ERRATUM

Erratum to: Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national, US sample

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Abstract

Purpose The psychometric properties of a health-related quality of life (HRQOL) instrument, the Cystic Fibrosis Questionnaire-Revised (CFQ-R), were evaluated in a national, US sample of patients with cystic fibrosis (CF). This is the first psychometric evaluation of the revised version of this instrument.

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Methods The Epidemiologic Study of CF is a national, US multicenter longitudinal cohort study containing CFQ-R and health outcomes data. Developmentally appropriate versions of the CFQ-R were available from 7,330 patients aged 6–70 years and a proxy version from 2,728 parents of school-age children. The CFQ-R was completed during a "stable" or "sick" visit before recording health outcomes such as weight, lung function, and pulmonary exacerbations.

Results There were few floor and ceiling effects and strong internal consistency (Cronbach alpha ≥ 0.70) for most scales. The CFQ-R consistently discriminated between patients seen for sick-versus-well visits, and among stages of disease severity based on lung function. As predicted, women with CF reported worse HRQOL than men on scales not related to body image and weight. Strong parent–child agreement was found on scales measuring observable behaviors (respiratory symptoms). Convergence between CFQ-R scales and health outcomes provided evidence of construct validity.

Conclusions The CFQ-R demonstrated robust psychometric properties and consistent associations with health outcomes in a large national, US sample. Normative data are available to aid in interpretation.

Keywords Cystic fibrosis · Health-related quality of life · Psychometric properties · Patient-reported outcomes

Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
ESCF	Epidemiologic Study of Cystic Fibrosis
FEV_1	Forced expiratory volume in 1 s
HRQOL	Health-related quality of life

IV	Intravenous
MID	Minimal important difference
PRO	Patient-reported outcome
SF-36	36-Item Short Form Health Survey

Introduction

In the past two decades, significant progress has been made in defining and measuring patient-reported outcomes (PROs). A PRO instrument is defined as any measure of a patient's health status that is directly elicited from the *patient* and assesses how the patient "survives, functions, or feels" in relation to his or her health condition [1, 2]. PROs are utilized for several purposes: (1) to serve as primary or secondary outcomes in clinical trials evaluating new pharmaceutical, behavioral, or surgical interventions [3], (2) to compare existing treatments, (3) to measure the impact of a disease and its treatments on daily functioning, (4) to aid in clinical decision-making, and (5) to analyze the costs and benefits of medical interventions [4, 5]. If used as an outcome measure in a clinical trial, it must meet rigorous psychometric criteria, including a well-defined conceptual framework, qualitative input from patients and health care providers, evidence of reliability and validity, and determination of the minimal important difference (MID) score to facilitate interpretation [1, 6, 7].

Although generic PRO instruments, such as the 36-Item Short Form Health Survey (SF-36) and the Quality of Well-Being Scale [8, 9], were initially the most widely used, numerous studies suggest that disease-specific measures are more sensitive to change and provide information that is more relevant for clinical interventions [2, 5, 10]. Efforts to develop reliable and valid PRO instruments have been very successful, resulting in numerous well-validated tools and a growing empirical and clinical database [11]. PROs are particularly important for patients with chronic diseases, such as cystic fibrosis (CF), whose daily lives are significantly impacted by their illness.

CF is an autosomal recessive disorder affecting multiple organs, including the lungs, pancreas, and digestive and reproductive systems. Median life expectancy has increased dramatically in the past 20–37.8 years in the United States; however, progression of lung disease continues to lead to shortened life spans [12], and in younger patients, achieving normal nutrition and growth are challenging. Despite the development of new palliative treatments for CF, patients experience frequent pulmonary exacerbations, hospitalizations, and segregation from peers due to multi-resistant bacteria. High rates of depression and anxiety have also been reported by both patients and caregivers [13, 14]. Beginning in adolescence, gender

differences in both morbidity and mortality have been identified, with women experiencing greater declines in lung function than men [15, 16].

In addition, the treatment regimen for CF is highly complex and time-consuming, requiring 2–4 h of treatment every day. The treatment regimen includes multiple inhaled therapies, airway clearance two times per day, oral medications, and boosting calories to 110–200% of the recommended daily allowance. The challenges of adhering to this regimen include the time required, the complexity of using and cleaning the equipment, and its considerable cost [17]. These difficulties increase the importance of including PROs in clinical trials of new therapies, to assess patients' perceptions of efficacy and treatment burden [18].

The Cystic Fibrosis Questionnaire was the first disease-specific PRO developed for CF patients and caregivers. It was developed using a life span approach, with developmentally appropriate versions for ages 6 years through adulthood. Its development began with a conceptual framework that included both disease-specific and generic domains, followed by qualitative interviews with patients, parents, and health care professionals. Cognitive testing of the items was then performed with revisions to the items and scales as necessary [19–21].

The instrument underwent psychometric testing in its original version [7, 19–21] and was then slightly revised. This revision included adding two items to the Role Functioning and one item to the Social Functioning scales of the teen/adult version, deleting one item from the Emotional Functioning and adding one item to the Social Functioning scales of the child version, and rewording one item on the Treatment Burden scale of the parent version.

In its revised form, the CFQ-R is currently the most widely used and well-validated PRO for CF [4, 10] and is the only instrument with versions for young children and parent caregivers [19]. The CFQ-R has now been translated into 34 languages, is being used in both international clinical trials and quality improvement initiatives at CF care sites in the US, and has appeared in dozens of publications [4, 10]. The CFQ-R Respiratory Symptom Scale has been used as an outcome measure in clinical trials evaluating the efficacy of new therapies, including inhaled antibiotics [3, 22], hypertonic saline [23, 24], and gene correctors and potentiators [25]. The CFQ-R Respiratory Symptoms Scale was recently used as a primary endpoint to support the approval of aztreonam for inhalation, a new inhaled antibiotic, for patients with CF [3]. The purpose of the current study was to evaluate the psychometric properties of the revised version of the CFQ-R, across all developmental versions (school-age children and their parents, adolescents, and adults with CF), and to provide normative data on a large, national sample of patients with CF ages 6 years through adulthood to aid in interpretation

of test scores. Test–retest reliability and the MID have been established previously [6, 7].

Objectives of the study

The overall objective of this study was to evaluate the psychometric properties of the CFQ-R in a national sample of children, teens, and adults with CF, as well as parent caregivers. Specific objectives included:

1. Evaluation of CFQ-R scores for children, teens, and adults with CF and parent caregivers to provide normative data, estimation of floor and ceiling effects, and internal consistency.
2. Evaluation of discriminant validity comparing patients seen for "well" versus "sick" visits and among stages of lung disease based on pulmonary function.
3. Evaluation of gender differences between males and females with CF on specific domains of functioning.
4. Evaluation of agreement between parent–child dyads.
5. Evaluation of convergence between CFQ-R scores and health outcomes, including pulmonary function, body mass index (BMI), and number of courses of intravenous (IV) antibiotics.

Methods

The Epidemiologic Study of Cystic Fibrosis (ESCF) is a multicenter, longitudinal cohort study initiated by Genentech, Inc., in 1994 to collect data on care practices and outcomes of CF patients in the US. Beginning in 2003, HRQOL was assessed using a disease-specific instrument, the CFQ-R, which was administered *before* evaluation of objective clinical measures (e.g., spirometry) in order to prevent any bias in completing the PRO [7, 19]. The child version has fewer items (35 items) than the parent (44 items) or teen/adult version (50 items; see Table 1 for a list of scales and exemplar items). Responses are made using 4-point Likert rating scales that include frequency (always, often, sometimes, never), intensity (a great deal, somewhat, a little, not at all), and true–false scales (very true, somewhat true, somewhat false, very false). Scores are standardized

Table 1 CFQ-R scales and exemplar items

Domains/scales	Teen/adult		Child		Parent	
	# Items	Example item	# Items	Example item	# Items	Example item
Physical Functioning	8	20. I have to limit vigorous activities, such as running or playing sports	6	4. You were able to run as quickly and as long as others	9	14. My child has trouble recovering after physical effort
Emotional Functioning	5	7. You felt worried	8	10. You felt worried	5	7. Seemed worried
Social Functioning/ School Functioning	6	23. I get together with my friends a lot	7	20. You felt left out	3	28. My child is able to keep up with his/her school work or summer activities
Body Image	3	25. I think I look different from others my age	3	27. You thought you were too thin	3	19. My child feels small compared to other kids the same age
Eating Problems	3	21. I have to force myself to eat	3	15. You had trouble eating	2	17. Mealtimes are a struggle
Treatment Burden	3	15. To what extent do your treatments make your daily life more difficult?	3	16. You had to stop fun activities to do your treatments	3	18. My child's treatments get in the way of his/her activities
Respiratory Symptoms	6	41. Have you been coughing during the day?	4	33. You coughed during the day	6	36. My child coughed during the day
Digestive Symptoms	3	49. Have you had abdominal pain?	1	35. Your stomach hurt	3	41. My child had abdominal pain
Vitality	4	10. You felt energetic			5	12. Seemed energetic
Health Perceptions	3	32. I feel healthy			3	22. My child feels healthy
Weight	1	39. Have you had trouble gaining weight?			1	33. My child has trouble gaining weight
Role Functioning	4	35. How often does CF get in the way of meeting your school, work, or personal goals?				

across scales and range from 0 to 100, with higher scores indicating better HRQOL.

Data on patient demographics, spirometry, anthropometric characteristics, and therapies were collected at each clinic encounter. For children ages 6–11 years, the CFQ-R was administered by a trained nurse coordinator. Children were trained to use the rating scales on two practice items that corresponded to blue and orange rating cards which were used during administration. Children and parents completed the CFQ-R in separate rooms. All sites entered the data using electronic data capture with edit checks. This study was approved by the institutional review board at each participating site, and all participants or their guardians provided written informed consent.

Study population

Patients completed the age-appropriate CFQ-R between February 2003 and November 2005. The first age-appropriate CFQ-R form for each patient was used in this analysis, regardless of whether patients completed measures at multiple assessments. A patient was considered "sick" when completing the CFQ-R if there was any indication of sickness (as noted by the clinician on the encounter form) within ±21 days of the CFQ-R date. A patient was classified as "well" when completing the CFQ-R if there was at least one well encounter within ±21 days of the CFQ-R date. If no encounters were observed within this window, the closest encounter within 90 days before administration of the CFQ-R was used; if this encounter was "well" and there were only well or missing pulmonary function tests since that date, then the patient was considered "well" at the point of CFQ-R administration. The remainder of CFQ-Rs (those not classified as sick or well) were considered ambiguous and excluded from analysis. Patients were categorized according to forced expiratory volume in 1 s (FEV_1) % predicted score closest to their date of CFQ-R (normal 100+; mild 70 to <100; moderate 40 to <70; severe <40).

Statistical analysis

Descriptive statistics were generated for demographic and clinical variables for each CFQ-R version (child, parent, teen/adult). Means and standard deviations of the domain scores were calculated within each version for all the CFQ-R forms and by visit type (sick versus well), disease stage (as defined by FEV_1% predicted), and gender. For the sick-versus-well analysis, all available CFQ-R forms were used, including multiple forms per patient. Comparisons were drawn between groups within each version by calculating effect sizes (for visit type and gender) or by performing one-way analyses of variation (ANOVAs) with Tukey adjustment (for disease stage). *P* values should not be

interpreted as tests of any specific null hypotheses, but rather as indexing the strengths of associations; hence, no adjustment for Type I error was made. The presence of linear trends of CFQ-R scores across disease stage categories was assessed for each version. Intraclass correlation coefficients were generated to assess agreement between parent–child dyads. Pearson correlation coefficients were calculated between CFQ-R scores and clinical outcomes (BMI, FEV_1% predicted, and the number of IV antibiotic–treated exacerbations within the past year for each version).

Results

Among the 32,585 patients enrolled in the ESCF, 14,268 unique CFQ-Rs were completed by patients or their parents during a clinic visit. Of the completed CFQ-Rs, 9,566 (67.1%) were from visits classified as "well" and 3,871 (27.1%) from visits classified as "sick." Another 831 (5.8%) were determined to be ambiguous and excluded from analysis. Therefore, 13,437 CFQ-Rs corresponding to 7,330 patients were included in the analysis: 4,679 teens and adults (ages ≥ 14 years), and 2,068 school-age children (ages 6–13 years). Additionally, 2,728 parents of school-age children (2,145 of whom were also included in the school-age children sample) completed proxy versions of the CFQ-R. Demographic and medical data for each sample are reported in Table 2. The demographic characteristics of this sample were similar to those reported in the national CF Foundation Patient Registry [26].

Descriptive statistics, floor and ceiling effects, and internal consistency

Means and standard deviations for each version of the CFQ-R (child, parent, teen/adult) are presented in Table 3. To examine potential floor and ceiling effects, distributions of scores (0–100 standardized values) were calculated for each domain and version of the CFQ-R. The percentage of respondents with scores less than or equal to 5 were considered at "floor" and those with scores greater than or equal to 95 were considered at "ceiling." Minimal floor effects were found across the eight domains of the CFQ-R Child version, ranging from 0.1 to 4.8%, with lowest scores found in Social and Emotional Functioning. Ceiling effects ranged from 6.9 to 46.5% and were most prevalent in three domains: Digestion (37.2%), Body Image (39.6%), and Eating (46.5%). Minimal floor effects were found across the 12 domains of the CFQ-R Parent instrument, ranging from 0.0 (Vitality and Emotional Functioning) to 16.8% (Weight). Ceiling effects ranged from 3.1 to 50.3% and were most prevalent in four domains: Body Image (32.8%), Eating (50.3%), School Functioning (34.6%), and Weight

Table 2 Patient demographics and clinical characteristics by CFQ-R version

Characteristic	Teen/adult	Child	Parent[a]
All patients (N)	4,679	2,068	2,728
Age at CFQ, mean ± SD	23.5 ± 9.6	9.7 ± 2.4	9.2 ± 2.8
Gender, n (%)			
Male	2,459 (52.6)	1,055 (51.0)	1,393 (51.1)
Female	2,220 (47.4)	1,013 (49.0)	1,335 (48.9)
Race/ethnicity, n (%)			
White	4,322 (92.4)	1,825 (88.3)	2,364 (86.8)
Black	126 (2.7)	63 (3.0)	98 (3.6)
Hispanic	157 (3.4)	124 (6.0)	177 (6.5)
Other	72 (1.5)	55 (2.7)	83 (3.0)
Number of IV exacerbations in past year, mean ± SD	0.7 ± 1.2	0.4 ± 0.8	0.4 ± 0.8
BMI (maximum within 21 days), mean ± SD	21.1 ± 3.3	17.0 ± 2.4	16.8 ± 2.5
BMI (closest within 21 days), mean ± SD	21.0 ± 3.3	17.0 ± 2.4	16.8 ± 2.5
FEV_1% predicted (maximum within 21 days), mean ± SD	66.5 ± 25.1	88.4 ± 20.4	88.6 ± 20.5
FEV_1% predicted (closest within 21 days), mean ± SD	65.5 ± 25.3	87.4 ± 21.2	87.6 ± 21.2
PA in past year, n (%)	3,044 (73.3)	886 (46.4)	1,094 (43.6)

BMI body mass index, *CFQ-R* Cystic Fibrosis Questionnaire-revised, *FEV$_1$* forced expiratory volume in 1 s, *PA Pseudomonas aeruginosa*, *SD* standard deviation

[a] Data from the children for whom the parents are reporting

(37.9%). Similarly, few floor effects were found in the teen/adult instrument, ranging from 0.0 to 14.5%. Ceiling effects ranged from 3.1 (Vitality) to 66.3% (Eating) and were most prevalent in two domains: Eating (66.3%) and Weight (47.4%).

Internal consistency coefficients for each domain were calculated using the Cronbach alpha, with a majority of scales demonstrating adequate reliability using a standard of 0.70, or 0.60 for newly developed scales [27]. Reliability for the majority of the CFQ-R Child scales was acceptable, with lower reliabilities found on the Treatment Burden and Social Functioning scales. The majority of scales in the Parent version also demonstrated acceptable reliability, with lower reliabilities found on the Treatment Burden and School Functioning scales. Good reliability was also found for the teen/adult measure, with lower reliabilities on the Treatment Burden and Social Functioning scales (see Table 3).

Discriminant validity

First, discriminant validity was evaluated by comparing CFQ-R scores completed during a "sick" versus "well" visit. For the Child version, 636 sick CFQ-Rs and 1,943 well CFQ-Rs were completed. Significant differences between the groups were found in all CFQ-R domains, with children who were sick consistently reporting worse HRQOL scores than children who were well (Student's *t* test; data not shown). Similar results were found for the CFQ-R Parent version. CFQ-R scores for 980 sick visits were significantly lower than the 2,984 scores generated during a well visit across all domains. Finally, comparisons of 2,255 sick visit scores for the teen/adult sample were

significantly different from the 4,639 well-visit scores. With the exception of the Digestion scale on the Teen/Adult version, all comparisons were statistically significant, with lower scores reported by those completing the measure during a sick visit; comparisons and effect sizes are reported in Table 4. Thus, CFQ-R scores on all scales and across all versions demonstrated strong discriminant validity.

Next, the ability of the CFQ-R scales to differentiate among levels of disease stage was evaluated using ANOVA with Tukey adjustments for all pairwise comparisons. Most scales were expected to vary by lung function, providing evidence of convergent validity. The Digestion scale was not expected to differ by lung function and, thus, provides a basis for comparison. Patients were categorized into four levels of disease stage on the basis of their FEV_1% predicted score. Strong support was found for this hypothesis. Significant differences in CFQ-R scores were found between all levels of disease stage for a majority of CFQ-R Child scales, except Emotional and Social Functioning and Treatment Burden. For these domains, significant differences were generally found between those with normal or mild disease and those with severe disease (see Fig. 1). As hypothesized, scores on Digestion did not differ significantly by disease stage. Similar results were found for the CFQ-R Parent version, with significant differences found for a majority of domains except Emotional Functioning, School Functioning, Weight, and Treatment Burden. In general, these scales differentiated between patients with normal and mild disease versus those with severe disease. As expected, Digestion did not differ across levels of lung disease stage. For the CFQ-R Teen/Adult version, all scales differed

Table 3 CFQ-R domains by version

Characteristic	Teen/adult	Cronbach alpha	Child	Cronbach alpha	Parent[a]	Cronbach alpha
All patients, n	4,679	0.88[b]	2,068	0.72[b]	2,728	0.81[b]
Physical Functioning, mean ± SD	71.7 ± 27.4	0.94	77.3 ± 21.1	0.75	83.8 ± 19.1	0.91
Role Functioning, mean ± SD	80.1 ± 20.2	0.83	NA	NA	NA	NA
Vitality, mean ± SD	59.5 ± 20.6	0.80	NA	NA	69.7 ± 15.5	0.73
Emotional Functioning, mean ± SD	76.4 ± 20.0	0.77	73.9 ± 14.8	0.67	82.7 ± 15.3	0.65
Social Functioning, mean ± SD	72.4 ± 17.9	0.58	67.9 ± 18.0	0.55	NA	NA
Body Image, mean ± SD	70.6 ± 26.7	0.65	77.8 ± 26.2	0.58	71.7 ± 28.0	0.72
Eating Problems, mean ± SD	89.7 ± 18.2	0.82	82.8 ± 22.2	0.69	78.4 ± 27.6	0.80
Treatment Burden, mean ± SD	61.5 ± 21.0	0.51	68.8 ± 22.1	0.34	63.5 ± 23.1	0.59
Health Perceptions, mean ± SD	67.2 ± 24.1	0.79	NA	NA	77.1 ± 19.3	0.67
Weight, mean ± SD	66.5 ± 37.2	SIS	NA	NA	60.3 ± 37.2	SIS
Respiratory Symptoms, mean ± SD	62.9 ± 22.6	0.87	73.6 ± 20.0	0.69	75.4 ± 19.2	0.82
Digestive Symptoms, mean ± SD	80.3 ± 19.1	0.68	71.8 ± 27.1	SIS	71.4 ± 19.2	0.63
School Functioning, mean ± SD	NA	NA	NA	NA	76.9 ± 23.2	0.55

[a] Data from the children for whom the parents are reporting

[b] Cronbach alpha depicting overall agreement between all scales; *NA* not applicable; *SIS* single-item scale (Cronbach alpha cannot be calculated)

significantly by disease stage, except for Eating Problems, Role Functioning, and Emotional Functioning, which differed significantly across all comparisons except that for normal versus mild disease. As hypothesized, Digestion scores did not differ significantly by any level of disease stage (see Fig. 1). Furthermore, significant linear trends across disease stage categories were observed for all CFQ-R scales and versions, except for Digestion (no trend for any version).

Gender differences in teens and adults with CF

Based on well-established differences in pulmonary functioning and survival between males and females with CF, with more rapid declines in pulmonary functioning and a shorter life span observed for women, gender differences were expected on the CFQ-R Teen/Adult instrument. Specifically, social pressures to be thin were expected to affect females differentially, leading to higher scores for them than for males on domains related to eating problems, body image, and weight. This hypothesis was partially supported; significant gender differences were found in the predicted direction on two of the three scales. Teen and adult males reported significantly better HRQOL in all CFQ-R domains except Body Image and Weight, in which females reported better scores (Table 5).

Agreement between parent–child dyads on the CFQ-R

Intraclass correlation coefficients were calculated between parent–child dyads to assess the extent of agreement (P values < 0.001, unless otherwise noted). Paired correlations indicated significant agreement between dyads across all scales (r's, 0.26–0.56); however, stronger agreement was found on domains that measured more *observable* signs and symptoms, such as Physical Functioning ($r = 0.46$), Eating Problems ($r = 0.56$), and Respiratory Symptoms ($r = 0.55$). Lower agreement was found for Emotional Functioning ($r = 0.28$) and Treatment Burden ($r = 0.26$), with children reporting significantly worse Emotional Functioning than parents; in contrast, parents, who are primarily responsible for daily treatments, reported worse Treatment Burden than children.

Associations between CFQ-R scales and health outcomes

To evaluate the construct validity and clinical utility of the CFQ-R, correlations were calculated between CFQ-R scores and several key health outcomes, including $FEV_1\%$ predicted, number of pulmonary exacerbations treated with IV antibiotics, and BMI. Given the large sample size, only correlations with magnitude of 0.20 or higher were reported. For children, moderate associations were found between the CFQ-R Physical Functioning and Respiratory Symptoms domains and $FEV_1\%$ predicted, with r's of 0.33 and 0.32, respectively. A similar pattern was observed for Physical Functioning and Respiratory Symptoms and number of IV-treated exacerbations, with r's of -0.23 and -0.24, respectively. The CFQ-R Eating scale was also modestly correlated with BMI ($r = 0.22$). In all cases, better HRQOL was correlated with better health outcomes.

Similar patterns were found for the CFQ-R Parent version. Significant associations were found between the

**Table 4** CFQ-R scores and effect sizes by visit type

CFQ-R scale	Teen/adult			Child			Parent[a]		
	Well CFQ Mean (95% CI) $n = 4,639$	Sick CFQ Mean (95% CI) $n = 2,255$	Effect Size[b]	Well CFQ Mean (95% CI) $n = 1,943$	Sick CFQ Mean (95% CI) $n = 636$	Effect size[b]	Well CFQ Mean (95% CI) $n = 2,984$	Sick CFQ Mean (95% CI) $n = 980$	Effect size[b]
Physical functioning	77.0 (76.3–77.8)	59.8 (58.7–60.9)	−0.697	79.5 (78.6–80.4)	70.5 (68.9–72.1)	−0.457	86.1 (85.5–86.8)	75.9 (74.8–77.1)	−0.579
Role functioning	84.0 (83.4–84.6)	72.7 (71.9–73.5)	−0.631	NA	NA	NA	NA	NA	NA
Vitality	63.3 (62.8–63.9)	51.4 (50.6–52.2)	−0.629	NA	NA	NA	71.3 (70.7–71.8)	64.3 (63.3–65.2)	−0.470
Emotional functioning	78.6 (78.0–79.2)	72.6 (71.8–73.4)	−0.319	74.9 (74.2–75.5)	72.6 (71.4–73.7)	−0.159	83.6 (83.1–84.2)	80.1 (79.1–81.0)	−0.242
Social functioning	74.5 (74.0–75.0)	67.8 (67.1–68.5)	−0.391	69.0 (68.2–69.8)	65.6 (64.1–67.0)	−0.194	NA	NA	NA
Body image	73.6 (72.8–74.4)	65.9 (64.8–67.0)	−0.301	79.0 (77.8–80.1)	75.5 (73.5–77.6)	−0.135	73.2 (72.2–74.2)	65.3 (63.5–67.0)	−0.293
Eating problems	92.2 (91.7–92.7)	85.1 (84.3–85.8)	−0.452	84.2 (83.2–85.1)	80.8 (79.1–82.5)	−0.159	80.3 (79.3–81.3)	75.7 (74.0–77.4)	−0.173
Treatment burden	63.7 (63.1–64.3)	57.1 (56.5–58.4)	−0.328	70.1 (69.1–71.1)	66.7 (65.0–68.5)	−0.153	65.4 (64.5–66.2)	58.3 (56.9–59.8)	−0.305
Health perceptions	71.7 (71.0–72.3)	57.5 (56.5–58.4)	−0.636	NA	NA	NA	79.8 (79.1–80.4)	68.4 (67.2–69.6)	−0.618
Weight	70.7 (69.7–71.8)	59.4 (57.9–60.9)	−0.325	NA	NA	NA	63.5 (62.2–64.8)	52.6 (50.3–54.9)	−0.303
Respiratory symptoms	68.6 (68.0–69.2)	52.1 (51.3–53.0)	−0.825	76.6 (75.8–77.5)	65.6 (64.1–67.1)	−0.594	79.3 (78.6–79.9)	63.0 (61.9–64.2)	−0.952
Digestive symptoms	81.2 (80.7–81.8)	79.6 (78.8–80.4)	−0.086	73.3 (72.0–74.5)	68.5 (66.4–70.6)	−0.181	72.5 (71.8–73.2)	69.8 (68.6–71.0)	−0.144
School functioning	NA	NA	NA	NA	NA	NA	78.3 (77.4–79.1)	74.1 (72.6–75.5)	−0.184

CFQ-R Cystic Fibrosis Questionnaire-Revised, CI confidence interval, NA not applicable

[a] Data from the children for whom the parents are reporting

[b] Effect size was calculated as difference in means (Well–Sick) divided by the standard deviation of well CFQ-R visits

Fig. 1 Mean CFQ-R score by disease severity.*For all significant linear trend was detected, except on the digestive symptoms scale
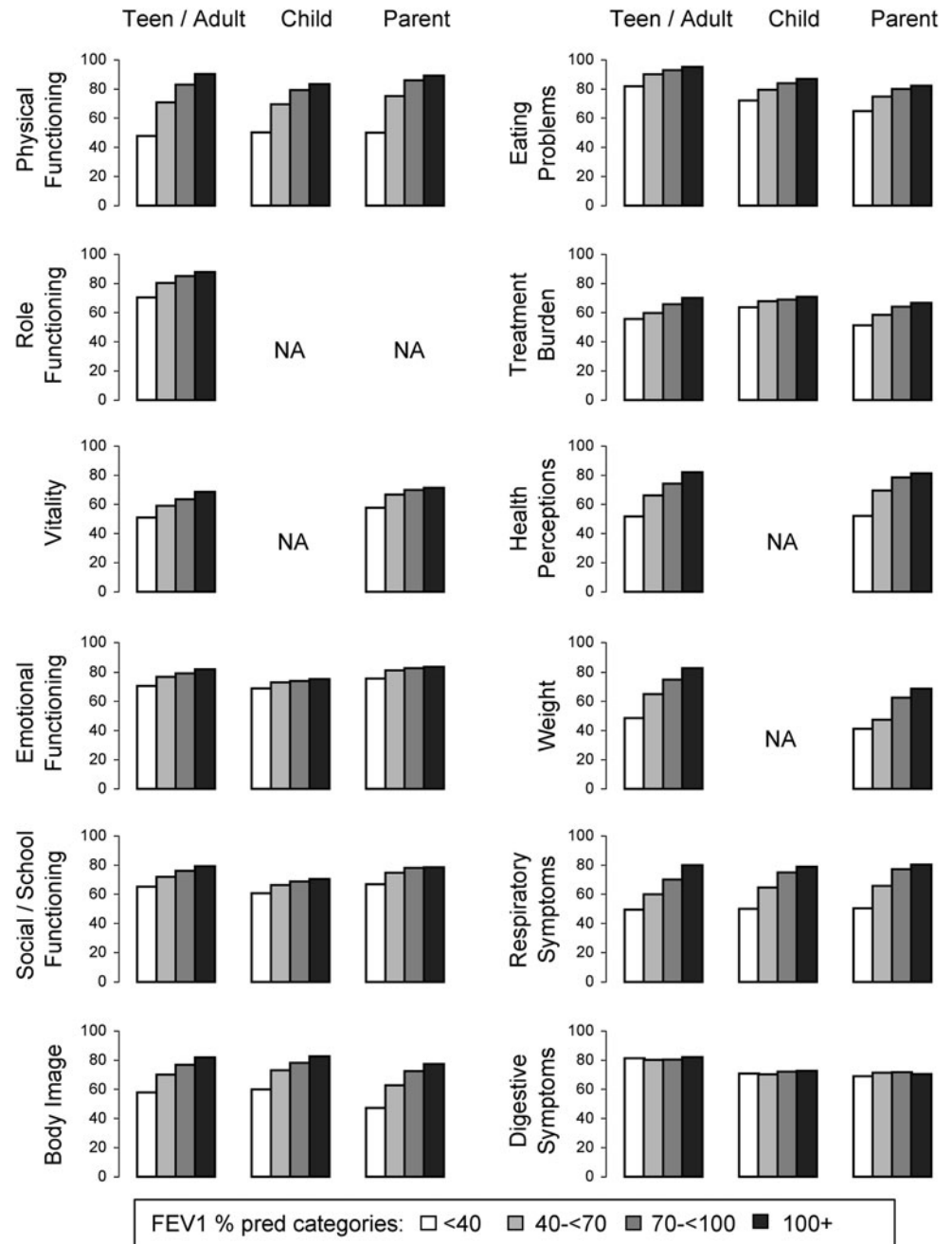
following CFQ-R scales and $FEV_1\%$ predicted: Physical Functioning ($r = 0.38$), Respiratory Symptoms ($r = 0.33$), Health Perceptions ($r = 0.30$), and Body Image ($r = 0.22$). Number of exacerbations was also significantly correlated with Physical Functioning ($r = -0.34$), Respiratory Symptoms ($r = -0.28$), and Health Perceptions ($r = -0.27$). Finally, BMI was significantly associated with Weight ($r = 0.42$) and Eating Problems ($r = 0.24$). In all cases, higher CFQ-R scores were associated with better health outcomes.

For the CFQ-R Teen/Adult measure, strong associations were found between the following CFQ-R scales and both $FEV_1\%$ predicted and number of exacerbations, respectively: Physical Functioning (r's = 0.51 and -0.35), Role Functioning (r's = 0.29 and -0.32), Vitality (r's = 0.26 and -0.25), Health Perceptions (r's = 0.40 and -0.30), and Respiratory Symptoms (r's = 0.42 and -0.27). Significant associations were also found between $FEV_1\%$ predicted and Social Functioning ($r = 0.25$), Body Image ($r = 0.29$), and Weight ($r = 0.29$). Moderate associations

Table 5 CFQ-R scores and effect sizes by gender

CFQ-R scale	Teen/Adult			Child			Parent[a]		
	Male mean (95% CI) n = 2,459	Female mean (95% CI) n = 2,220	Effect size[b]	Male mean (95% CI) n = 1,055	Female mean (95% CI) n = 1,013	Effect size[b]	Male mean (95% CI) n = 1,393	Female mean (95% CI) n = 1,335	Effect size[b]
Physical functioning	75.7 (74.6–76.8)	67.3 (66.2–68.5)	−0.306	78.0 (76.7–79.3)	76.6 (75.3–77.9)	−0.065	85.2 (84.2–86.2)	82.3 (81.3–83.3)	−0.153
Role functioning	82.3 (81.5–83.1)	77.6 (76.8–78.4)	−0.234	NA	NA	NA	NA	NA	NA
Vitality	61.8 (61.0–62.6)	56.9 (56.1–57.8)	−0.237	NA	NA	NA	70.3 (69.5–71.1)	69.2 (68.3–70.0)	−0.074
Emotional functioning	77.7 (77.0–78.5)	75.0 (74.2–75.8)	−0.137	74.8 (73.9–75.7)	72.9 (72.0–73.9)	−0.128	82.6 (81.8–83.4)	82.9 (82.1–83.7)	0.020
Social functioning	73.9 (73.2–74.6)	70.7 (70.0–71.5)	−0.177	67.3 (66.2–68.4)	68.6 (67.56–69.7)	0.073	NA	NA	NA
Body image	67.2 (66.2–68.3)	74.4 (73.3–75.5)	0.267	77.5 (75.9–79.1)	78.1 (76.4–79.7)	0.021	71.4 (69.9–72.8)	72.0 (70.5–73.5)	0.022
Eating problems	90.6 (89.9–91.3)	88.6 (87.9–89.4)	−0.110	82.5 (81.1–83.8)	83.2 (81.9–84.6)	0.034	77.7 (76.2–79.1)	79.1 (77.6–80.5)	0.050
Treatment burden	62.9 (62.0–63.7)	60.0 (59.1–60.9)	−0.137	68.2 (66.9–69.5)	69.5 (68.1–70.8)	0.057	64.3 (63.1–65.5)	62.6 (61.4–63.9)	−0.072
Health perceptions	68.3 (67.3–69.2)	66.0 (65.0–67.0)	−0.093	NA	NA	NA	78.1 (77.0–79.1)	76.1 (75.1–77.2)	−0.100
Weight	59.9 (58.5–661.4)	73.8 (72.2–75.3)	0.372	NA	NA	NA	58.2 (56.2–60.2)	62.5 (60.5–64.5)	−0.115
Respiratory symptoms	65.0 (64.1–65.9)	60.7 (59.8–61.6)	−0.189	74.4 (73.2–75.6)	72.8 (71.5–74.0)	−0.084	76.3 (75.3–77.3)	74.6 (73.5–75.6)	−0.090
Digestive symptoms	80.9 (80.1–81.7)	79.6 (78.8–80.4)	−0.066	72.0 (70.4–73.7)	71.6 (69.9–73.3)	−0.015	70.2 (69.1–71.2)	72.7 (71.7–73.8)	−0.133
School functioning	NA	NA	NA	NA	NA	NA	74.5 (73.2–75.7)	79.5 (78.2–80.7)	−0.215

CFQ-R Cystic Fibrosis Questionnaire-Revised, CI confidence interval, NA not applicable

[a] Data from the children for whom the parents are reporting

[b] Effect size was calculated as difference in means (male–female) divided by the pooled standard deviation

were found between BMI and Body Image ($r = 0.34$) and Weight ($r = 0.44$). In all cases, higher CFQ-R scores were correlated with better health outcomes.

Discussion

Overall, the results of this study supported the psychometric properties of the CFQ-R, a PRO measure that can be completed by patients across the life span from early childhood through adulthood, with a proxy report for parents of school-age children. We tested this instrument using a national sample that was similar to the CF Foundation Patient Registry data in terms of demographic and health variables, suggesting that our results are generalizable to the larger US community of CF patients. Minimal floor and ceiling effects were observed on a majority of scales, suggesting that the items cover a broad range of functioning, which allows for differentiation among patients. Scores on the CFQ-R discriminated between patients attending the sites for a sick visit versus a well visit and between patients who differed in lung function. Little evidence of "response shift" was observed: patients who had more severe pulmonary disease reported worse symptoms and greater impairments in daily functioning. Further, the CFQ-R scales were significantly associated with relevant health outcome variables (e.g., lung function, BMI).

As expected, teen and adult females reported worse HRQOL in a majority of domains when compared to males. This may be partially related to differences in health outcomes between women and men with CF, with women experiencing greater morbidity and earlier mortality. However, women reported *better* functioning on scales that measured body image and weight, which could be related to a societal preference for thinness in women, regardless of the health consequences of low body weight in CF. This suggests that targeted education on the links between poor nutritional status and worse lung function should be emphasized because of nutrition's effects on long-term health. Clinicians may need to more directly address issues related to eating and weight gain in young women with CF.

Parents and children demonstrated good agreement on symptoms and behaviors that were observable, such as eating, ability to climb stairs, and frequency of cough. These results parallel those found in the child psychology literature, which have consistently found higher agreement on externalizing behaviors, such as oppositional behavior, than internalizing symptoms of depression [28, 29]. In the recently published FDA Guidance, parent proxy measures were recommended only for symptoms and behaviors that can be observed by parents [1]. Our findings, and those reported in Belgium and Germany [30, 31], also show that

children reported worse emotional functioning than their parents were aware of, suggesting that measuring both respondents' perceptions of HRQOL is important. The CFQ-R is one of the few PRO tools with a validated version for children. We are currently developing a pictorial version of the CFQ-R for preschoolers (3–6 years) with CF [32].

This study had several limitations. First, the study coordinators at each site were responsible for entering the data into an electronic data capture system; however, there was no source verification. Second, although good discriminant validity was demonstrated across CFQ-R versions, the Child instrument was limited by less variability in disease stage as measured by lung function: few school-age children had FEV_1 below 70% predicted [33]. Finally, although the means and standard deviations showed a reasonable distribution of responses and good discrimination between sick and well visits, ceiling effects were observed on the Eating Problems scale across the three versions. In general, both patients and parent caregivers tended to report minimal eating problems and relatively good HRQOL in this domain.

Our results demonstrated strong convergence between CFQ-R scales and key health outcomes. For example, good correlations were found between the CFQ-R Respiratory Symptoms scale and FEV_1% predicted and number of IV antibiotic courses. Convergent validity was found between CFQ-R scales and both pulmonary and nutritional outcomes, indicating that these items accurately reflect their underlying constructs.

Newly available descriptive statistics (Online Resource appendices 1–4) have been calculated to provide clinicians with values that can be used to compare individual patients to this large, national sample, which should greatly facilitate interpretation of these scores. For patients with CFQ-R forms during "well" visits, score deciles were generated for each CFQ-R domain, stratified by disease severity (FEV_1% predicted), gender, and age group (teens/adults and children). For example, providers can look up the normative CFQ-R values for an adolescent female with mild lung disease obtained during a "well" visit and compare her scores to a similar patient being seen that day. If that young woman scored, for instance, at the 10th percentile of same-age peers on the Eating Problems and Body Image domains, a referral to the dietitian on the multidisciplinary team could be made. Further, if a new medication is added to the CF treatment regimen, clinicians can monitor potential improvements in respiratory or digestive symptoms on the CFQ-R, as well as its impact on perceptions of treatment burden.

In conclusion, this measure has demonstrated robust psychometric properties in a large national sample of patients with CF and their parents. Strong evidence of

reliability, discriminant validity, and convergence with pre-specified health outcomes was found. It is also one of the few PRO measures with developmentally appropriate versions across the life span.

References

1. Center for Drug Evaluation and Research. (2009). *Guidance for industry. Patient-reported outcome measures: Use in medical product development to support labeling claims*. US Department of Health and Human Services, Food and Drug Administration. December 2009. http://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed July 1, 2010.

2. Fayers, P., & Hays, R. (Eds.). (2005). *Assessing quality of life in clinical trials: Methods, practice* (2nd ed.). New York: Oxford University Press.

3. Retsch-Bogart, G. Z., Quittner, A. L., Gibson, R. L., Oermann, C. M., McCoy, K. S., Montgomery, A. B., et al. (2009). Efficacy and safety of inhaled Aztreonam Lysine for airway *Pseudomonas* in cystic fibrosis. *Chest, 135*(5), 1223–1232.

4. Goss, C. H., & Quittner, A. L. (2007). Patient-reported outcomes in cystic fibrosis. *Proceedings of the American Thoracic Society, 4*(4), 378–386.

5. Quittner, A. L., Modi, A., & Cruz, I. (2008). Systematic review of health-related quality of life measures for children with respiratory conditions. *Paediatric Respiratory Reviews, 9*(3), 220–232.

6. Quittner, A. L., Modi, A. C., Wainwright, C., Otto, K., Kirihara, J., & Montgomery, A. B. (2009). Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. *Chest, 135*(6), 1610–1618.

7. Quittner, A. L., Buu, A., Messer, M. A., Modi, A. C., & Watrous, M. (2005). Development and validation of the cystic fibrosis Questionnaire in the United States: A health-related quality-of-life measure for cystic fibrosis. *Chest, 128*(4), 2347–2354.

8. Kaplan, R. M., Anderson, J. P., Wu, A. W., Mathews, W. C., Kozin, F., & Orenstein, D. (1989). The quality of well-being scale. Applications in AIDS, cystic fibrosis, and arthritis. *Medical Care, 27*(3 Suppl), S27–S43.

9. Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473–483.

10. Palermo, T. M., Long, A. C., Lewandowski, A. S., Drotar, D., Quittner, A. L., & Walker, L. S. (2008). Evidence-based assessment of health-related quality of life and functional impairment in pediatric psychology. *Journal of Pediatric Psychology, 33*, 983–996.

11. Scoggins, J. F., & Patrick, D. L. (2009). The use of patient-reported outcomes instruments in registered clinical trials: Evidence from ClinicalTrials.gov. *Contemporary Clinical Trials, 30*(4), 289–292.

12. Cystic Fibrosis Foundation Patient Registry. (2007). *Annual data report 2007*. Bethesda, MD: Cystic Fibrosis Foundation.

13. Quittner, A. L., Barker, D. H., Snell, C., Grimley, M. E., Marciel, K. K., & Cruz, I. (2008). Prevalence and impact of depression in cystic fibrosis. *Current Opinion in Pulmonary Medicine, 14*(6), 582–588.

14. Smith, B. A., Modi, A. C., Quittner, A. L., & Wood, B. L. (2010). Depressive symptoms in children with cystic fibrosis and parents and its effects on adherence to airway clearance. *Pediatric Pulmonology, 45*(8), 756–763.

15. Rosenfeld, M., Davis, R., FitzSimmons, S., Pepe, M., & Ramsey, B. (1997). Gender gap in cystic fibrosis mortality. *American Journal of Epidemiology, 145*(9), 794–803.

16. Courtney, J. M., Bradley, J., McCaughan, J., O'Connor, T. M., Shortt, C., Bredin, C. P., et al. (2007). Predictors of mortality in adults with cystic fibrosis. *Pediatric Pulmonology, 42*(6), 525–532.

17. Briesacher, B. A., Quittner. A. L., Fouayzi, H., Zhang, J., & Swensen, A. (2011). *Nationwide trends in the medical care costs of privately-insured patients with cystic fibrosis, 2001–2007*. Pediatric Pulmonology (in press).

18. Sawicki, G. S., Sellers, D. E., & Robinson, W. M. (2009). High treatment burden in adults with cystic fibrosis: Challenges to disease self-management. *Journal of Cystic Fibrosis, 8*(2), 91–96.

19. Modi, A. C., & Quittner, A. L. (2003). Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. *Journal of Pediatric Psychology, 28*(8), 535–545.

20. Henry, B., Aussage, P., Grosskopf, C., & Goehrs, J. M. (2003). Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Quality of Life Research, 12*(1), 63–76.

21. Quittner, A. L., Sweeny, S., Watrous, M., Munzenberger, P., Bearss, K., Gibson Nitza, A., et al. (2000). Translation and linguistic validation of a disease-specific quality of life measure for cystic fibrosis. *Journal of Pediatric Psychology, 25*(6), 403–414.

22. McCoy, K. S., Quittner, A. L., Oermann, C. M., Gibson, R. L., Retsch-Bogart, G. Z., & Montgomery, A. B. (2008). Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine, 178*(9), 921–928.

23. Donaldson, S. H., Bennett, W. D., Zeman, K. L., Knowles, M. R., Tarran, R., & Boucher, R. C. (2006). Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *New England Journal of Medicine, 354*(3), 241–250.

24. Elkins, M. R., Robinson, M., Rose, B. R., Harbour, C., Moriarty, C. P., Marks, G. B., et al. (2006). A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *New England Journal of Medicine, 354*(3), 229–240.

25. Accurso, F. J., Rowe, S. M., Clancy, J. P., Boyle, M. P., Dunitz, J. M., et al. (2010). Effect of VX-770 in persons with cystic fibrosis and the G551D-*CFTR* mutation. *New England Journal of Medicine, 363*, 1991–2003.

26. Cystic Fibrosis Foundation. (2010). *Cystic fibrosis foundation patient registry: 2009 annual data report*. Bethesda, MD: Cystic Fibrosis Foundation.

27. Ware, J. E., Brook, R. H., Davies-Avery, A. R., Williams, K. N., Stewart, A., Rogers, W. H., et al. (1980). *Conceptualization and*

measurement of health for adults in the health insurance study: Vol. I, model of health and methodology. Rand Corporation, Santa Monica. Pub. no. R-1987/1-HEW.

28. Martin, J. L., Ford, C. B., Dyer-Friedman, J., Tang, J., & Huffman, L. C. (2004). Patterns of agreement between parent and child ratings of emotional and behavioral problems in an outpatient clinical setting: When children endorse more problems. *Journal of Developmental and Behavioral Pediatrics, 25*(3), 150–155.

29. Levi, R., & Drotar, D. (1998). *Measuring health-related quality of life in children and adolescents: implications for research and practice.* Mahwah, NJ: Lawrence Erlbaum Associates Publishers.

30. Havermans, T., Vreys, M., Proesmans, M., & De Boeck, C. (2006). Assessment of agreement between parents and children on health-related quality of life in children with cystic fibrosis. *Child: Care, Health and Development, 32*(1), 1–7.

31. Schmidt, A., Wenninger, K., Niemann, N., Wahn, U., & Staab, D. (2009). Health-related quality of life in children with cystic fibrosis: Validation of the German CFQ-R. *Health and Quality of Life Outcomes, 7,* 97.

32. Cruz, I., Marciel, K. K., Cheney, J., Wainwright, C., Campbell, M., & Quittner, A. L. (2009). The preschool cystic fibrosis questionnaire-revised: initial validation results. *Pediatric Pulmonology, 32*(Suppl), 421 (abstract).

33. VanDevanter, D. R., Rasouliyan, L., Murphy, T. M., Morgan, W. J., Ren, C. L., Konstan, M. W., et al. (2008). Trends in the clinical characteristics of the U.S. cystic fibrosis patient population from 1995 to 2005. *Pediatric Pulmonology, 43*(8), 739–744.