

Health-Related Quality of Life and Physical Activity in Children with Cystic Fibrosis

Lothar Stein^{1,2*}, Frauke Schülke¹, Arno Kerling², Momme Kück², Manfred Ballmann³ and Sibylle Junge¹

¹*Pediatric Pneumology and Neonatology, Hannover Medical School, Germany*

²*Institute of Sports Medicine, Hannover Medical School, Germany*

³*Pediatric Hospital, University Rostock, Germany*

***Corresponding Author:** Lothar Stein, Pediatric Pneumology and Neonatology, Hannover Medical School, Germany.

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Abstract

Health-related Quality of Life (HRQoL) is an important aspect of the clinical course of Cystic Fibrosis (CF), and physical activity (PA) is a proven option in therapeutic care. The purpose of this prospective, cross-sectional, single-center, observation study was to evaluate, whether HRQoL is positively correlated to objectively measured PA in 6 - 17-year-olds with CF. Additionally, the relationships between HRQoL and lung function, body composition and exercise capacity (EC; cycle ergometry according the Godfrey protocol) were studied. A total of 87 patients with CF (m = 40; age: 11.8 ± 2.9 years) participated. HRQoL with the German revised multi-dimensional disease-specific questionnaire (CFQ-R) and PA (one-week of monitoring with a multisensory activity monitor/SenseWear Pro-Armband) were assessed. We found an FEV₁ of $88.5 \pm 19.5\%$, BMI Z-score of -0.51 ± 0.99 , HRQoL dimensions in the range of 62-86, generic score of 370 ± 50 and disease-specific score of 452 ± 83 . Mean PA was 2.06 ± 0.43 METs/day and 12142 ± 4307 steps/day. EC was $91.7 \pm 19.9\%$ predicted. There was no correlation found between HRQoL and PA, but a strong correlation was found between HRQoL and lung function, body composition and EC.

Conclusion: Young patients with CF in good clinical condition presented good HRQoL and high levels of PA, but HRQoL and PA were not correlated (as hypothesized); however, FEV₁, BMI Z-score and EC correlated with HRQoL. Further studies are needed to confirm these results.

Keywords: Cystic Fibrosis; Children; Health-Related Quality of Life; Physical Activity; Exercise

Introduction

Cystic fibrosis (CF) is the most common fatal, autosomal recessive disorder in Caucasian populations with a rate of 1 case per 2.500 births. The pathophysiology is based on a defective chloride channel, the cystic fibrosis transmembrane conductance regulator (CFTR), in the apical membrane of epithelial cells. This progressive disease affects a multitude of organs including the exocrine glands of lungs, liver, pancreas, skin, and digestive and reproductive systems.

Because of its complexity, CF strongly impacts patients in many areas of daily life. Tangibly, CF constrains patients' lung function and alters their nutritional status and physical conditions; in addition CF also impacts their health-related and disease-specific quality of life (HRQoL) [13].

HRQoL measurements take into account the subjective sensations of each patient and are important outcome parameters in clinical studies and therapeutical care [1,16]. HRQoL, which includes physical, mental, and social components of health according to the World Health Organization (WHO) [43], has become a well-studied measure in patients with CF [1,24]. Abbott, *et al.* [1] showed that HRQoL can predict survival in patients with CF. Different variables lead to improved HRQoL for patients with CF, especially in children and adoles-

cents. Clinical conditions, such as lung function, nutritional status and EC, and other disease-specific variables need to be studied in the future. The correlation of HRQoL and physical activity (PA) is unclear and not well studied. In this study, the most frequently used HRQoL questionnaire in CF, the revised German version of the Cystic Fibrosis Questionnaire (CFQ-R) [37,50], was used to measure each patient's HRQoL. It combines the disease-specific and generic aspects of a patient's HRQoL, which is necessary to properly evaluate Quality of life (QoL) in chronically ill patients [14].

PA is an important therapeutic component in the care of patients with CF. PA is a key indicator of normal development in children and adolescents [10]. Tschanz, *et al.* [47] reported that healthy adolescents who participate in sports activities feel better than their peers. Furthermore, improved EC has a positive impact on the course of disease in patients with CF [27], and PA programs in CF have been shown to improve pulmonary function, mucociliary clearance, the combination of EC and HRQoL [18,22,40,29,38]. CF guidelines recommend yearly routine testing for EC [17].

Few studies have investigated HRQoL and PA in patients with CF, and even fewer have studied them in children and adolescents; some studies have found a positive correlation between the two [16,20], whereas others have found no correlation.

To investigate the correlation between HRQoL and PA and to assess whether PA standards for children and adolescents are being reached, PA measurement needs to be accurate. Objective and subjective methods are available, with objective methods having a clear advantage [4]. In this study, an objective, high-accuracy, easy-to-wear device, a multisensory activity monitor, was used [11].

In healthy people of all ages, HRQoL is consistently positive related to PA and EC. Therefore, a correlation between HRQoL and PA, as well as between HRQoL and EC, might be expected in patients with CF. To our knowledge, there is no cross-sectional study with more participants than the work presented here, which assessed the correlations between HRQoL and PA and between HRQoL and EC in 6-17-year-olds with CF.

The primary research objective was to investigate the relationship between HRQoL and PA, and the secondary objective was to evaluate how HRQoL is related to clinical status and EC.

Methods

Participants

All patients between the age of 6 and 17 years at the CF center at Hannover Medical School that had been diagnosed with CF either by an abnormal sweat test or by detection of a CFTR mutation of both alleles and typical pulmonary or digestive symptoms [36] were asked to participate in the study. Patients with acute exacerbations, *Burkholderia cepacia*, or MRSA colonization, or patients listed for lung transplantation or who already received transplants were excluded.

Patients were included in the study if they had no exclusion criteria and performed all tests for HRQoL, PA, clinical status (FEV₁, BMI Z-score) and EC.

Study Design

In this prospective, cross-sectional, single-center observation study HRQoL, PA, clinical status and EC were evaluated at one study visit. Objective PA assessment was carried out in the following week.

Measurements

Quality of Life was measured with the validated, multi-dimensional, disease-specific, health-related Cystic Fibrosis Questionnaire (CFQ-R) [19], which was revised in German. All versions, including CFQk-R (6 - 13 years) [37], CFQe-R (parents), and CFQ14+R for adolescents (14 - 17 years) [50] are based on a two-week recall. The questionnaire measures HRQoL with two sum scores, generic (physical well-be-

ing, energy, social and emotional function, subjective health perception) and disease-specific score (respiratory and digestive symptoms, eating disturbances, weight problems, body image and treatment burden).

CFQ-R uses closed questions that are later summarized into HRQoL dimensions from 0 to 100 and converted into standardized scores, where higher scores represent higher HRQoL. It takes approximately 15 minutes to complete the questionnaire. The parents, not the children themselves, answer the questions on subjective health perception, energy and weight. These data were compared with data collected from adolescents to see if the perceptions were different while considering possible falsification because of different perspectives in parents and their children. CFQ-R has two distinct advantages. First, its age-appropriate versions cover patients with CF from 6 years to adulthood; second, CFQ-R considers disease-specific characteristics, which are more accurate than non-specific instruments in this field of research [42].

Physical Activity was measured over one week. The patients wore a multisensory activity monitor, the SenseWear® Pro3-Armband (HealthWear Bodymedia, Pittsburgh, USA) [44], on their upper arm for 24h/day for one week following the manual. The multisensory activity monitor uses a 2-axis accelerometer, a heat flux sensor, a galvanic skin response sensor, a skin temperature sensor, and a near-body ambient temperature [44]. The data were processed by algorithms (Software InnerView Version 6.1 Bodymedia, Pittsburgh, USA) and shown in average METs (metabolic equivalent in kcal/h/kg)/ day, METs/ basal metabolic rate (calculated according the procedure described in the multisensory activity monitor manual) and steps per day. Additionally, different intensities of PA were calculated by the software: low intensity PA (< 3 METs; activities such as active computer games or slow walking), moderate PA (3 - 6 METs; fast walking or cycling) and high PA (> 6 METs; running or football) [3] and displayed in minutes per day. A predominantly inactive lifestyle is characterized by more time spent in low PA and little time spent in moderate or high PA. Data were included if the multisensory activity monitor was worn outside of school holidays consecutively for a minimum of four days and over 80% of the time with at least one weekend day included. These assumptions were based on average times in comparable studies with COPD patients [9,33].

Clinical status was assessed with the clinical parameters BMI Z-score and FEV₁.

Body composition: Body weight was measured on an electronic scale to the nearest 100g (Seca 910, calibration class III). Body height was measured to the nearest 0.1 cm (Ulmer Stadiometer). BMI Z-score was used as an age-independent parameter of nutritional status and body composition [23].

Lung function was measured with a spirometer (Ganshorn Body-Scope N or Jaeger Master Screen). Forced expiratory volume in one second (FEV₁)% predicted was calculated using the Knudson equations [21].

Exercise Capacity was tested with a continuous maximum incremental cycle ergometry (Ergometrics 900s, ergoline, Bitz, Germany) following the Godfrey protocol [15] in accordance with a statement on exercise testing in CF [17]. Maximal performance was measured in Watt % predicted and Watt per kg bodyweight. Depending on the height of the patient with CF, work is increased by 10 (< 120 cm), 15 (120 - 150 cm) or 20 W (> 150 cm) per minute until fatigue.

Statistical Analysis

Parameters of HRQoL, PA, clinical status and EC were characterized by the mean and standard deviation (mean ± SD). A normal distribution was determined with Kolmogorov-Smirnov-tests. The distribution of gender in the two age groups was tested using Chi-Square-tests (χ^2). Differences between subgroups were made with an unpaired Student-t-test for parametric data or a Mann-Whitney-U-test for non-parametric data. For effect size, Hedges' g was calculated, for which g = 0.2 represents a small effect, g = 0.5 represents a medium effect and g = 0.8 represents a strong effect. A possible interaction between the factors age and gender was evaluated with a two factorial variance analyses with the partial Eta square (η^2) as effect size, for which $\eta^2 = 0.01$ represents a small effect, $\eta^2 = 0.06$ represents a medium effect and $\eta^2 = 0.14$ represents a strong effect. Pearson and Spearman correlations were calculated to investigate the correlations between HRQoL, PA, EC and clinical condition, for parametric and non-parametric data, respectively. P-values < 0.05 were considered significant.

To identify their relationships between the dependent variables and HRQoL, generic and disease-specific scores, multiple regressions with the independent variables of PA (METs/day, METs/basal metabolic rate, steps/day), clinical status (FEV₁ % predicted), BMI Z-score and EC (Watt % predicted and Watt per kg/bodyweight) were evaluated stepwise with the inclusion criterion $p < 0.05$. Data were analyzed using IBM SPSS Statistics for Windows (Version 22.0, Armonk, NY, IBM Corp.)

Ethics

This study was approved by the ethics committee of Hannover Medical School. It was carried out following the guidelines for “good clinical practice” (GCP) and the declaration of Helsinki [39,51].

Results

Complete datasets were obtained from 87 (40 m/ 47f) out of 153 (76 m/ 77f) eligible patients. Only patients with complete datasets of HRQoL, PA, clinical data and EC were calculated. A total of 66 (36 m/ 30f) patients were excluded from the analysis (Figure 1).

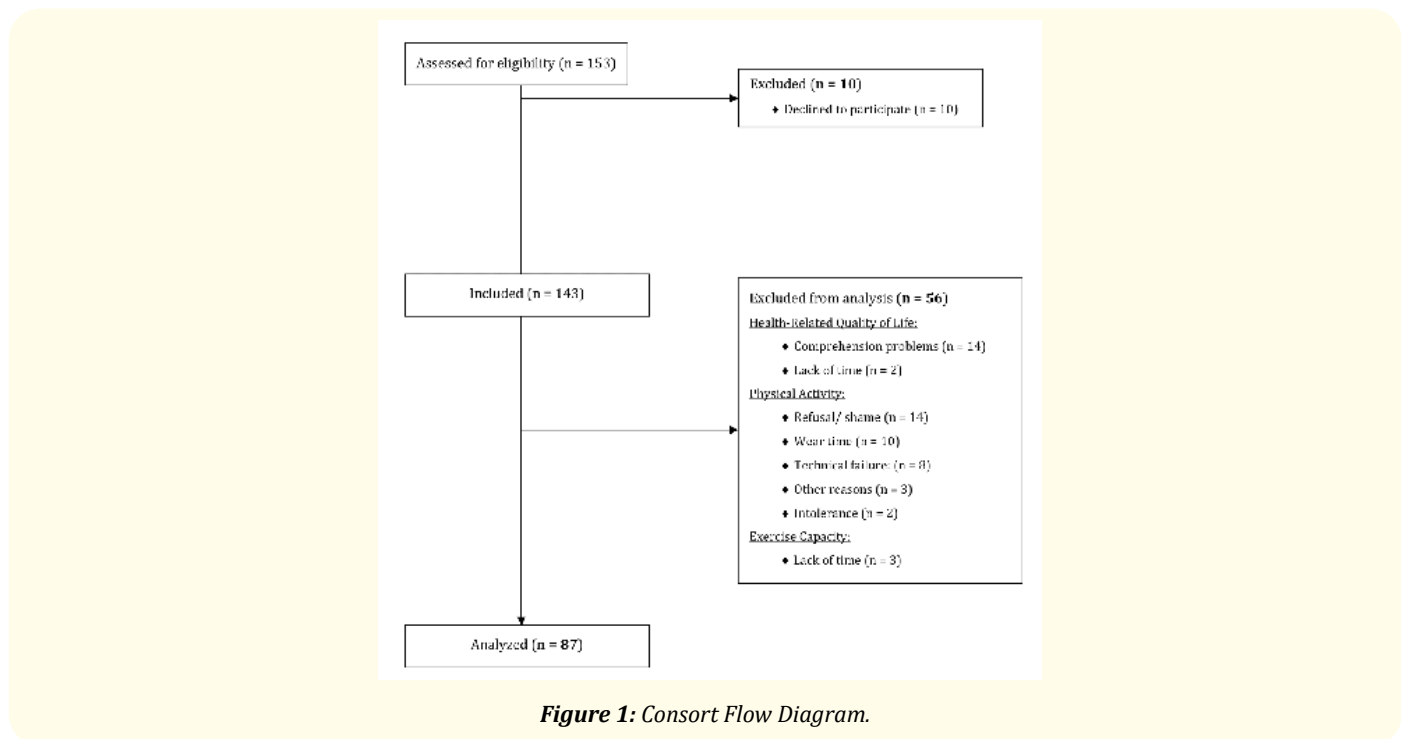


Figure 1: Consort Flow Diagram.

Demographic data and clinical status (age, gender, FEV₁ and BMI Z-score) are shown in table 1. The groups of participants and non-participants did not differ in gender, FEV₁ or BMI Z-score, but non-participants were significantly younger ($p = 0.034$; $g = 0.31$). Some patients under 8-years-old were not able to understand the CFQ-R and were consequently excluded.

Variables	Participants (n = 87)	Non-participants (n = 66)
Age (years)	11.8 ± 2.9	10.8 ± 3.7*
6 - 13 years (n)	66	43
14 - 17 years (n)	21	23
Male/female (n)	40/47	36/30
FEV ₁ (%)	88.5 ± 19.5	91.7 ± 19.5
BMI Z-score	-0.51 ± 0.99	-0.34 ± 0.95

Table 1: Clinical characteristics of the study group and comparison to the non-participants.

Definition of abbreviations: FEV₁ (%): force expiratory volume in 1 second in percentage predicted; BMI: body mass index;

* indicates p-value < 0.05

In participants only, the group between 6-13 years of age was bigger (n = 66) compared with the older group (n = 21). The groups were significantly different in clinical status, in terms of FEV₁ (6 - 13 years: 91.0 ± 17.6%, 14 - 17 years: 78.2 ± 23.1%; p = 0.013; g = 0.67) and BMI Z-score (6 - 13 years: -0.39 ± 0.98, 14 - 17 years: -0.87 ± 0.93; p = 0.005; g = 0.74). There were no significant differences between the clinical status of male and female participants regarding FEV₁ and BMI Z-score.

Health-Related Quality of Life

HRQoL values of the generic and disease-specific scores in the whole study group were 370 ± 50 with a possible maximum of 500 and 452 ± 83 with a possible maximum of 600, respectively (Table 2).

	Generic Score	Disease-specific Score
All	370 ± 50	452 ± 83
6 - 13 years	363 ± 42	445 ± 85
14 - 17 years	392 ± 65	472 ± 73
Male	370 ± 53	450 ± 75
Female	370 ± 47	452 ± 89

Table 2: Generic and disease-specific scores of CFQ-R by age and gender.

In the HRQoL dimensions, scores ranged from 62 to 86 with a possible maximum of 100 (Figure 2). No significant differences existed between genders regarding the generic or disease-specific scores or the HRQoL dimensions.

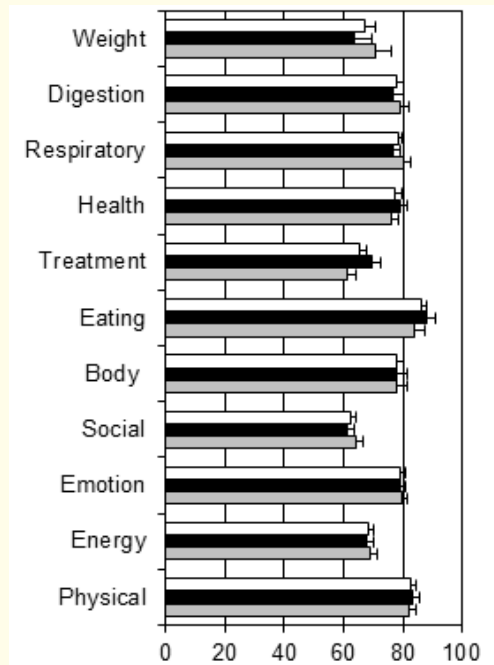


Figure 2: The scores of the different HRQoL dimensions of CFQ-R in the whole group (□), female (■) and male (■).

Figure 3 shows that in three of the eleven CFQ-R dimensions the age groups had significantly different results. In comparison to 6 - 13-year-old participants, 14 - 17-year-olds reported better digestion (p = 0.047; g = 0.55) and better social (p < 0.001; g = 1.47) and emo-

tional function ($p = 0.027$; $g = 0.59$), which is also reflected in a trend ($p = 0.074$) of higher generic scores in the 14 - 17-year-olds. There was no age-related significant difference in the disease-specific score.

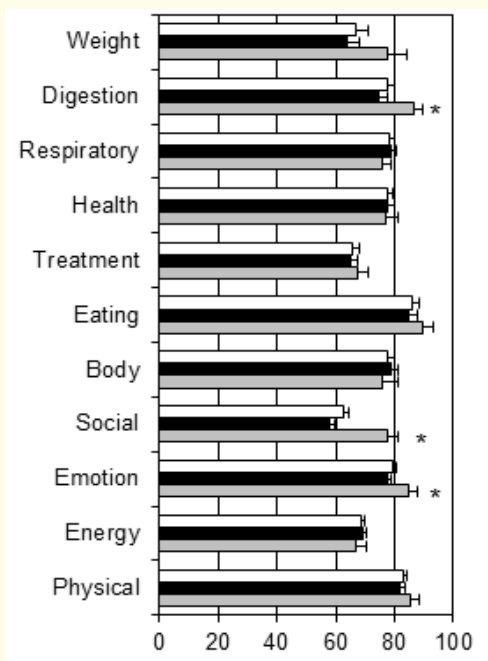


Figure 3: The scores of the different HRQoL dimensions of CFQ-R in the whole group (□), 6 - 13-year-olds (■) and 14 - 17-year-olds (■). Differences between groups with a significance of $p < 0.05$ are marked with*.

Health-Related Quality of Life and Physical Activity

Table 3 presents the PA results. Male participants were significantly more active than female participants in all measured parameters (METs/day: $p = 0.001$; $g = 0.66$; METs % of BMR: $p = 0.001$; $g = 0.55$, steps/day: $p = 0.022$; $g = 0.51$, low PA: $p = 0.002$; $g = 0.60$, moderate PA: $p = 0.014$; $g = 0.43$, high PA: $p = 0.001$; $g = 0.77$), and children were significantly more active in these three parameters than adolescents (steps/day: $p = 0.001$; $g = 0.96$, low PA: $p = 0.036$; $g = 0.42$, moderate PA: $p = 0.013$; $g = 0.50$).

PA (Mean ± SD)	All n = 87	Male n = 40	Female n = 47	6 - 13 years n = 66	14-17 years n = 21
METs/day	2.06 ± 0.43	2.2 ± 0.38	1.9 ± 0.42**	2.1 ± 0.46	1.9 ± 0.28
METs % of BMR	193 ± 38.9	204 ± 35.4	184 ± 39.6**	195 ± 42.4	187 ± 24.7
Steps/day	12142 ± 4307	13277 ± 467	11175 ± 2704*	13051 ± 420	9285 ± 2946**
Low PA min/day	1171 ± 138	1129 ± 122	1207 ± 143**	1158 ± 150	1214 ± 85*
Moderate PA min/day	219 ± 100	242 ± 83	201 ± 111*	231 ± 108	183 ± 61**
High PA min/day	48 ± 51	68 ± 56	32 ± 41**	51 ± 56	43 ± 38

Table 3: Results for PA compared within gender and age groups.

Definition of abbreviations: METs: metabolic equivalent in kcal/h/kg; BMR: basal metabolic rate; Low PA min/day: < 3 METs physical activity minutes/day; Moderate PA: 3-6 METs physical activity minutes/day; High PA: > 6 METs physical activity minutes/day; * indicates p -value < 0.05; ** indicates p -value < 0.001

The CFQ-R dimensions were correlated with the parameters of PA. In the whole group only two negative correlations were detected. One was between digestive symptoms and steps/day ($R^2 = -0.303$; $p < 0.004$), and the other was between digestive symptoms and moderate PA ($R^2 = -0.236$; $p < 0.028$).

In the subgroups, sporadic, weak and only positive correlations were found, mainly in female participants (Table 4).

Steps	RES	DIG	TRB
6 - 13-years-old	-	0.271*	-
14 - 17-years-old	0.578**	-	-
Male	-	-	0.389*
Female	0.322*	0.360*	-
Low PA (< 3 METs)			
6 - 13-years-old	-	-	-
14 - 17-years-old	-	-	0.451*
Male	-	-	-
Female	0.292*	-	-
Moderate PA (3-6 METs)			
6 - 13-years-old	-	-	-
14 - 17-years-old	-	-	-
Male	-	-	-
Female	0.291*	0.298*	-
METs/day			
6 - 13-years-old	-	-	-
14 - 17-years-old	-	-	-
Male	-	-	-
Female	0.296*	-	-

Table 4: Correlation between the dimensions of CFQ-R and PA parameters.

Definition of abbreviations: PA: Physical Activity; METs: Metabolic Equivalent in kcal/h/kg; RES: Respiratory Symptoms; DIG: Digestive Symptoms; TRB: Treatment Burden; *indicates p-value < 0.05; ** indicates p-value < 0.001

Furthermore, no correlations between the generic and disease-specific scores with the parameters of PA were detected. Regression analysis showed a relationship between the disease-specific score and steps/day; in the whole group, the disease-specific score had a relationship with FEV1 and BMI Z-score of 33%, in the subgroup of male participants, it had a relationship with FEV1 of 40%. No other dependencies were found.

Correlation between Health-Related Quality of Life and Clinical Status

Overall a positive correlation between the disease-specific score the CFQ-R and clinical status was found (Table 5). FEV₁ and BMI Z-score were positively correlated with the disease-specific score in the whole group and in the subgroups of 6-13-year-olds, 14-17-year-olds and male participants. No correlation between FEV₁ and the disease-specific score could be found in female participants.

	CFQ-R Disease-specific Score				
	All	Male	Female	6 - 13-years-old	14 - 17-years-old
FEV ₁	0.36**	0.52**	0.28	0.35*	0.64*
BMI Z-score	0.49**	0.33*	0.62**	0.56**	0.49*

Table 5: Correlation between the CFQ-R disease-specific score and clinical status.

Definition of abbreviations: FEV₁: force expiratory volume in 1 second; BMI: Body Mass Index; * indicates p-value < 0.05; ** indicates p-value < 0.001

In multiple regression analysis of the whole group, FEV₁ and BMI Z-score were significant predictors of the disease-specific score; together with the PA parameter steps/day, they were responsible for 33% of variance. Furthermore, the subgroups female participants

and 6 - 13-year-olds showed a relationship between the disease-specific score and the BMI Z-score (30% and 41%, respectively) and in the subgroups male participants and 14 - 17-year-olds, there was a relationship between FEV₁ (40% and 41%, respectively) and the disease-specific score.

There is only one correlation between the generic score and clinical status; this occurred between the generic score and FEV₁ in male participants (R² = 0.37; p < 0.05).

Health-Related Quality of Life and Exercise Capacity

EC is shown in table 6. No difference was found between the age groups, but males had significantly higher values of Watt/kgBW than females.

	Exercise capacity				
	All	Male	Female	6 - 13-years-old	14 - 17-years-old
Watt/kgBW	2.89 ± 0.62	3.12 ± 0.63	2.69 ± 0.55*	2.89 ± 0.53	2.90 ± 0.85
Watt % predicted	91.7 ± 19.9	92.1 ± 19.7	91.3 ± 20.5	93.55 ± 18.66	86.44 ± 23.05

Table 6: Exercise capacity.

*Definition of abbreviations: Watt/kgBW: Watt per kilogram bodyweight; Watt in percentage of age related norm; * p = 0.002*

The whole group, male participants and 14-17-year-olds showed positive correlations between the HRQoL generic score and EC (Table 7).

	CFQ-R Generic- Score				
	All	Male	Female	6 - 13-years-old	14 - 17-years-old
Watt/kg BW	0.31*	0.41*	0.25	0.21	0.44*
Watt % predicted	0.27*	0.38*	0.17	0.22	0.50*

Table 7: Correlation of CFQ-R generic score and EC.

*Definition of abbreviations: Watt/kgBW: Watt per kilogram bodyweight; Watt in percentage of age related norm; * indicates p-value < 0.05*

Multiple regression analysis proved this relationship and showed a relationship between Watt/kgBW and the generic score of 11% in the whole group and 24% in the subgroup of male participants.

In the subgroup of 14 - 17-year-olds, Watt % predicted was a significant predictor of the generic score, accounting for 33% of the observed variance.

Discussion

HRQoL, PA, clinical parameters and EC in 6-17-year-olds with CF were observed in this prospective, cross-sectional, single-center study. PA was measured with an objective multisensory activity monitor, and HRQoL was evaluated with CFQ-R, which has some distinct advantages over other questionnaires. CFQ-R is a validated and well-established tool for CF that is easy for the study participants to complete. Furthermore, age-appropriate versions cover patients with CF from 6-years-old to adulthood, and the CFQ-R includes disease-specific characteristics, which are more meaningful than non-specific instruments in this field of research [7,14,42].

The primary hypothesis that HRQoL is positively correlated with PA could not be proven in this group of 6-17-year-olds with CF in good clinical condition. Only a few weak correlations were found. These correlations were mainly in subgroups and somehow contradicted each other; there was no opportunity for a clear conclusion, especially when the negative correlations in the whole group were

compared to the positive correlations in the subgroups. The only two weak correlations in the whole group were negative; they were between digestive symptoms and steps/ day and between digestive symptoms and moderate PA.

The present study results were confirmed by a review of Cox, *et al.* [8], which could not identify studies that reported the longitudinal influence of a PA intervention on QoL independent of the length of this intervention, nor any cross-sectional relations between HRQoL and PA.

The present study results are contradictory to an older study [41] that reported that patients with CF with higher PA had better HRQoL. Hebestreit, *et al.* [16] obtained this result in a cross-sectional and longitudinal study, but it was determined only from PA data that was acquired by a questionnaire and not from objectively measured data. Two other studies found moderate to strong direct correlations of HRQoL with PA after an exercise intervention based on the non-disease-specific Quality of Well-being Scale [20,32]. The conflicting results compared to the present study could be because the PA was too high in this study sample to detect impairment of HRQoL. Other reasons for this discrepancy could be that different patient samples were used in other studies, the aspect of intervention in the other studies was different or different methods were used to measure HRQoL and PA, i.e., the use of a non-disease specific HRQoL questionnaire in the other studies and less accurate tools for PA evaluation (diaries, step counter, accelerometer) compared to the multisensory activity monitor in the present study.

Regarding the secondary research objective the present study showed a strong correlation between HRQoL, clinical status and EC in children and adolescents with CF. This result was expected and is in accordance with earlier studies [14,31]. Orenstein showed a moderate to strong correlation between HRQoL evaluated with the non-disease-specific Quality of Well-being Scale and peak oxygen uptake as the main parameter of EC [31].

The HRQoL scores in this study were similarly high as those in other studies using the same questionnaire [34,50]. In this study, 14 - 17-year-old participants reported higher values of social and emotional function than 6 - 13-year-olds. Thomas, *et al.* [45] found similar results with the same questionnaire and argued that the desire for normality in adolescents with CF could be a reason for these relatively higher scores.

The disease-specific score was highly correlated with clinical status, which includes the additional CF-related parameters of lung function and body composition. Because only one correlation was found between the generic score and clinical parameters, this result underlines the importance of the use of CFQ-R in this study contrast to non-disease-specific instruments, and the results show the expected and hypothesized correlations.

Habitual PA is very difficult to measure objectively in normal, daily life. Methods to measure PA differ in quality and practicality. The doubly labelled water method and indirect calorimetry are reference methods, but they are not practical for measuring habitual, daily physical activities [4]. Many studies in healthy people use subjective methods to observe PA, such as questionnaires or diaries; however, these methods are predisposed for inaccuracy and have higher levels of subjectivity and cognitive limitations in children [25]. Step counters and accelerometers are practical tools for PA evaluation, but they offer lesser data quality than the multisensory activity monitor used in this study, which is an objective device that can be integrated into daily life routines and provides data quality that is similar to the reference methods [44]. The SenseWear® Pro-Armband has been validated and used in children in several studies [6] and has been used in patients with different diseases. Dwyer, *et al.* [11] showed that the multisensory activity monitor is a tool with high compliance and accuracy in adult patients with CF. Van Remoortel, *et al.* [48] compared various activity monitors in healthy people and showed that the SenseWear® Pro-Armband is the most valid device during PA [48]. Even in cycle ergometry, good agreement between the multisensory activity monitor and indirect calorimetry was observed despite an underestimation during the first ten minutes [5]. A limit of the multisensory activity monitor, which is similar to that of step counters and accelerometers, is that not all PA can be measured; for example water activities are excluded. Compared to a study group of adult patients with CF, which reported low levels of PA with the same multisensory activity monitor [46], the present study group of children and adolescents with CF reached higher levels of PA and had much better FEV1 (88.5% vs. 65.0%). The results of this study showed that patients with CF had similar durations of PA as healthy children and that the

results for adolescents supported earlier reports. Nixon, *et al.* [28] found the mean PA level of children and adolescents with CF to be the same as that of their healthy peers; however, children with CF spent less time performing vigorous physical activities. Selvadurai, *et al.* [41] reported that children with mild CF were even more active than the healthy control group. Similar to a previous report [26], female adolescents in this study were significantly less physically active than same-aged males and children. Nixon, *et al.* [27] described the positive impact of regular participation in sports activities on the course of disease and speculated that aerobic fitness might ultimately impact survival [28]. Even in an otherwise healthy population, PA positively influences the health status of children and adolescents and has long-term effects on their health status into adulthood [49]. These results are what we expect for young patients with CF in good clinical condition. In a review, Radtke, *et al.* [35] described the different positive effects of exercise, sports and PA in CF populations. PA as a fun activity and life-style element is associated with normality much more than other long-term therapies. Therefore, PA should be accepted and implemented in a patient's daily life. This assumption is supported by a previous study that described good adherence in adult CF patients to aspects of exercise [2]. Because PA has been shown to positively impact health and because adult patients with CF have been shown to improve with exercise programs, young and adolescent patients with CF should be early encouraged to pursue high levels of PA to improve their health status in the long term. Higher PA leads to higher EC, which is a contributor to health-related quality of life in patients with CF and provides an additional rationale for regular routine exercise testing in this population [30].

The results for EC in this study are comparable to data from other patients with CF (91.7 ± 19.9 vs. $98.6 \pm 18.5\%$ of age related norm) [16] from a previous study using the same test protocol; similar to the current study, the previous study also reported the good clinical condition of its study group. Therefore, the differences in clinical status in our patient group might be too small for the patients to change their habitual PA and influence HRQoL or the PA of the patients is too high to detect any impairment of HRQoL. Even if HRQoL and PA are not correlated in this study group of patients with nearly normal pulmonary function but they are in severely ill patients with CF, it may be beneficial to document and routinely monitor individual PA and HRQoL for additional clinical long-term follow up as CF is a progressive disease. This study has some limitations. The evaluation of exercise ability followed the recommended protocol, but it was carried out without spirometry for practical reasons at the outpatient center. Another limitation is linked to the German CFQ-R and is connected to age. Twenty patients aged six- to seven-years-old could not be evaluated because of difficulties with answering the questionnaire. Therefore, it may be better to use the instrument for patients over age seven, such as what is recommended in the American version [24]. A third limitation might be that although the participants were asked to behave normally during PA measurement, PA was high in this study; this high PA could be a reason that no correlation was found between QoL and PA. These potentially misleading high PA results could be due to participant that they were a study participant, which led them to perform extra PA, such as biking to school or performing extra jogging exercise; this influence is known as the so-called Hawthorne effect [12].

The present study is not an interventional study, but it is an excellent prospective cross-sectional observation study with a large number of cases that could enable longitudinal follow-up studies in the future.

Conclusion

HRQoL, PA, clinical parameters and EC in children and adolescents with CF were observed in this prospective, cross-sectional, single-center study. Young patients with CF in good clinical condition presented good HRQoL and high levels of PA, but HRQoL and PA were not correlated as hypothesized. However FEV₁ and EC correlated with HRQoL. These results need to be confirmed in additional studies, but as long as the children and adolescents with CF are not in worse clinical condition with possible effects on their PA, there seems to be no measurable influence of PA on HRQoL. Individual HRQoL, PA and EC should be routinely monitored as clinical long-term follow up parameters in patients suffering from CF. Additionally, early encouragement and motivation for high levels of PA in children with CF is important, because the positive effects of regular PA, sports and exercise can impact the course of the disease.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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