Qual Life Res (2012) 21:1837–1845
DOI 10.1007/s11136-011-0100-8

Health-related quality of life of Spanish children with cystic fibrosis

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Accepted: 18 December 2011 / Published online: 5 January 2012

Abstract
Purpose To investigate (1) the contributions of sex, age, nutritional status- and physical-fitness-related variables on health-related quality of life (HRQOL) in Spanish children with cystic fibrosis, and (2) the agreement on HRQOL between children and their parents.
Methods In 28 children aged 6–17 years, body mass index percentile, percentage body fat, physical activity, pulmonary function, cardiorespiratory fitness, functional mobility, and dynamic muscle strength were determined using objective measures. HRQOL was measured using the revised version of the cystic fibrosis questionnaire. Simple and multiple linear regression analyses were performed to determine the variables associated with HRQOL. To assess the agreement on HRQOL between children and parents, intra-class correlation coefficients (ICCs) were calculated.
Results Girls reported worse emotional functioning, a higher treatment burden, and more respiratory problems than boys. Greater functional mobility appeared associated with a less favourable body image and more eating disturbances. Agreement on HRQOL between children and parents was good to excellent, except for the domain of treatment burden.
Conclusions Sex and age were stronger predictors of HRQOL than nutritional status- or physical-fitness-related variables. Children reported a lower treatment burden than their parents perceived them to have.

Keywords Cystic fibrosis · Quality of life · Children · Parents · Physical fitness · Nutritional status

Abbreviations

CF	Cystic fibrosis
BMI	Body mass index
PA	Physical activity
HRQOL	Health-related quality of life
CFQ-R	Cystic fibrosis questionnaire-revised version
FEV_1	Forced expiratory volume in one second
VE_{peak}	Peak minute ventilation
VO_{2peak}	Peak oxygen uptake
TUG	Timed up and go
TUDS	Timed up and down stairs
ICC	Intra-class correlation coefficient

Background

Cystic fibrosis (CF) is a progressive autosomal-recessive disease, affecting ~1:2,500 Caucasian newborns [1]. Due to a defect in the CF transmembrane conductance regulator gene, excess mucus is produced in lungs, liver, pancreas, and reproductive organs [2]. In persons with CF, lung function is impaired and bacterial infections frequently

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occur [2]; absorption of nutrients is suboptimal, and resting energy expenditure is usually elevated due to chronic inflammation and excess mucus in the lungs [3]. Treatment of CF is mainly aimed at minimizing symptoms by means of, among others, chest physiotherapy, bronchodilators, and corticosteroids. To prevent rapid health deterioration in people with CF, a healthy lifestyle is vital. Sufficient calorie intake is stimulated because a healthy body weight is positively related to exercise capacity, pulmonary function, and survival [4, 5]. A sex- and age-adjusted body mass index (BMI) percentile $\geq$50 is recommended [5]. Regular physical activity (PA) is encouraged, as PA may slow the decline in pulmonary function [6], improve the ability to cope with activities of daily living, and prolong survival [4]. However, not only quantity, but also quality of life is an issue of concern in this chronically ill population. Health-related quality of life (HRQOL) is defined as 'a multidimensional construct comprising (at least) physical, psychological and social well-being and functioning as perceived by the individual' [7].

When aiming to improve HRQOL, insight into the physical-health-related factors associated with HRQOL should be obtained first. Various studies have been performed on this topic, all focusing on specific variables such as nutritional status or pulmonary function. A higher body-weight-for-age z-score has been associated with a more favourable body image and less eating disturbances [8]. Likewise, a higher BMI has been associated with a more favourable body image and better physical functioning [9]. Pulmonary function has been positively associated with HRQOL regarding respiratory symptoms and physical functioning [8]. We expected that most of these associations would be confirmed in Spanish children aged 6–17 years. However, the associations between PA-related variables and HRQOL are less well known. We hypothesized that a positive association would exist between cardiorespiratory fitness and most domains of HRQOL, as previously described for adults with CF [10]. Second, we hypothesized that being more physically active, having greater muscle strength, and having a better functional mobility would be positively associated with HRQOL regarding physical functioning. Third, we expected that PA would be negatively associated with HRQOL regarding respiratory symptoms. Probably, these associations would not be homogeneous across sex and age. Male sex has been consistently shown to be positively associated with various domains of HRQOL [11, 12]. Also, age differences in HRQOL have been reported [8]. As sex and age may be related to both HRQOL and the physical-health-related variables [13, 14], both variables were adjusted for in our analyses (see below).

Another issue to be further explored is the agreement between parents and children with regards to HRQOL. Parents, children, and care providers could benefit from parents' understanding of their children's HRQOL. In case the child is unable to complete the questionnaire independently, insight into his/her HRQOL can still be obtained using parent versions of HRQOL questionnaires. However, in previous studies with children with CF, parents appeared to lack sufficient insight into their children's HRQOL [15]. So far, a poorer agreement between parents and chronically ill children in the less-observable domains, for example, emotional and social functioning, and a higher agreement in the observable domains, for example, eating disturbances, digestive problems, and respiratory problems, has been described [15, 16]. We will explore whether this pattern is also true for a Spanish paediatric population.

The first aim of the present study was to determine the association of each domain of HRQOL as assessed by the CFQ-R, with (1) BMI percentile, (2) per cent body fat, (3) PA, (4) forced expiratory volume in one second (FEV_1), (5) peak minute ventilation (VE_{peak}), (6) peak oxygen uptake (VO_{2peak}), (7) dynamic muscle strength, (8) functional mobility, (9) sex, and (10) age. The second aim of our study was to assess the agreement between children and their parents on each domain of HRQOL.

Methods

Study population

Children with CF, 6–17 years of age, previously diagnosed by means of a genetic test and treated at the *Hospital Niño Jesús* or the *Hospital La Paz* in Madrid, were invited to participate. All children had CF of low-to-moderate severity and stable clinical condition. Children with the following conditions were excluded from the study: severe lung deterioration, as defined by FEV_1 below 40% of expected, hospitalization within the previous 3 months, or having *Burkholderia cepacia* infection. All children and one of their parents or caregivers provided written informed consent prior to the study. Ethical approval for this study was obtained from the Ethics Committee of the *Hospital Niño Jesús* in Madrid (approval number 006-09). The study was performed in accordance with the Declaration of Helsinki.

Measurements

Body weight was measured using a digital balance (Seca, Madrid, Spain) to the nearest 0.1 kilogram (kg), with the children wearing no shoes. Body height, without shoes, was measured using a stadiometer (Seca, Madrid, Spain) with the children in standing position, their heels and head against the wall and their faces in a horizontal plane, to the nearest 0.1 cm. Body mass index was calculated by

dividing weight in kg by height in metres (m) squared (kg/m^2). Body mass index percentiles were determined using the Centre of Disease Control BMI-for-age charts for boys and girls [17]. Additionally, triceps, abdominal, suprailiac, and thigh skinfolds were measured with a calliper (Holtan Crymych, United Kingdom). Body fat percentage was estimated using the equation described by Jackson and Pollock [18].

Physical activity (PA) was assessed using accelerometers (Actigraph 7164, Manufacturing technology Inc., Shalimar, Florida, USA), following the protocol of Ortega et al. [19], and the data on PA were processed using MAH/UFFE (version 1.9.0.3). Participants were instructed to wear the accelerometer on their lower back attached by an elastic belt during all waking hours. Since the monitors were not waterproof, participants were asked to take them off while bathing or swimming. Count data were stored each minute. Each sequence of 10 or more zero counts was deleted, assuming that the accelerometer was not worn at that interval. At least 5 days of recording including 2 weekend days, with a minimum of 10 h of registration per day, were necessary to be included in the study. Levels of PA were expressed as counts per minute.

Pulmonary function was determined according to the spirometry protocol by the American Thoracic Society [20], and we calculated the percentage of FEV_1 expected. As an additional indicator of pulmonary function, peak minute ventilation (VE_{peak}; litres [l]/min) was measured. The VO_{2peak} (ml/kg/min) was determined using open-circuit spirometry and paediatric face masks during a graded treadmill test (Technogym Run Race 1400HC; Gambettola, Italy). Gas exchange was measured breath-by-breath (Vmax 29c; Sensormedics; CA, USA). The test was performed after one familiarization session. According to the protocol of San Juan et al., treadmill speed began at 1 km/h, with an inclination of 5%. Every 15 s, the speed and inclination were increased by 0.1 km/h and 5%, respectively [21]. The test was terminated upon volitional fatigue or when the child showed loss of ability to maintain the required workload.

Dynamic upper- and lower-body muscle strength (kg) were measured using a seated bench, seated lateral row, and seated leg press machine, designed for use by a paediatric population (Strive Inc. Philadelphia, USA). We determined the six-repetition maximum (6RM) lifting ability, within the full rage of motion, in each muscle group, that is, pectoral, dorsal, and legs, until momentary muscular exhaustion. The protocol for these tests has been described in detail by San Juan et al. [21]. These tests showed a high reliability (all intra-class correlation coefficients for test–retest: $R \geq 0.98$, $P < 0.01$).

Functional mobility was assessed with the 3 m Timed Up and Go (TUG 3 m) test: the time (s) needed to stand up from a chair, walk 3 m, turn around, return to the chair, and sit down was recorded. Children also performed the Timed Up and Down Stairs (TUDS) test, in which the time (s) to ascent and descent 12 stairs was recorded. In both tests, performance time was measured to the nearest 0.1 s. The aforementioned functional mobility tests are reliable ($R = 0.99$, $P < 0.01$) and valid in paediatric patient populations [22].

The HRQOL was determined with the Spanish version (1.0) of the CF questionnaire (CFQ-R). The CFQ was originally developed by Henry et al. [23] and translated, validated, and partly revised by Modi and Quittner [24]. Three versions of the CFQ-R exist: for children aged 6–13 years, for parents of children aged 6–13 years, and for adolescents and adults aged 14 years and over. The 6–11-year-old group completed the CFQ-R by means of an interview, whereas the 12–13-year-old group completed the same CFQ-R themselves. Adolescents aged 14 and over completed the CFQ-R version 14+. In the majority of cases, the parent was present during the completion of the questionnaire by his/her child. In order to get insight into the parents' perception of their children's HRQOL, parents or caregivers of all 6–13-year-old children were asked to fill the parents' version of the CFQ-R. In the analyses of the associations between HRQOL and the physical-fitness-related variables, we used the eight domains that the age 6–13 and age 14+ groups had in common, that is, physical functioning, emotional functioning, social functioning, treatment burden, eating disturbances, body image, respiratory symptoms, and digestive symptoms. In the analyses of parent–child agreement, we used the seven domains that children aged 6–13 years and parents had in common, that is, all of the abovementioned, except for social functioning. Response choices of the CFQ-R included ratings of frequency or likelihood on four-point scales. Raw scores were converted into standardized scores (0–100) for each of the scales, with higher scores indicating better HRQOL. For example, the following statements were verified: 'In the past 2 weeks you were able to run, jump and climb as you wanted' (1 = very true, 4 = not at all true; domain of physical functioning), 'Let us know how often in the past two weeks you coughed during the day' (1 = always, 4 = never; domain of respiratory symptoms), 'During the past 2 weeks, doing your treatments bothered you' (1 = very true, 4 = not at all true; domain of treatment burden). Regarding the internal consistency of the Spanish CFQ-R 14+, Cronbach's α is $\geq$0.70 for most domains except for digestive symptoms (0.31) and treatment burden (0.57) [9]. As for test–retest reliability, Spearman's r oscillates between 0.49 and 0.95 [9]. The validity of the Spanish version of the CFQ-R 6–13 has not been investigated yet. In the English version for children aged 6–13, Cronbach's α for internal consistency is $\geq$0.60 for all scales, except for treatment burden (0.44). Furthermore, the CFQ-R 6–13 has demonstrated adequate content and discriminant validity, and minimal floor and ceiling effects [24].

Data analyses

Data were analysed using SPSS, version 15.0 (Chicago, IL, USA). For addressing the first objective, we included all children, aged 6–17 years, with complete data on all variables. Values are presented as means and standard deviations (SD), medians and inter-quartile ranges. For comparing differences between groups, parametric or non-parametric tests were used as appropriate. For the regression analysis, a normal distribution of the residuals of the variable was a prerequisite. To investigate the associations of each domain of HRQOL with BMI percentile, body fat, PA, pulmonary function, cardiorespiratory fitness, dynamic muscle strength, and functional mobility, simple linear regression analyses were performed. Variables that showed an association with a P value <0.1 in the simple linear regression model were tested for association in a multiple linear regression model, using a stepwise forward procedure. The threshold of 0.1 was used for the selection of variables, to prevent potentially relevant variables from being missed in the multiple linear regression model. In the final—multiple linear regression—model, only the associations with a P value <0.05 were considered statistically significant. All multiple linear regression analyses were adjusted for sex and age by entering these two variables first. Given the small sample size, the results of multiple regression analysis should be considered exploratory.

As to the second objective, data on the seven domains of HRQOL reported by children aged 6–13 and their parents were used. The differences in median scores between parents and children were examined by means of a Wilcoxon signed ranks test. The correlations between child and parent reports on each domain of HRQOL were examined using intra-class correlation (ICC) analysis. The ICC was used instead of Spearman's or Pearson's correlations, as it corrects for systematic differences between raters. An ICC <0.4, =0.4–0.6, =0.6–0.8, or >0.8 was considered as an indicator of poor, moderate, high, or excellent agreement, respectively [25].

Results

Descriptive data

In total, 38 outpatients with CF participated in the study; 100% of those invited. Of the ones who provided data on CF-related symptoms, 87% had digestive tract problems such as pancreas insufficiency or gastrostomies, and 100% had previous episodes of lung problems, for example, bacterial infections or pneumothorax. Ten children refused to wear the accelerometer. Thus, 28 children (14 female, 14 male; mean age, 11.6; SD, 3.1 years) provided data on all variables and were included in the analyses regarding the primary aim of the study. The descriptive data of this group are shown in Table 1. In the analyses of agreement between children's and parents' HRQOL reports, 27 children aged 6–13 years were included (17 female, 10 male), of whom 17 had also been included in the analyses regarding the primary study aim. The mean age of the children in this subgroup was 9.0 (SD, 2.2) years. With respect to their parents, in 96% of all cases ($n = 26$), it was the mother who completed the questionnaire.

Associations between HRQOL and other variables

The results of the simple and multiple linear regression analyses are shown in Table 2. No significant associations between nutritional status, pulmonary function, cardiorespiratory fitness, muscle strength or PA and HRQOL were found with the multiple linear regression model. A better functional mobility was associated with a less favourable body image and more eating disturbances, after adjustment for sex and age. Girls reported worse HRQOL regarding social functioning, treatment burden, and respiratory symptoms than boys, when adjusting for age. A higher age was associated with a less favourable body image, when

Table 1 Mean (SD) and median (25th–75th percentile) values for age, scores on health-related quality of life domains, and physical-fitness-related variables in children with cystic fibrosis aged 6–17

Variable	n	Mean (SD)	Median (25th–75th percentile)
Age	28	11.6 (3.1)	12.0 (10.0–14.0)
Physical functioning	28	88.8 (12.9)	93.1 (78.1–100.0)
Emotional functioning	28	80.4 (15.2)	80.0 (73.8–95.2)
Social functioning	28	75.1 (14.9)	77.0 (63.1–85.7)
Treatment burden	28	73.8 (19.4)	77.8 (66.7–88.9)
Eating disturbances	28	71.8 (30.0)	88.9 (47.2–97.2)
Body image	28	83.7 (20.8)	88.9 (77.8–100.0)
Respiratory symptoms	28	76.2 (21.0)	69.4 (66.7–98.6)
Digestive symptoms	28	82.9 (23.5)	100.0 (66.7–100.0)
BMI percentile	28	47.3 (25.6)	50.0 (10.0–72.5)
Body fat (%)	28	10.7 (6.1)	11.5 (5.1–15.2)
PA (counts/min)	28	549.7 (189.0)	476.9 (402.1–749.6)
FEV_1 (% of expected)	26	85.3 (20.9)	83.9 (66.5–99.3)
VE_{peak} (l/min)	27	57.2 (18.1)	57.4 (44.9–69.0)
VO_{2peak} (ml/kg/min)	28	38.2 (6.5)	38.2 (35.1–43.3)
Muscle strength (kg)	23	153.8 (64.1)	154.0 (108.0–198.0)
TUG 3 m test (s)	23	3.6 (0.4)	3.7 (3.2–4.0)
TUDS test (s)	23	6.2 (1.1)	5.9 (5.7–6.4)

BMI body mass index, *PA* physical activity, FEV_1 forced expiratory volume in one second (pulmonary function), VE_{peak} peak minute ventilation (pulmonary function), VO_{2peak} peak oxygen uptake (cardiorespiratory fitness), *TUG* timed up and go (functional mobility), *TUDS* timed up and down stairs (functional mobility)

Table 2 The variables associated with quality of life (QoL) in the simple linear regression analysis ($P < 0.1$), starting with the variable with the strongest association; the variables entered into the multiple linear regression model; their strength of association with QoL; and the explained variance of the model

HRQOL domain	Simple regression	β (95% CI)	Multiple regression	β (95% CI)	Adjusted R^2
Physical functioning	VO_{2peak} (ml/kg/min)	0.8 (0.04; 1.5)*	Sex (1: female)	−6.8 (−17.2; 3.5)	0.11
	Body fat (%)	−0.8 (−1.6; 0.02)	Age (year)	−0.9 (−2.6; 0.7)	
	Sex (1: female)	−9.1 (−18.7; 0.4)			
	Age (y)	−1.4 (−2.9; 0.2)			
Emotional functioning	Sex (1: female)	−12.6 (−23.5; −1.6)*	Sex (1: female)	−11.3 (−23.4; 0.7)	0.12
	Body fat (%)	−1.0 (−1.9; −0.1)*	Age (year)	−0.5 (−2.4; 1.4)	
	VO_{2peak} (ml/kg/min)	0.9 (0.03; 1.8)*			
Social functioning	Sex (1: female)	−15.8 (−25.7; −5.8)*	Sex (1: female)	−14.9 (−25.9; −3.9)*	0.24
	VO_{2peak} (ml/kg/min)	1.0 (0.2; 1.8)*	Age (year)	−0.4 (−2.1; 1.4)	
	Body fat (%)	−1.0 (−1.9; −0.1)*			
	TUDS (s)	−5.5 (−11.5; 0.5)			
Treatment burden	Sex (1: female)	−27.0 (−37.8; −16.1)*	Sex (1: female)	−25.9 (−37.9; −13.9)*	0.47
	Body fat (%)	−1.6 (−2.7; −0.5)*	Age (year)	−0.5 (−2.4; 1.5)	
	VO_{2peak} (ml/kg/min)	1.1 (0.04; 2.2)*			
	Age (y)	−2.1 (−4.4; 0.2)			
Eating disturbances	TUDS (s)	−16.0 (−26.8; −5.2)*	Sex (1: female)	−14.8 (−41.5; 11.9)	0.30
	FEV_1 (%)	0.5 (−0.04; 1.1)	Age (year)	3.1 (−1.2; 7.4)	
	Age (y)	3.2 (−0.4; 6.8)	TUDS (s)	−12.9 (−24.4;−1.4)*	
Body image	TUDS (s)	−7.4 (−15.4; 0.5)	Sex (1: female)	1.4 (−16.7; 19.6)	0.26
			Age (year)	−3.2 (−6.2; −0.3)*	
			TUDS (s)	−9.5 (−17.3; −1.7)*	
Respiratory symptoms	Sex (1: female)	−16.7 (−31.9; −1.5)*	Sex (1: female)	−20.0 (−36.5; −3.4)*	0.13
	BMI percentile	−0.3 (−0.6; −0.04)*	Age (year)	1.4 (−1.3; 4.0)	
	Body fat (%)	−1.3 (−2.6; −0.1)*			
Digestive symptoms	VE_{peak} (l/min)	0.5 (−0.1; 1.0)	Sex (1: female)	−12.1 (−31.4; 7.3)	0.06
	BMI percentile	−0.3 (−0.6; 0.1)	Age (year)	2.7 (−0.4; 5.8)	

* $P < 0.05$. *HRQOL* health-related quality of life, *CI* confidence intervals, VO_{2peak} peak oxygen uptake (cardiorespiratory fitness), *TUDS* timed up and down stairs (functional mobility), FEV_1 forced expiratory volume in one second (pulmonary function), *BMI* body mass index, VE_{peak} peak minute ventilation (pulmonary function)

adjusting for sex. The median scores on each HRQOL domain of boys versus girls are graphically presented in Fig. 1. To note is that the sample size needed to detect a small effect size would be $N \sim 780$.

Agreement between parents and children

The median scores of children aged 6–13 years for each domain of HRQOL, and the differences between children and parents, are presented in Table 3. Children had median scores between 66.7 (digestive symptoms) and 100.0 (body image). Parents had median scores between 66.7 (eating disturbances) and 92.6 (physical functioning). Most ICCs were higher than 0.8, indicating excellent agreement between parents and children. The ICC in the domain of treatment burden was lowest (0.63), indicating that, on average, the parents rated the children's HRQOL in this domain lower than their children.

Discussion

In this cross-sectional study among Spanish children with CF, we expected to find positive associations between physical-health-related variables and various HRQOL domains. However, only few of the hypothesized associations were confirmed by our analyses. In our participants, nutritional status and pulmonary function were not associated with better physical functioning or a more favourable body image. In fact, functional mobility was negatively associated with body image, when adjusting for sex and age. Physical activity was not associated with any of the HRQOL domains. As expected, cardiorespiratory fitness was associated with half of the domains, including physical functioning, but only when not adjusting for age and sex. The previously described sex difference [11] became apparent. Male sex was associated with more favourable HRQOL scores in the domains of treatment

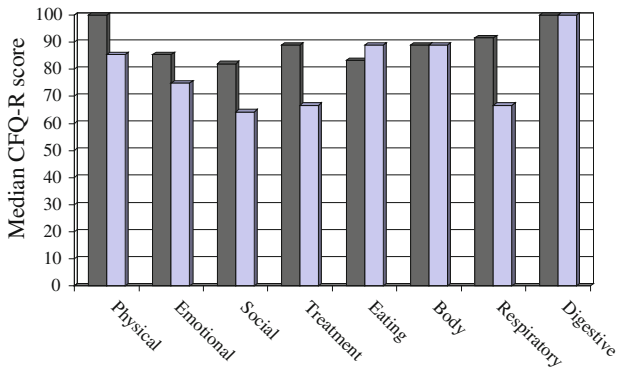

Fig. 1 Median scores on eight health-related quality of life domains of boys ($n = 14$) and girls ($n = 14$) with cystic fibrosis aged 6–17. *Black bar*: boys. *Grey bar*: girls

burden, respiratory symptoms, and social functioning, when adjusting for age. A higher age was associated with a less favourable body image, when adjusting for sex.

We found no associations between the physical-health-related variables and HRQOL, partly because a relatively large amount of the variation in HRQOL was explained by sex and age. It should also be noted that in our study population, CF was of low-to-moderate severity, as reflected by nutritional status (average BMI percentile, 47.3), pulmonary function (average FEV_1 85% of expected), and level of PA [26]. Consequently, in our population, ceiling effects may partly have obscured associations between HRQOL and several variables [7]. Also, the low sample size may have contributed to the lack of statistically significant associations. Still, for several variables, the simple linear regression analyses showed associations with HRQOL in the expected direction.

Previous studies have shown that pulmonary functioning in children with CF declines with age. This decline starts earlier in girls than in boys [27], which would explain the sex difference in the HRQOL domain of respiratory symptoms in our study. Possibly, girls might be more susceptive to the opinion of (healthy) others and more aware of their frequent coughing and sputum production [12], consequently reporting more respiratory symptoms. The perception of being different from others might also affect their social functioning. Moreover, due to the deterioration in pulmonary function, girls are more frequently hospitalized than boys [28], which would explain their lower HRQOL score regarding respiratory symptoms as well as the larger treatment burden.

In contrast to expectations, we found a negative association between body image and eating disturbances, and functional mobility. More eating disturbances were related to better results on the stair climbing (TUDS) test. There might be an explanation for this apparently surprising finding. The children reporting most eating disturbances ('did not enjoy eating'/'was pushed to eat') appeared to be the smallest and the lightest. Having a low body weight can be advantageous in speed exercises [29]. The fact that the fastest children were small and light might also explain their unfavourable body image ('thought you were too small'/'thought you were too thin'), but this was not confirmed by our data. Overall, children had a favourable body image (median HRQOL score of 88.9). Probably, most children did not consider themselves as 'too thin', but rather slender as compared to their peers, which may have contributed to their overall satisfaction with body image [30]. The HRQOL scores on the domain of body image decreased with age, after adjustment for sex. This may be explained by the onset of puberty, a period in which body image changes and peer pressure increases. Given the small sample size, it will be important to confirm these relationships in larger samples.

As to the second study goal, we found that the agreement between parents and children on most HRQOL domains was high. The domain of digestive symptoms was scored relatively low by the children, and treatment burden was perceived as more problematic by parents than by their children. Like in the Belgian sample studied by Havermans et al. [16], our children reached high scores on the HRQOL domains physical functioning and body image (>85/100). The lowest score was found in the domain digestive symptoms (<70/100). The domain of treatment burden was scored lower by parents than by children, which is in line with the findings of Havermans et al. [16] and Hegarty

Table 3 Median (25th–75th percentile) scores on health-related quality of life (HRQOL) of children aged 6–13 years and their parents; significance of the results of the non-parametric tests for comparison between children and parents, and intra-class correlation coefficients (ICC), for each QoL domain

HRQOL domain	*n*	Children's median (25th–75th percentile)	Parents' median (25th–75th percentile)	*P* value	ICC
Physical functioning	27	88.9 (77.8–100.0)	92.6 (88.9–100.0)	0.32	0.83
Emotional functioning	27	83.3 (75.0–95.8)	86.7 (80.0–100.0)	0.53	0.76
Body image	27	100.0 (88.9–100.0)	88.9 (77.8–100.0)	0.63	0.83
Eating disturbances	27	77.8 (44.4–100.0)	83.3 (33.3–100.0)	0.73	0.84
Treatment burden	27	88.9 (66.7–100.0)	66.7 (44.4–77.8)	0.001	0.63
Respiratory symptoms	27	83.3 (75.0–91.7)	83.3 (72.2–88.9)	0.99	0.82
Digestive symptoms	27	66.7 (66.7–100)	77.8 (77.8–88.9)	0.35	0.80

et al. [31]. Children may indeed have lower difficulties with treatment than their parents perceive them to have, or they may deny its impact to better cope with it. In contrast, parents feel worried about their child and are aware of the possible prognosis of CF. Moreover, parents might have difficulties managing the treatment regimen of their children, including home-based physiotherapy and provision of medication. These perceived difficulties could lead to a poorer well-being of the parents themselves [32], which might be reflected in their answers to the questionnaire on their children's HRQOL. The previously described phenomenon of a poorer agreement between parents and chronically ill children in the less-observable domains, for example, emotional and social functioning, and a higher agreement on the observable domains, for example, eating disturbances, digestive and respiratory problems [15], was not confirmed in our study. In fact, there was a remarkably good-to-excellent agreement between parents and children in all domains.

The fact that the agreement between children and parents was overall excellent might indicate, at least partly, a weakness of our study. The child's answers may have been influenced by their parent(s), as the latter were present during the interview. Despite the 100% participation rate, another limitation of our study stems from the fact that the sample size was small, which increases the probability of a type II error and lowers the external validity (and therefore generalizability) of the results. Therefore, the findings of our study should be interpreted with caution. Ten children refused to wear the accelerometer, which greatly reduced the sample size. The fact not that we did not include these children in our analyses could have introduced bias, since wearing the accelerometer might be related to their level of PA. To increase the number of children completing all measurements, a different method of estimating PA may be considered in future studies. Still, the reliability of PA results would remain questionable. Another potential threat to external validity was the fact that our sample only comprised children with CF of low-to-moderate severity ($FEV_1 \geq 40\%$ of expected) and stable clinical condition. We considered it unethical to subject severely ill children to maximal exercise testing. However, our results are representative for the large majority of the paediatric CF population; indeed, only less than 3% of children aged <18 years have a $FEV_1 < 40\%$ of expected, according to Canadian [33] as well as Spanish statistics [34]. To enlarge the sample size and raise the external validity in future studies, a multicenter study should be performed, including CF patients with a broader range of disease severity. Furthermore, the relatively weak internal consistency for treatment burden, as well as in the CFQ-R 14+ for digestive symptoms, can be considered as a limitation that might slightly have distorted our results. Nevertheless, we chose to use the CFQ-R because owing to its overall strong psychometric properties as compared to other HRQOL instruments, and because both a child and a parent version are available. Last, because of the cross-sectional type of design we used, no conclusions on causality can be drawn; a favourable cardiorespiratory fitness could be the cause as well as the consequence of good physical functioning. Longitudinal, preferably interventional studies should be conducted to determine the influence of changes in physical-health-related variables on HRQOL.

On the other hand, we believe there are several strong methodological aspects in our design. First, we assessed several variables that are not frequently investigated although they are highly relevant, such as PA levels and functional mobility during activities of children's daily living, that is, climbing stairs and getting up from a chair. Second, for measuring HRQOL, we used an age- and disease-specific questionnaire, to ensure a valid and reliable determination of all relevant aspects of HRQOL in this paediatric population. Likewise, for measuring all other variables, we used objective methodologies, such as accelerometry and maximal exercise testing. Third, we adjusted our analyses for sex and age. Consequently, we believe we presented a realistic picture of the differences in HRQOL between boys and girls.

In conclusion, when adjusting for sex and age, no significant associations were found between HRQOL and BMI percentile, PA, pulmonary function, cardiorespiratory fitness, and dynamic muscle strength. Nevertheless, there was a trend towards a more positive HRQOL regarding physical, social, and emotional functioning and treatment burden in children with a favourable cardiorespiratory fitness and better nutritional status, which is a promising finding. The small sample size was an important study limitation. Longitudinal studies with larger cohorts are needed to confirm these associations. We consistently found significant influences of age and sex on the outcome variables. In future research, additional analyses could be conducted to reveal the moderating effects of sex and age. Moreover, sex and age may not only be related to HRQOL but also to the physical-fitness-related variables. In order to unravel such relations, more complex statistical models should be tested. We confirmed the findings of others that girls had a lower HRQOL on most domains than boys. Thus, care providers of children with CF should realise that treatment and respiratory symptoms may have a larger impact on girls than on boys. On the other hand, we found overall good agreement between children and parents on HRQOL, although children reported a lower treatment burden than their parents perceived them to have. We recommend that treatment burden should be discussed with care providers, parents, and children together, to raise parents' understanding of their children's HRQOL, and get

better insight into the child's opinion on the burden of his/her treatment.

Acknowledgments We are grateful to the *Fondo de Investigaciones Sanitarias* (FIS, ref. # PS09/00194) and *Federación Española de Fibrosis Quística* (*II convocatoria investigación Pablo Motos*, Spain) for covering the costs of the research project. We thank the *Dutch Cystic Fibrosis Foundation* and the *Van Coeverden Adriani Foundation* for covering the costs of analysing and reporting the data.

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