The QLIM study

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CHAPTER 6

Effects of combined physical exercise and psychosocial training program for children with cancer: a randomized controlled trial

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ABSTRACT

Both physical and psychosocial function is often decreased in children during or after cancer treatment. Exercise interventions have shown beneficial effects on these outcomes in adults but evidence for children is lacking due to a limited number of studies with small sample sizes.
This study evaluates the effect of a combined physical exercise and psychosocial intervention on physical fitness and health-related quality of life (HrQoL) in children during or shortly after cancer treatment. In addition, a process evaluation was performed based on examination of intervention mediators, applicability and adherence.
The multicenter randomized controlled trial was performed in 4 Dutch University Hospitals.
From 174 eligible patients 68 children (39%) with cancer [mean age 13.2 (SD: 3.1) years; 54% male] during treatment or within 12-months post-treatment, were included. Drop-out rate was 22% mainly due to recurrence of the disease.
The 12-week intervention consisted of 24 physical therapy, and 6 child and 2 parent psychosocial training sessions.
Physical fitness, physical and psychosocial function, fatigue and HrQoL were assessed at baseline, at 4 months and at 12 months post-baseline. Generalized estimating equations were used to simultaneously assess short and long-term intervention effects. Physical and psychosocial mediators in the intervention effect on HrQoL were examined using the product of coefficient test. Applicability and adherence were assessed by trainer-report.
No significant beneficial effects were found on physical fitness, physical and psychosocial function at 12 months, or on HrQoL at 4 months. At 12-months follow-up significant beneficial intervention effect was found for lower body muscle strength (β=56.5 Newton; 95% CI: 8.5; 104.5). Intervention effects on HrQoL were not significantly mediated by physical and psychological function. Intervention applicability was satisfactory with 67% average session attendance and 22% dropout (mainly due to disease recurrence).
This 12-week physical and psychosocial training intervention for children with cancer showed no significant beneficial effects on the short and long term, except for lower body muscle strength. Therefore reluctance to implement the current intervention in clinical practice is necessary.

INTRODUCTION

Physical fitness is considerably reduced in children during and after cancer treatment.[26,214,240] As a consequence of anti-cancer treatment, children with cancer are at increased risk for cardiovascular disease[248,249], osteoporosis[250,251] and obesity[249], as well as for depressive symptoms and anxiety[252–254]. Exercise may help to improve physical fitness and reduce these side and late effects. In adult cancer survivors exercise can improve physical fitness and health-related quality of life (HrQoL) during and after cancer treatment[73,77] and a dose-response relationship has been found with exercise intensity[82,85]. However, studies evaluating the effects of exercise in children with cancer are limited. A few controlled trials with small sample sizes (n=14-51) have reported significant improvements in cardiorespiratory fitness, muscle strength, flexibility and body composition.[63–65,186] Randomized controlled trials studying psychosocial interventions in children with cancer are also scarce and show limited effects for the children themselves.[255,256] However, in relation to physical exercise, a psychosocial intervention may improve psychosocial functioning[255,257] and increase the willingness and motivation to engage in physical exercise programs. To our knowledge, no studies have evaluated the effects of a combined exercise and psychosocial intervention program.
Therefore, this study aimed to evaluate the short- and long-term effects of the Quality of Life in Motion (QLIM) intervention (a 12-week combined physical exercise and psychosocial training intervention) on physical fitness and HrQoL, compared to a usual care control group. A process evaluation was also performed to examine intervention applicability and adherence, and to identify whether intervention effects on HrQoL are mediated by physical fitness, activity and psychological function.

PATIENTS AND METHODS

Procedure

Patients were recruited from March 2009 to July 2013 in four Dutch university hospitals: VU University Medical Center, Amsterdam; Academic Medical Center, Amsterdam; University Medical Center Utrecht, Utrecht; and Erasmus University Medical Center, Rotterdam. The Medical Ethics Committees of all hospitals approved the study. The trial was registered at the Dutch Trial Registry (NTR1531). Eligible participants were aged 8-18 years with cancer and currently receiving treatment or within the first year following treatment with chemotherapy and/or radiotherapy.[148]
Exclusion criteria were (previous) treatment with growth hormone, stem-cell transplant, cardiomyopathy, inability to ride a stationary bike, and inability to read and write Dutch, to self-reflect, or to follow instructions due to learning difficulties. Par-

ticipation was possible as long as the remaining treatment period included no scheduled hospitalization, and when the clinical condition (according to the treating pediatric oncologist) made participation possible. After baseline measurements, block randomization was performed by an independent data manager and stratified by age, gender, cancer type (hematological cancer vs. solid tumor), and treatment phase (during vs. after treatment).[148] Measurements were performed by blinded assessors. No serious adverse events were reported during the entire study.

Intervention

The 12-week QLIM intervention included two 45-min physical exercise sessions per week at a local physical therapy practice and one 60-min psychosocial training sessions once every two weeks for the child in the treating pediatric oncology hospital; the parents also received two psychosocial training sessions. Details on the study protocol are reported elsewhere.[148]

The physical exercise training was developed for children and included circuit training with balls, hoops, and running activities. Intensity of *physical exercise* gradually increased from 66-77% of the maximum heart rate (HRmax) during the first eight training sessions with focus on muscle strength training in combination with aerobic training: 77-90% of HRmax during weeks 5-8 focusing on aerobic fitness supplemented by moderate intensity strength training and a HRmax of 90-100% during the final 4 weeks reached by high intensive combination training. All physical therapists received an instruction manual accompanied by verbal explanation.

The *psychosocial training* intervention consisted of psycho-education and cognitive-behavioral techniques including, for example, items on expression of feelings, self-perception and coping skills.[258] Sessions were performed parallel to the physical exercise intervention. The parent sessions were scheduled at the start and end of the child's training. The training was performed by a trained pediatric psychologist according to an instruction manual. Details of the psychosocial training, its applicability and evaluation are published elsewhere.[258] In short, adherence was good with 90% completion of all sessions and patients reported to be satisfied with the intervention.[258]

The control group received usual care according to local guidelines and preferences. Physical therapy and/or psychological care were available on demand at all centers.

Data collection and instruments

Measurements took place in the treating hospitals at baseline, after completion of the intervention at 4 months and at long-term (12-months) follow-up.

Primary outcomes

Cardiorespiratory fitness was assessed by peak oxygen uptake (VO_{2peak} expressed in ml•kg•min) during a cardiopulmonary exercise test using the Godfrey protocol[102] on an electronically braked cycle ergometer with a paddling frequency of 60-80 rpm. During the test, expired air was collected, heart rate was monitored, and ventilator-gas exchange data were determined breath-by-breath. The VO_{2peak} was defined as the mean score of the final 30 s of the test. Cardiorespiratory fitness data were included in the analyses for children that achieved a HR_{peak} of at least 180 beats per minute, and/or a RER_{peak} of ≥ 1.0.

Muscle strength was assessed by use of a hand-held dynamometer (CITEC; C.I.T. Technics, Groningen, the Netherlands).[259] All children performed three repetitions (both left and right) per muscle group; the highest score out of six was used for further analyses. Upper-body muscle strength was calculated by summing the highest score of the shoulder, elbow and grip strength, and the sum of the highest hip, knee and ankle-dorsiflexion scores was used for lower body muscle strength.

Secondary outcomes

Body composition was determined using percentage of fat mass (%FM) and lumbar spine (L1-L4) bone mineral density (BMD) as measured by Dual energy X-ray absorptiometry (DXA).

Physical activity was measured for 4 days with a Respironics Actical accelerometer by a 15-s epoch and expressed as mean counts per min.[42,109]

Fatigue was assessed with the overall-fatigue score of the child self-report version of the PedsQL™ Multidimensional fatigue scale (acute version).[57,128] Calculated scores ranged from 0-100 with lower scores indicating higher levels of fatigue.[57]

Total General-HrQoL was measured with the Dutch self-report version of the PedsQL™ Generic Core Scales for children aged 8-12 and 12-18 years.[57,131] Scores ranged from 0-100 with higher scores indicating higher levels of HrQoL.[57]

Athletic Competence and Global Self-Worth were assessed with the 'Self-Perception Profile' for children aged 8-11 years and for adolescents aged 12-18 years.[232,260] Higher scores (0-100) reflect more positive self-perceptions.[232,260]

Behavioral problems were assessed in children aged ≥ 11 years using the Youth Self-Report with higher T-scores indicating more behavioral problems.[245] For the present study the total problem behavior scale was taken into the analyses.

Depressive symptoms were assessed with the Children's Depression Inventory.[261] The total (raw) score was used in the analyses.

Demographic and medical characteristics including age, gender, height, weight and body mass index, diagnosis and treatment type and phase (during vs. post) were obtained from medical records.

Adherence

Session attendance of the physical and psychosocial training intervention was recorded by the therapists. The applicability of physical exercises was recorded by an interview with the therapists, as well as the reported adaptations during the training period and performed training intensity (heart rate). In case changes in the protocol were <10%, the applicability was rated as good. Applicability of the psychosocial intervention was assessed by questionnaires (details are published elsewhere[258]).

Sample size calculation

Based on a previous study, the intervention group was expected to show an at least 20% greater improvement on cardiorespiratory fitness than the control group shortly after the intervention.[93] Therefore, at least 26 patients per group were required to detect an effect size of 0.8[262] between the intervention and control group with a power of 80% and an alpha of 0.05.[148] Taking dropout into account, we aimed to include 100 patients in order to assess a minimum of 60 children.[148]

Statistical analysis

The data were analysed using IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp.). We presented mean (standard deviation [SD]) or median (interquartile range) of the outcomes.

Generalized estimating equations (GEE) analyses with an exchangeable correlation structure were used to simultaneously assess intervention effects on the outcome variable at short and long term. Study group, time, the interaction between study group and time, and the baseline value of the outcome, were entered in the regression model as independent variables. Intervention effects were evaluated using an intention-to-treat principle. In addition we performed per-protocol analyses on 100% attendance to the intervention (as a dichotomy variable) to assess the influence of non-attendance on the primary study-outcomes.

Mediation analysis was conducted to evaluate whether physical fitness, activity, fatigue, self-perception, depressive symptoms and behavioral problems mediated the intervention effects on general HrQoL using series of linear regression analyses according to the products-of-coefficients test[263] (Figure 6.1). First, we evaluated the intervention effect on HrQoL on the long term adjusted for the baseline value of HrQoL (c path). Second, we evaluated the intervention effects on the potential mediator at 4 months controlled for the mediator at baseline (a path). Third, the association between the potential mediator at 4 months and the outcome variable at 12 months was calculated, controlled for the intervention and baseline values of the mediator and outcome variable (general HrQoL) (b path); this step also provides information on the direct intervention effect on HrQoL at 12 months adjusted for the mediator variable (c' path). The product of coefficients (axb) was used to estimate the relative strength of the mediation effect. We used bootstrapping techniques with 5000 bootstrap resamples to calculate the bias-corrected and accelerated 95% confidence intervals (CI) around the proposed mediators (axb) using the SPSS macro provided by Preacher and Hayes.[264]

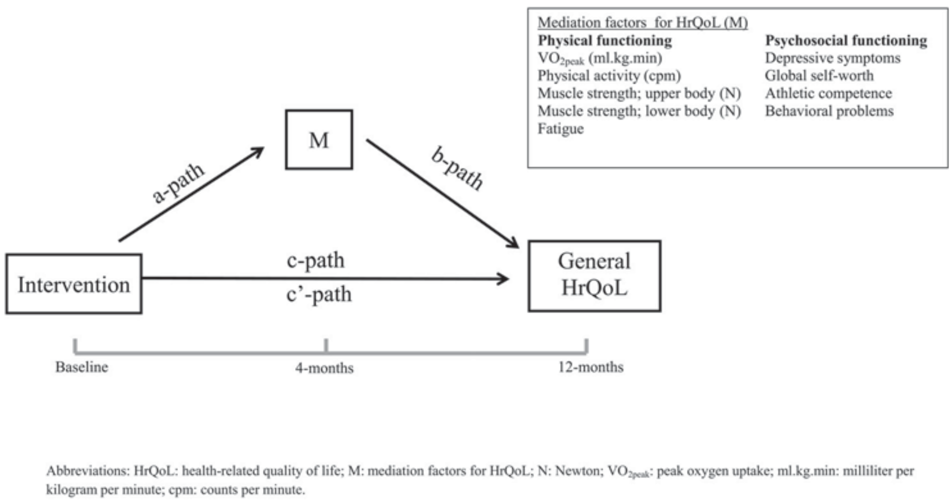

Figure 6.1 Hypothesized physical and psychosocial mediators of the intervention effect on general HrQoL

RESULTS

Of the 174 eligible patients, 68 (39%) participated (Figure 6.2). Mean (SD) age of the children was 13.2 (SD 3.1) years and 54% were boys (Table 6.1). Thirty children were randomized to the intervention group and 38 to the control group. No significant differences were found in age, gender and medical characteristics between patients in the intervention and control group, or between participants and non-participants (Table 6.1).[157]

Table 6.1: Baseline characteristics of the 'Quality of Life in Motion (QLIM) study' participants

	Intervention group n=30	Control group n=38
Age, mean years (SD)	13.4 (3.1)	13.1 (3.1)
Gender, n male (%)	16 (53%)	21 (55%)
Height, cm (SD)	159 (16.5)	154 (17.2)
Weight, kg (SD)	52 (16.0)	49 (16.9)
Cancer type, N (%)		
ALL	8 (27%)	12 (32%)
AML, HL, non-HL, CML, Burkitt	12 (40%)	13 (34%)
CNS/brain tumour	1 (3%)	6 (16%)
Solid tumour	9 (30 %)	7 (18%)
During treatment, N (%)	9 (30%)	12 (32%)
Lower body amputations	2 (3%)	2 (3%)
Upper body amputations	2 (3%)	1 (1%)

Abbreviations: SD: standard deviation; N: number; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; HL: Hodgkin lymphoma; non-H: non-Hodgkin lymphoma; CML: chronic myeloid leukemia; CNS: central nervous system
*no significant baseline differences between the two study groups were found

Nine (13%) participants dropped out between baseline and short-term follow-up, mainly due to recurrence of the disease or medical complications (7/9). An additional six (9%) participants dropped out between the short- and long-term follow-up measurements for the same reasons (Figure 6.2).

Intervention effects on primary and secondary outcomes

No significant intervention effect in VO_{2peak} were found at short (β= -0.6 ml•kg•min; 95% CI: -3.1;2.0) and long-term (β= -0.6; ml•kg•min; 95% CI: -3.6;2.5) (Table 6.2).
Per-protocol analyses (full training-attendance) did not show a significant intervention effect on these outcomes either.
At short-term follow-up, we found no significant intervention effects on lower body and upper body muscle strength. However, at long-term follow-up, lower body muscle strength was significantly higher than the control group (β= 56.5 Newton; 95% CI: 8.5;104.5), but no differences between groups were found for upper body muscle strength (Table 6.2).

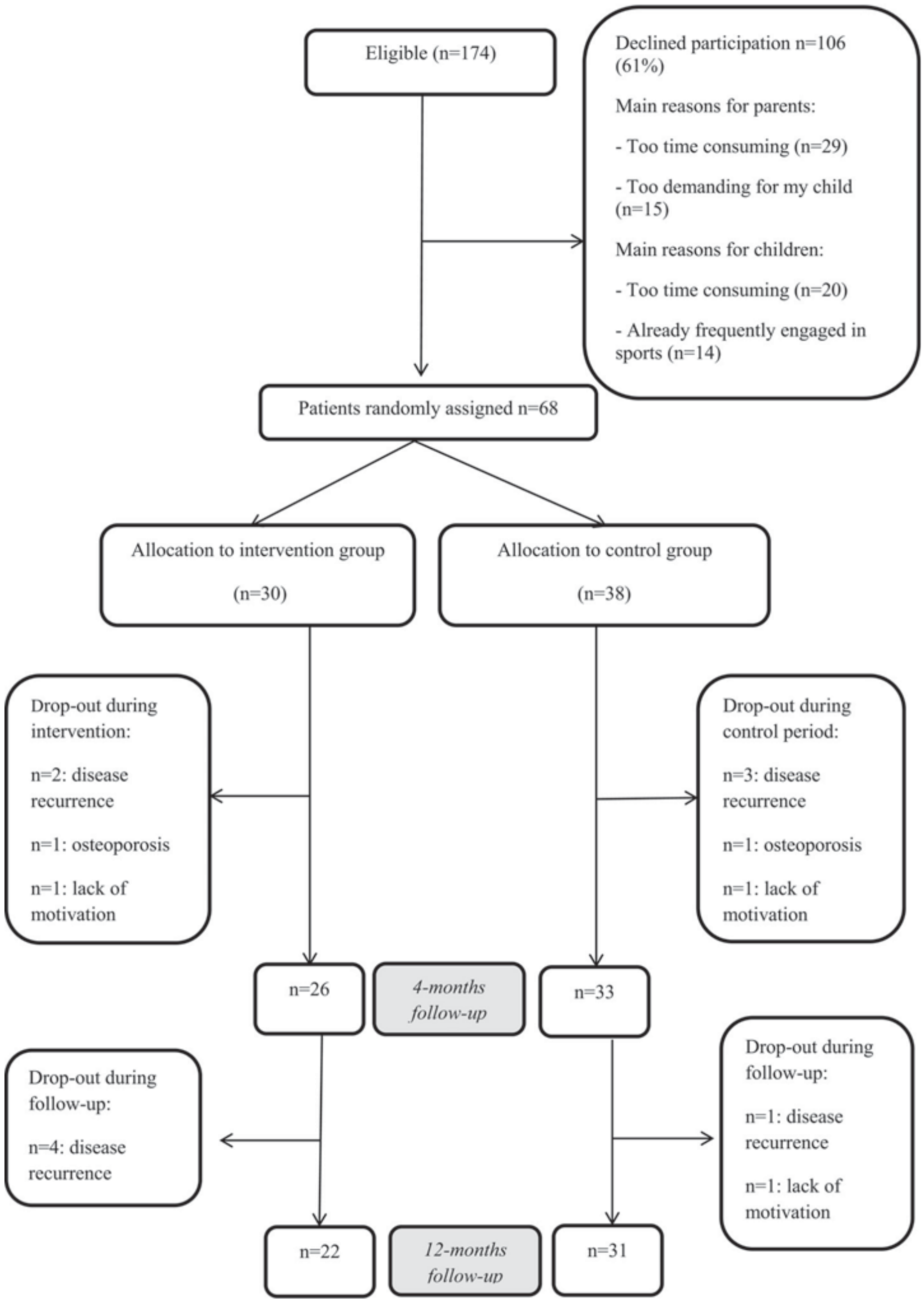

Figure 6.2 CONSORT diagram: flowchart of the study

Table 6.2: Intervention effects on primary and secondary outcomes in the Quality of Life in Motion study participants

	Intervention			Control			I vs C[%]	I vs C[%]
	(n=30)	(n=26)	(n=22)	(n=38)	(n=33)	(n=31)		
	Pre	Short Term	Long Term	Pre	Short Term	Long Term	Short Term	Long Term
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	β (95% CI)	β (95% CI)
Primary outcomes								
VO_{2peak}, (ml.kg.min)	30.1 (8.5)	31.2 (9.5)	33.8 (8.7)	31.4 (9.5)	33.0 (9.3)	35.8 (8.4)	-0.6 (-3.1; 2.0)	-0.6 (-3.6; 2.5)
Upper body muscle strength (N)	367.4 (114.0)	363.1 (110.2)	382.1 (95.8)	370.2 (133.7)	402.2 (148.7)	416.0 (144.5)	-20.4 (-47.4; 6.5)	4.5 (-21.3; 30.3)
Lower body muscle strength (N)	587.7 (174.2)	619.8 (197.5)	660.5 (206.9)	564.0 (206.6)	595.5 (216.4)	622.0 (219.2)	22.7 (-19.8; 65.2)	56.5 (8.5; 104.5)*
Secondary outcomes								
Physical activity (cpm)	153.4 (120.1)	157.8 (81.7)	213.1 (135.3)	169.2 (97.4)	156.5 (76.8)	191.8 (110.1)	29.2 (-6.2; 64.8)	8.2 (-44.3; 60.7)
BMD Lumbar spine (g/cm2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)	-0.0 (-0.0; 0.0)	0.0 (-0.0; 0.0)
% fat mass	31.2 (8.5)	30.1 (8.4)	31.2 (8.6)	31.0 (6.3)	29.3 (6.9)	29.2 (7.1)	0.6 (-0.7; 2.0)	0.6 (-1.3; 2.5)
General HrQoL	68.4 (18.2)	70.1 (15.7)	77.2 (16.4)	73.8 (14.1)	73.8 (17.6)	84.5 (13.1)	1.6 (-5.0; 8.2)	-2.5 (-9.1; 4.1)
Fatigue	67.7 (19.8)	71.7 (17.9)	76.5 (19.9)	74.3 (15.7)	76.7 (16.9)	82.0 (17.3)	-1.6 (-7.5; 4.3)	-1.8 (-9.8; 6.2)

Abbreviations: SD: standard deviation; n: number; CI: confidence interval; β: regression coefficient; I: intervention group; C: control group; VO_{2peak}: peak oxygen uptake; ml.kg.min: milliliter per kilogram per minute; N: Newton; counts per minute; cpm: counts per minute; BMD: bone mineral density; g/cm2: gram per square centimeter; %: percentage; HrQoL: health-related quality of life; * $p<0.05$; [%]Corrected for baseline scores

No significant intervention effects at short- and long-term were found on physical activity, bone mineral density of the lumbar-spine, % fat mass, HrQoL and fatigue (Table 6.2).

Mediators of the intervention on HrQoL

The intervention showed no significant effect on one of the potential mediators (path-a) (Table 6.3). Depressive symptoms (b= -1.4, 95% CI=-2.4;-0.5), athletic competence (b= 0.2, 95% CI: 0.0;0.4), global self-worth (b= 0.2, 95% CI: 0.0;0.3) and total behaviour problems (b = b -0.5, 95% CI: -0.9;-0.1) at short-term were significantly associated with HrQoL at long-term (b-path). No significant associations with long-term HrQoL were found for physical variables and fatigue. No significant mediation effects (axb) on HrQoL were found for physical and psychosocial factors.

Applicability and adherence to protocol

The mean attendance at the physical exercise training sessions was 21 sessions (SD 6.0). Of 30 children, 20 (67%) attended all physical exercise training sessions within the intended time span. The number of exercise sessions attended by the six children who did not complete the full program ranged from 10-23 of the total 24 sessions. Three other children dropped-out completely during the intervention period due to recurrence of the disease after attending 8, 12 and 20 sessions, respectively; one child never started.

The psychosocial training intervention was completed by all 27 children who did not drop-out of the study during the intervention period (90%) and, according to patients and psychologists, the training was applicable. One patient dropped-out after 20 physical exercise sessions but had, at that time, already completed the entire psycho-social intervention. In the total group, 93% of all psychosocial exercises were carried out.[258]

Adaptations in exercises or intensity of the physical training intervention were reported by 54% of the physical therapists. Three adaptations were made due to functional disabilities after a limb amputation; the remaining seven (temporary) adaptations were related to fatigue, or other disease-related symptoms of the participant. In three cases no reason for adaptation was reported. Ten children (33%) performed (some of) the exercises at a lower heart rate than described in the study manual. All others reached the requested heart rate during training.

Table 6.3: Direct and indirect intervention effects on general Health-related quality of life, intervention effects on potential mediators, effects of the mediators on general Health-related quality of life and the univariate mediation effects

	Intervention effect on the potential mediator	Effect of the potential mediator on HrQoL	Intervention effect through the mediator on HrQoL	Mediation effect
	(a-path)	**(b-path)**	**(c'-path)**	**(a x b path)**
Main outcome: General HrQoL	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**estimate (95% CI)**
Potential mediators				
VO_{2peak}(ml.kg.min)	-0.5 (-3.2; 2.1)	0.3 (-0.6; 1.1)	0.3 (-6.5; 7.1)	-0.3 (-3.3; 0.8)
Lower body strength (N)	22.7 (-21.6;67.0)	-0.0 (-0.0; 0.0)	-3.3 (-10.4; 3.8)	-0.1 (-2.6; 0.7)
Upper body strength (N)	-20.3 (-48.6; 7.7)	0.0 (-0.0; 0.1)	-2.6 (-9.7; 4.6)	-0.5 (-3.9; 0.5)
Physical activity (cpm)	29.1 (-9.8; 68.0)	-0.0 (-0.1; 0.1)	0.6 (-9.4; 10.7)	-0.7 (-8.5; 1.5)
Fatigue	-1.2 (-7.6; 5.1)	0.2 (-0.1; 0.5)	-2.9 (-10.1; 4.2)	-0.3 (-3.7; 1.0)
Depressive symptoms	0.2 (-1.6; 2.0)	-1.4 (-2.4; -0.5)*	-3.5 (-9.9; 3.0)	0.7 (-2.4; 3.6)
Athletic competence	-1.5 (-11.0; 8.1)	0.2 (0.0; 0.4)*	-4.2 (-11.3; 3.0)	0.0 (-2.8; 3.0)
Global Self-Worth	-0.3 (-13.2; 12.6)	0.2 (0.0; 0.3)*	-5.2 (-12.5; 2.2)	1.0 (-1.2; 4.8)
Behaviour problems	1.1 (-5.1; 7.2)	-0.5 (-0.9; -0.1)*	0.6 (-7.8; 8.9)	0.3 (-6.7; 3.6)

Abbreviations: SD: standard deviation; n: number; CI: confidence interval; β: regression coefficient; I: intervention group; C: control group; VO_{2peak}: peak oxygen uptake; ml.kg.min: milliliter per kilogram per minute; N: Newton; counts per minute; cpm: counts per minute; BMD: bone mineral density; g/cm2: gram per square centimeter; %: percentage; HrQoL: health-related quality of life; * $p<0.05$; %Corrected for baseline scores

DISCUSSION

This study describes the short- and long-term effects of a combined physical exercise and psychosocial intervention for children with cancer during or shortly after treatment. In addition, a process evaluation to explore feasibility was undertaken. Except for significant improvements in lower body strength at 12 months follow-up, no significant effects of the intervention were found on physical and psychosocial function and general HrQoL.

The significant beneficial effects of the interventions on lower body muscle strength is in line with results from two earlier RCTs[63,186] showing that children with cancer improved their leg and ankle strength after exercise. However, in contrast to previous studies, the intervention did not lead to a greater improvement in cardiorespiratory fitness or upper body muscle strength.[63–65,92,186] In the present study, cardiorespiratory fitness improved in both the intervention and control group; this might indicate that, in this phase of the cancer trajectory, exercise is unable to accelerate natural recovery. This study shows low physical and psychosocial responses to the physical exercise training. Future studies should examine whether personalized interventions, or offering interventions to specific subgroups, exercise interventions with a longer duration, or exercise interventions performed at an earlier/later phase of the disease, may be more beneficial. A study evaluating the effects of exercise intervention on motor performance and body composition, directly following acute lymphoblastic leukemia diagnosis[65], also showed no significant effects of exercise[65]. Offering an exercise intervention after a period of natural recovery might result in more pronounced effects in children, as they may be more able to perform intensive exercise. Nevertheless, the impact is expected to be small since no children dropped-out of the present study due to the intensity of the program. In addition, no significant improvements in physical fitness were found in a related pilot study evaluating a comparable exercise program, performed at least 6 months after completion of treatment for acute lymphoblastic leukemia.[92] Additional studies with larger sample sizes should investigate whether offering exercise at a later stage significantly improves physical fitness.

The adherence and applicability of the study intervention was satisfactory: 66% of the children were able to fully complete the intervention. Therefore, non-adherence can not explain the absence of intervention effects.

In contrast to previous studies in adult cancer survivors, we found no significant mediation effects of physical and psychosocial function on general HrQoL. However, finding a significant association between psychosocial variables (depressive symptoms, athletic competence, global self-worth, and behavioral problems) and HrQoL indicates that those variables are important intervention targets to improve HrQoL. However, the current intervention did not significantly improve these psychosocial variables.

Future studies should aim to find more effective strategies to improve psychosocial function, as this may enhance HrQoL of these children.
To our knowledge, the present study is the first RCT with a relatively large sample size to evaluate the effects of a combined physical and psychosocial training intervention, at both short and long term. However, some limitations need to be considered. First, mainly due to recurrence of the disease and medical complications, at 12-months follow-up the minimum number of participants required for each study group was not reached. This implies that, especially when assessing the effects on secondary outcomes, the study may have been underpowered to detect significant differences. Secondly, the number of patients in each study arm was skewed due to the four factor stratification rules; however, as a result of the stratification, the characteristics of both study groups were highly comparable. Thirdly, it is possible that our participants are biased towards a more positive attitude on physical and psychosocial training. Although analysis of differences between participants and non-participants showed that participants rated their physical fitness lower than the non-participants[157], we may have reached the children and parents who had the most physically active children, or were more aware of their exercise behaviors. These children might have experienced more negative effects of cancer on physical fitness and, therefore, may have rated their physical fitness lower. Children in the control group were allowed to find their own way to increase their fitness level. In the control group (apart from self-report data derived from an activity questionnaire and cost diaries) visits to physical therapists or sport centers were not monitored, leading to intervention contamination. Future studies need to monitor this item more strictly.

CONCLUSION

In conclusion, although a combined physical and psychosocial intervention is applicable in children with cancer during or shortly after treatment, we found no significant beneficial effects of a combined physical and psychosocial intervention, except for improved lower-body muscle strength on the long term. Future research should determine whether this intervention may be beneficial to improve physical fitness and HrQoL for specific subgroups of children, or when offered at a later stage in the disease trajectory. To enhance HrQoL, it may be important to improve psychosocial factors such as depressive symptoms, athletic competence, global self-worth and behavioral problems.