number/frequency of medications prescribed (23) and minority status (i.e., African American and Hispanic) (24) were associated with worse HRQoL based on the CFQ-R in individual studies but were not summarized in this review. However, this criterion was incorporated to minimize conclusions based on single studies with potentially spurious findings. Second, we focused on the cross-sectional associations between the factors of interest and CFQ-R domain scores. CFQ-R domain scores can change over time in response to treatment and changes in health status. However, with the exception of studies focused on the impact of exacerbations on CFQ-R, most studies examined the association between factors and the CFQ-R when study subjects were clinically stable, which would have increased the likelihood that self-reported CFQ-R scores were representative of their usual health status. Last, cross-sectional associations cannot be used to infer cause and effect, and therefore longitudinal studies are required to evaluate the impact of the candidate factors on HRQoL.

Although this systematic review has found several sociodemographic and clinical factors associated with CFQ-R domains among adolescents and adults, the HRQoL impact of other chronic disease-related complications (e.g., CFRD, chronic rhinosinusitis, depression, osteoporosis, arthritis) requires further examination. For example, with nearly 50% of the adult population developing CFRD, it is important to understand the relative impact this condition has on HRQoL, as it often necessitates frequent blood glucose monitoring and insulin therapy. Other sociodemographic factors (e.g., race, income, education), psychosocial factors (e.g., coping, interpersonal relationships, marriage, parenthood), and treatment-related factors (e.g., number of medications, methods of administration, frequency of dosing) also must be examined, given the growing complexity in life experiences and treatment burden of the adult CF population.

In conclusion, HRQoL is an important outcome measure in CF, and we have summarized a number of sociodemographic and clinical factors relating to multiple domains of the CFQ-R 14+. FEV_1 % predicted and pulmonary exacerbations have the broadest impact on HRQoL and should remain the focus of attention for CF clinicians. Future studies examining HRQoL in adults with CF should also focus on the impact of other chronic CF-related conditions, psychosocial factors, and treatment-related factors that rise in prevalence or complexity with age and could adversely impact on HRQoL. ■

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References

1 Cystic Fibrosis Canada. Annual Report. Toronto, Ontario, Canada: Cystic Fibrosis Canada; 2012.
2 Quon BS, Aitken ML. Cystic fibrosis: what to expect now in the early adult years. *Paediatr Respir Rev* 2012;13:206–214.
3 Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. 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.
4 Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, Konstan MW. Erratum to: Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national, US sample. *Qual Life Res* 2012;21:1279–1290.
5 Gee L, Abbott J, Conway SP, Etherington C, Webb AK. Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. *Thorax* 2000;55:946–954.
6 Goss CH, Quittner AL. Patient-reported outcomes in cystic fibrosis. *Proc Am Thorac Soc* 2007;4:378–386.
7 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
8 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–2012.
9 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; Iniciativa STROBE. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [in Spanish]. *Rev Esp Salud Publica* 2008;82:251–259.
10 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–926.
11 Quittner AL, Sweeny S, Watrous M, Munzenberger P, Bearss K, Gibson Nitza A, Fisher LA, Henry B. Translation and linguistic validation of a disease-specific quality of life measure for cystic fibrosis. *J Pediatr Psychol* 2000;25:403–414.
12 Henry B, Aussage P, Grosskopf C, Goehrs J-M. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res* 2003;12:63–76.
13 Wenninger K, Aussage P, Wahn U, Staab D; German Cystic Fibrosis Questionnaire study group. The revised German Cystic Fibrosis Questionnaire: validation of a disease-specific health-related quality of life instrument. *Qual Life Res* 2003;12:77–85.
14 Wenninger K, Weiss C, Wahn U, Staab D. Body image in cystic fibrosis—development of a brief diagnostic scale. *J Behav Med* 2003;26:81–94.
15 Klijn PH, van Stel HF, Quittner AL, van der Net J, Doeleman W, van der Schans CP, van der Ent CK. Validation of the Dutch cystic fibrosis questionnaire (CFQ) in adolescents and adults. *J Cyst Fibros* 2004;3:29–36.
16 Dobbin CJ, Bartlett D, Melehan K, Grunstein RR, Bye PTP. The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis. *Am J Respir Crit Care Med* 2005;172:99–104.

17 Riekert KA, Bartlett SJ, Boyle MP, Krishnan JA, Rand CS. The association between depression, lung function, and health-related quality of life among adults with cystic fibrosis. *Chest* 2007;132: 231–237.
18 Bregnballe V, Thastum M, Lund LD, Hansen CR, Preissler T, Schiøtz PO. Validation of the Danish version of the revised cystic fibrosis quality of life questionnaire in adolescents and adults (CFQ-R14+). *J Cyst Fibros* 2008;7:531–536.
19 Havermans T, Colpaert K, Dupont LJ. Quality of life in patients with cystic fibrosis: association with anxiety and depression. *J Cyst Fibros* 2008;7:581–584.
20 Sawicki GS, Sellers DE, Robinson WM. Self-reported physical and psychological symptom burden in adults with cystic fibrosis. *J Pain Symptom Manage* 2008;35:372–380.
21 Dunnink MA, Doeleman WR, Trappenburg JC, de Vries WR. Respiratory muscle strength in stable adolescent and adult patients with cystic fibrosis. *J Cyst Fibros* 2009;8:31–36.
22 Havermans T, Colpaert K, Vanharen L, Dupont LJ. Health related quality of life in cystic fibrosis: to work or not to work? *J Cyst Fibros* 2009;8:218–223.
23 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.
24 Quittner AL, Schechter MS, Rasouliyan L, Haselkorn T, Pasta DJ, Wagener JS. Impact of socioeconomic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. *Chest* 2010;137:642–650.
25 Casier A, Goubert L, Theunis M, Huse D, De Baets F, Matthys D, Crombez G. Acceptance and well-being in adolescents and young adults with cystic fibrosis: a prospective study. *J Pediatr Psychol* 2011;36:476–487.
26 Cohen MA, Ribeiro MA, Ribeiro AF, Ribeiro JD, Morcillo AM. Quality of life assessment in patients with cystic fibrosis by means of the Cystic Fibrosis Questionnaire. *J Bras Pneumol* 2011;37:184–192.
27 Hayes M, Yaster M, Haythornthwaite JA, Riekert KA, McMillan KN, White E, Mogayzel PJ Jr, Lechtzin N. Pain is a common problem affecting clinical outcomes in adults with cystic fibrosis. *Chest* 2011; 140:1598–1603.
28 Sawicki GS, Sellers DE, Robinson WM. Associations between illness perceptions and health-related quality of life in adults with cystic fibrosis. *J Psychosom Res* 2011;70:161–167.
29 Ashish A, Shaw M, McShane J, Ledson MJ, Walshaw MJ. Health-related quality of life in cystic fibrosis patients infected with transmissible *Pseudomonas aeruginosa* strains: cohort study. *JRSM Short Rep* 2012;3:12.
30 Bouka A, Tiede H, Liebich L, Dumitrascu R, Hecker C, Reichenberger F, Mayer K, Seeger W, Schulz R. Quality of life in clinically stable adult cystic fibrosis out-patients: associations with daytime sleepiness and sleep quality. *Respir Med* 2012;106:1244–1249.
31 Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *Eur Respir J* 2013;41:571–577.
32 Dill EJ, Dawson R, Sellers DE, Robinson WM, Sawicki GS. Longitudinal trends in health-related quality of life in adults with cystic fibrosis. *Chest* 2013;144:981–989.
33 Platten MJ, Newman E, Quayle E. Self-esteem and its relationship to mental health and quality of life in adults with cystic fibrosis. *J Clin Psychol Med Settings* 2013;20:392–399.
34 Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *J Cyst Fibros* 2013;12: 461–467.
35 Targett K, Bourke S, Nash E, Murphy E, Ayres J, Devereux G. Employment in adults with cystic fibrosis. *Occup Med (Lond)* 2014; 64:87–94.
36 Wojewodka G, De Sanctis JB, Bernier J, Bérubé J, Ahlgren HG, Gruber J, Landry J, Lands LC, Nguyen D, Rousseau S, *et al*. Candidate markers associated with the probability of future pulmonary exacerbations in cystic fibrosis patients. *PLoS One* 2014;9:e88567.
37 Hogg M, Braithwaite M, Bailey M, Kotsimbos T, Wilson JW. Work disability in adults with cystic fibrosis and its relationship to quality of life. *J Cyst Fibros* 2007;6:223–227.
38 Corey M, Farewell V. Determinants of mortality from cystic fibrosis in Canada, 1970-1989. *Am J Epidemiol* 1996;143:1007–1017.
39 Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am J Epidemiol* 1997;145:794–803.
40 Olesen HV, Pressler T, Hjelte L, Mared L, Lindblad A, Knudsen PK, Laerum BN, Johannesson M; Scandinavian Cystic Fibrosis Study Consortium. Gender differences in the Scandinavian cystic fibrosis population. *Pediatr Pulmonol* 2010;45:959–965.
41 Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326: 1187–1191.
42 Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: *Pseudomonas aeruginosa* infection. *J Clin Epidemiol* 1995;48: 1041–1049.
43 Chotirmall SH, Smith SG, Gunaratnam C, Cosgrove S, Dimitrov BD, O'Neill SJ, Harvey BJ, Greene CM, McElvaney NG. Effect of estrogen on *Pseudomonas* mucoidy and exacerbations in cystic fibrosis. *N Engl J Med* 2012;366:1978–1986.
44 Abbott J, Hart A, Morton AM, Dey P, Conway SP, Webb AK. Can health-related quality of life predict survival in adults with cystic fibrosis? *Am J Respir Crit Care Med* 2009;179:54–58.
45 Gee L, Abbott J, Conway SP, Etherington C, Webb AK. Quality of life in cystic fibrosis: the impact of gender, general health perceptions and disease severity. *J Cyst Fibros* 2003;2:206–213.
46 Abbott J, Conway S, Etherington C, Fitzjohn J, Gee L, Morton A, Musson H, Webb AK. Perceived body image and eating behavior in young adults with cystic fibrosis and their healthy peers. *J Behav Med* 2000;23:501–517.
47 Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41:583–591.
48 Bregnballe V, Schiøtz PO, Boisen KA, Pressler T, Thastum M. Barriers to adherence in adolescents and young adults with cystic fibrosis: a questionnaire study in young patients and their parents. *Patient Prefer Adherence* 2011;5:507–515.
49 Dodd ME, Webb AK. Understanding non-compliance with treatment in adults with cystic fibrosis. *J R Soc Med* 2000;93:2–8.