

Chapter 5

Effects of a combined physical and psychosocial intervention program for childhood cancer patients on

quality of life and psychosocial functioning: results of the QLIM randomized clinical trial

Elisabeth M. van Dijk-Lokkart
Katja I. Braam
Eline van Dulmen-den Broeder
Gertjan J.L. Kaspers
Tim Takken
Martha A. Grootenhuis
Isabelle C. Streng
Marc B. Bierings
Johannes H.M. Merks
Marry M. van den Heuvel-Eibrink
Margreet A. Veening
Jaap Huisman

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ABSTRACT

Objective: Although survival rates in childhood cancer have improved, prevention and reduction of late effects remain important. This study evaluates the effects of a combined physical exercise and psychosocial intervention on health-related quality of life (HrQoL) and psychosocial functioning in childhood cancer patients.

Methods: In this multicenter randomized controlled trial, cancer patients (aged 8-18 years) and their parents filled in questionnaires on HrQoL, depressive symptoms, behavioral problems and self-esteem. Measurements were conducted at baseline, shortly after the 12-week intervention period, and 12 months after baseline. Generalized estimating equations analyses were performed to assess short and long-term psychosocial effects.

Results: Of the 174 eligible patients, 68 (39.1%) participated. The intervention group consisted of 30 participants at baseline [mean age 13.0 (SD 3.0) years; 53% male], 26 at short-term and 22 at long-term follow-up. The 'care as usual' control group consisted of 38 participants at baseline [mean age 12.6 (SD 3.1) years; 53% male], 33 at short-term and 31 at long-term follow-up. Overall the intervention did not improve psychosocial functioning and HrQoL. According to parent-proxy reports, the intervention led to a greater improvement on pain-related HrQoL on both the short ($\beta=13.4$; 95% CI: 3.0; 23.8) and long term ($\beta=13.0$; 95% CI: 1.6; 24.4), and to greater improvement on procedural anxiety immediately after the intervention ($\beta=12.6$; 95% CI: 1.9; 23.3).

Conclusion: A combined physical and psychosocial training for children with cancer did not have effects on HrQoL or psychosocial functioning, with exception of modest positive effects on parent-reported pain and procedural anxiety.

INTRODUCTION

Although survival rates for childhood cancer patients have increased significantly, most patients ($\pm 75\%$) experience at least one treatment-related adverse health effect after a median follow-up of 17 years [1]. Impaired health-related fitness has been reported both during and after childhood cancer treatment [2-6]. This can lead to fatigue, obesity and/or mental health problems and, consequently, have a negative impact on health-related quality of life (HrQoL) [7-13]. Therefore, current research also focuses on rehabilitation of physical fitness.

In adult cancer patients rehabilitation programs combining physical exercise and psychosocial support have demonstrated positive effects on physical fitness and HrQoL [14-15]. However, a recent Cochrane review on childhood cancer patients reported limited effects, albeit mainly performed in small samples and in studies with significant methodological limitations [16]. Also, the few studies evaluating the effects of a stand-alone psychosocial training to enhance psychosocial wellbeing for childhood cancer patients, show limited evidence for effectiveness [17-19]. To our knowledge, no data are available on rehabilitation programs combining physical and psychosocial training for childhood cancer patients.

Therefore, the Quality of Life in Motion (QLIM) study was initiated. This randomized controlled trial (RCT) evaluates the effects of a 12-week combined physical exercise and psychosocial intervention. This intervention, implemented during or shortly after treatment, aims to improve physical functioning and enhance wellbeing, self-esteem and HrQoL of childhood cancer patients [20].

The present study investigates the short and long-term effects of the combined QLIM intervention on changes in HrQoL and psychosocial functioning in childhood cancer patients. We studied the results of the 12-week intervention program on short- and long-term changes in HrQoL and psychosocial functioning. We expected (1) a greater improvement in HrQoL, (2) a greater reduction in behavioral problems and depressive symptoms, and (3) greater improvement in self-esteem in the intervention group in comparison to the control group.

METHODS

Procedure

Between March 2009 and July 2013 patients were recruited for the QLIM study. Eligible participants (aged 8-18 years) were diagnosed with any type of childhood malignancy, were ≤ 12 months off treatment, and were treated with chemotherapy and/or radiotherapy. Excluded from the study were patients requiring stem cell transplantation and/or growth hormone therapy, as well as patients who were wheelchair-dependent, not able to 'ride a bike', and not able to read, write, self-reflect and/or follow instructions due to learning difficulties.

Recruitment took place in four pediatric oncology centers in the Netherlands: VU University Medical Center (Amsterdam), Wilhelmina Children's Hospital UMC (Utrecht), Emma Children's Hospital/Academic Medical Center (Amsterdam) and Erasmus Medical Center/Sophia Children's Hospital (Rotterdam). Patients and parents individually received written and verbal information about the study, an informed consent form, and an addressed return envelope. Written informed consent was obtained from the parents or legal guardian of each patient, and also separately from each patient aged ≥ 12 years.

The study protocol was approved by the Medical Ethics committee of the VU University Medical Center (No. 2008/208) and is registered at the Dutch Trial Register (No. NTR1531).

After baseline measurement, participants were randomized (block randomization) to either the intervention or the control group by an independent data manager. To get balanced groups, prior to randomization, stratification took place based on pubertal stage, sex, diagnosis (solid tumor versus hematological malignancies), and whether recruitment took place during or shortly after treatment.

Intervention

The physical exercise training was highly intensive with a combination of cardiorespiratory and muscle strength training. Duration and intensity of the sessions gradually increased throughout the training. The training included two sessions per week (45 min each) for 12 weeks in a local physiotherapy practice. The local physiotherapist had an instruction manual in which every session with the patient was clearly described.

The psychosocial training was an individualized structured program to reinforce socio-emotional functioning and coping with disease-related effects. The training included six child sessions of 60 min each (once every two weeks in the treating hospital), and two parent sessions (at the start and end of the program) which were offered during the same 12 weeks as the physical exercise training. The psychosocial training consists of psycho-education and cognitive-behavioral techniques covering the following topics: increasing self-awareness and self-belief; expressing positive characteristics about oneself; core feelings of fear, anger, happiness and sadness; feelings, thoughts and behavior; coping with (non) disease-related difficult situations; relaxation exercises; possible changes in social contacts with peers, sexuality and relationships (for adolescents); possible changes in relation with parents and siblings; looking toward the future in general and plans to continue physical exercises in daily life. The psychosocial training appeared applicable with good adherence rates and positive evaluations by patients and psychologists [21].

'Care as usual' for patients in the control group varied between the hospitals due to local guidelines and preferences, but did not involve routine exercise or psychosocial training in any of the centers. However, psychological care and/or physiotherapy were available on demand.

Data collection and instruments

Before randomization, baseline measurements took place in the patient's treating hospital. These measurements included questionnaires to assess their HrQoL and psychosocial functioning. At 4 and 12 months after baseline, the same evaluations were made again among all participants that were still available. Data derived from these questionnaires are used in the present study to evaluate short and long-term psychosocial effects of the combined physical and psychosocial intervention.

Health-related quality of life (HrQoL)

Both self-report and parent-proxy report of HrQoL were assessed using three versions of the Dutch PedsQL. First, the 23-item PedsQL 4.0 Generic Core scale was used. This consists of 4 multi-item subscales: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Psychosocial health status was derived from the last three

subscales and a total HrQoL score was calculated. Second, the PedsQL 3.0 Cancer module was used: this is a 27-item multidimensional cancer-specific questionnaire which includes 8 multi-item subscales: pain and hurt (2 items), nausea (3 items), procedural anxiety (3 items), treatment anxiety (3 items), worry (3 items), cognitive problems (5 items), perceived physical appearance (3 items), and communication (3 items) [22-23]. Third, fatigue was assessed by the 18-item PedsQL Multidimensional Fatigue Scale Acute Version. This instrument is designed to measure both the child's and the parent's perception of fatigue in pediatric patients [24]. The module encompasses 3 subscales: general fatigue (6 items), sleep/rest fatigue (6 items), and cognitive fatigue (6 items).

For all three PedsQL forms, per item, the child or parent indicated on a 5-point Likert scale to what extent the child had difficulties with the stated problem in the past month: never (0), almost never (1), sometimes (2), often (3), and almost always (4). Each answer was reversed, scored and rescaled to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0). The items on each subscale were summarized and divided by the amount of items in the subscale to get a total score between 0 and 100 for each subscale, with higher scores indicating higher levels of functioning or better quality of life [23]. Both parent and child reports of the PedsQL have proven reliable and valid in pediatric patients [22]. The Dutch version has adequate psychometric properties and normative scores of the Dutch population are available [23-24].

Behavioral problems

To assess parental perception of behavioral problems in children aged 6-18 years, the Child Behavior Checklist (CBCL) [25] was used. All participants aged ≥ 11 years also completed the Youth Self-Report (YSR) to assess self-reported behavioral problems. In the present study the total problem scale, as well as the internalizing and externalizing scales, were used. Scores of the subscales are computerized to the Aseba program (ADM) and converted to T-scores, with higher scores indicating more behavioral problems [25]. Both the CBCL and the YSR are useful, valid and reliable instruments to assess evaluation of internalizing and externalizing behavioral problems [25].

Depressive symptoms

Patients completed the Children's Depression Inventory (CDI) which assesses depressive symptoms in the last two weeks before measurement. The normative sample of this 27-item questionnaire used for scoring is divided into age groups

(6-11 and 12-17 years) and gender. For this questionnaire, good internal consistency and test-retest reliability, and a positive correlation with clinicians' independent global depression ratings, are reported [26].

Self-perception

The Dutch versions of the Self Perception Profile for children (CBSSK) and adolescents (CBSA) were used to measure self-perception of the patients. The questionnaires assess the self-perception of scholastic competence, athletic competence, social acceptance, physical appearance, behavioral conduct, global self-worth and close friendships, and have good reliability and validity when used in children aged ≥ 8 years [27-28].

General and medical characteristics

Information on sex, age, diagnosis, and whether the participant was recruited during or shortly after treatment, was obtained from the patient's medical records.

Statistical analysis

For this RCT, power calculations were performed on expected changes in physical fitness (VO₂ peak; ml/l kg/min) resulting in a minimum requirement of 26 participants per group [20]. The Statistical Package for Social Sciences (SPSS) for Windows version 20 was used for the analyses.

Independent sample t-tests, Mann-Whitney U tests and chi-square tests for independence were used for group comparisons (intervention vs. control) on baseline characteristics. Longitudinal generalized estimating equations (GEE) analyses with an exchangeable correlation structure were used to simultaneously evaluate the short and long-term effects of the intervention. Group, time, and the interaction of group x time, were entered in the regression model as independent variables and adjustments were made for baseline values. Multivariate regression analysis was used on significant results in favor of the intervention group, to assess which factors might predict the likelihood of patients in the intervention group showing greater improvement after the intervention, compared to the control group. The factors diagnosis (hematological malignancies/solid tumor), recruitment during/after treatment, puberty stage, age and sex were entered into a backward selection procedure. Stepwise, the variable with the highest p-value was removed until all variables had a p-value ≤ 0.05 .

RESULTS

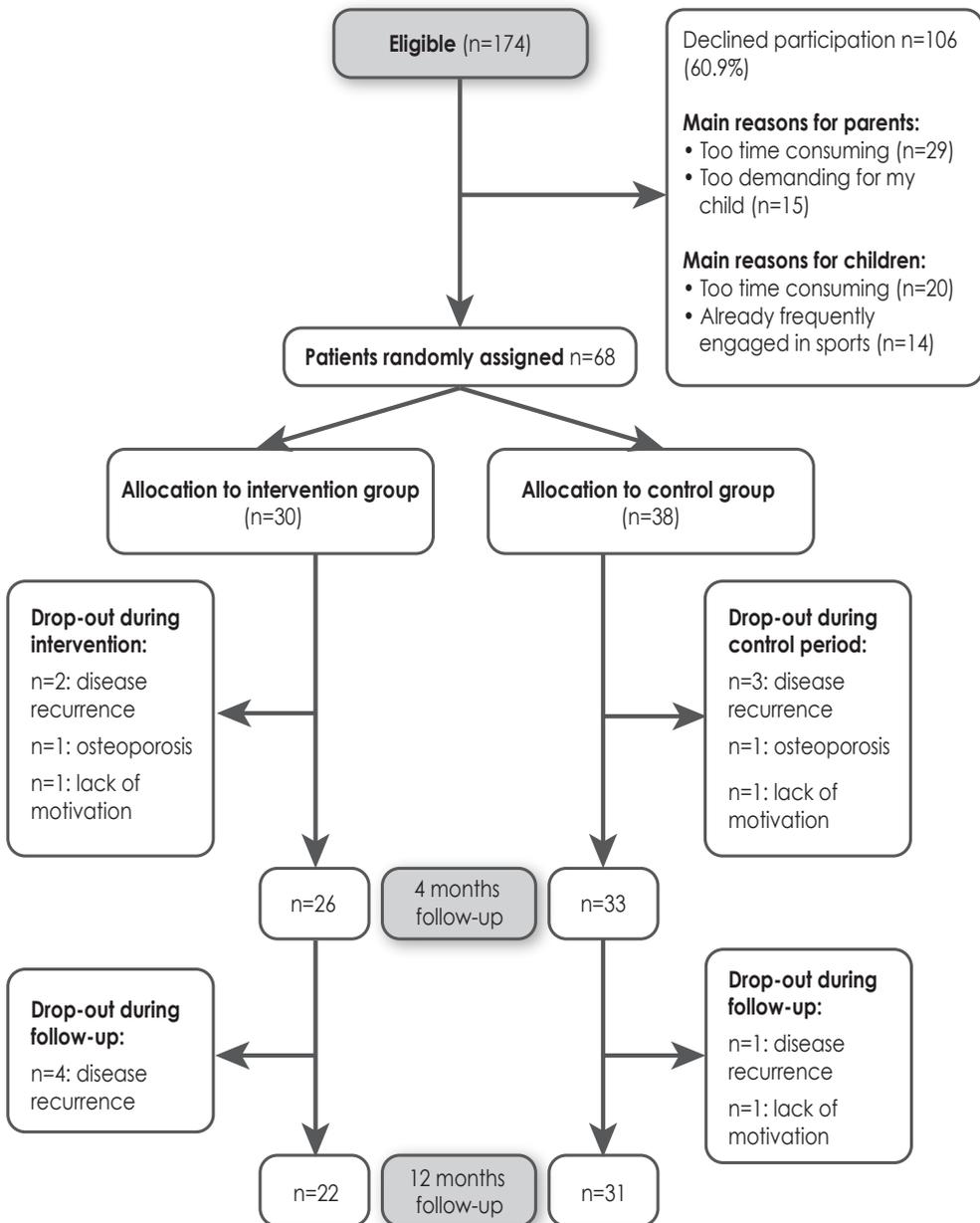
Of the 174 patients eligible for the QLIM study, 68 (39.1%) participated. No differences were found in general and medical characteristics between the participants and the non-participants [29]. However, non-participants rated their fitness level higher compared with participants. Patients with more (internalising) behavioral problems seem more likely to participate in the study [29].

Table 1. General and medical characteristics at baseline

	Intervention (n=30) Mean (SD)	Control (n=38) Mean (SD)
Age in years	13.0 (3.0)	12.6 (3.1)
	n (%)	n (%)
Male	16 (53.3)	20 (52.6)
Center		
VU University Medical Center, Amsterdam	15 (50.0)	19 (50.0)
Wilhelmina's Childrens Hospital/UMC Utrecht	4 (13.3)	5 (13.2)
Emma's Childrens Hospital/AMC, Amsterdam	7 (23.3)	9 (23.7)
Erasmus Medical Center, Rotterdam	4 (13.3)	5 (13.2)
Diagnosis		
Leukemia/lymphoma	20 (66.7)	26 (68.4)
Brain tumors/central nervous tumors	2 (6.7)	5 (13.2)
Solid tumors	8 (26.7)	7 (18.4)
When eligible for study		
During treatment	9 (30.0)	13 (34.2)
Within the first year after treatment	21 (70.0)	25 (65.8)
Puberty		
yes	20 (66.7)	26 (68.4)
no	10 (33.3)	12 (31.6)

According to the stratification procedure, 30 participants were randomized to the intervention group and 38 to the control group (Table 1). Between baseline and short-term follow-up, 9 (13.2%) participants dropped out, mainly due to the recurrence of disease or medical complications (7/9); for the same medical reasons, an additional 6 (8.8%) participants dropped out between the short and long-term follow-up measurements (Figure 1). With exception of the few drop-outs, all participants completed all psychosocial sessions and 2/3 of the

Figure 1. CONSORT diagram



participants completed all physical training sessions. The remaining third of the participants completed on average 18 (of 24) physical training sessions (range 10-23). So adherence rates for both the psychosocial and physical training were pretty good considering the demanding nature of the intervention.

Health-related quality of life

From all participants aged ≤ 12 years, 10.8% reported a general HrQoL of lower than -2SD than the healthy Dutch norm group. 23.1% of the participants aged ≥ 13 years reported a lower general HrQoL than -2 SD of the norm population.

After correction for baseline scores, analyses of the self-reported data showed no significant differences on all HrQoL domains between the two groups at both measurement points (Table 2). However, corrected for baseline scores, parents in the intervention group reported a significant improvement in levels on the Pain and Hurt subscale indicating less pain, in contrast to the parents in the control group, both shortly after the intervention ($\beta=13.4$; 95% CI: 3.0; 23.8) and at long-term follow-up ($\beta=13.0$; 95% CI: 1.6; 24.4). At short-term follow-up parents in the intervention group reported significantly less perception of Procedural Anxiety in their children than parents in the control group ($\beta=12.6$; 95% CI: 1.9; 23.3). However, this effect did not persist into long-term follow-up.

At long-term follow-up, parents in the control group reported significantly more improvement in scores on the Nausea subscale indicating less nausea ($\beta=-8.8$; 95% CI: -16.3; -1.4), compared to parents in the intervention group.

Behavioral problems and depressive symptoms

At baseline 17.2% of the parents reported clinical significant total problem behavior, 28.1% clinical significant internalising behavior and 5.9% clinical significant externalising behavior. The children aged ≥ 11 years reported less clinical significant problem behavior: respectively 2.6%, 12.8% and 0% on total problem behavior, internalising behavior and externalising behavior. Of all participants 6.8% reported depressive symptoms in the clinical range.

After the intervention period, at both measurement points (corrected for baseline scores), no significant differences were found in behavioral problems and depressive symptoms between the two groups, as reported by both the parents and the children.

Self-perception

On most domains of the Self-Perception Profile, 7 to 15% of the total study group scored below average, with an exception of 32.2% of the participants rating their athletic competence below average.

Both at short-term and long-term follow-up (after correction for baseline scores), no differences were found in improvement on all aspects of self-perception between the intervention and control group.

Multivariate regression analysis

A backward selection procedure was applied to reveal predictors of greater improvement in the intervention group as reported by the parents, compared to the controls, on the subscale in which univariate analysis on long-term follow-up showed a significant difference between the two groups in favor of the intervention group: Pain and Hurt subscale.

In this model, at long-term follow-up the score on parent-reported Pain and Hurt (corrected for baseline scores) was predicted by study arm and treatment phase, i.e. parents of patients in the intervention group who were after treatment, reported a greater improvement.

Table 2: Intervention effects on Health-Related Quality of Life

	Intervention				Control				I vs C ^a		I vs C ^b	
	Pre	Post Short Term	Post Long Term	Pre	Post Short Term	Post Long Term	Short Term	Long Term	β (95% CI)	β (95% CI)		
PedsQL generic - parent-report^c												
Physical functioning	56.7 (21.5)	69.6 (20.2)	70.3 (24.0)	63.2 (25.6)	70.0 (24.2)	76.7 (20.7)	6.6 (-1.3; 14.4)	0.9 (-8.1; 9.9)				
Emotional functioning	62.8 (20.4)	74.4 (16.1)	70.9 (20.5)	65.1 (21.5)	72.6 (21.2)	79.5 (17.7)	5.4 (-2.0; 12.7)	-6.7 (-15.8; 2.5)				
Social functioning	72.3 (20.0)	78.3 (17.4)	76.1 (21.9)	74.9 (18.8)	83.1 (15.6)	87.0 (15.4)	-2.0 (-9.3; 5.3)	-8.9 (-17.7; -0.0)				
School functioning	61.1 (22.7)	61.2 (19.8)	69.5 (23.2)	62.4 (21.7)	71.7 (20.6)	78.8 (17.6)	-4.4 (-12.7; 3.9)	-5.8 (-15.2; 3.6)				
Psychosocial health status	65.5 (16.7)	71.0 (14.6)	72.3 (18.8)	67.8 (17.4)	75.6 (16.1)	81.7 (14.9)	1.4 (-4.4; 7.2)	-5.5 (-13.0; 2.0)				
Total score	57.2 (15.7)	70.1 (15.7)	71.6 (19.8)	60.5 (17.9)	73.8 (17.6)	80.0 (16.2)	3.0 (-2.9; 8.8)	-2.7 (-10.1; 4.7)				
PedsQL generic - self-report^d												
Physical functioning	62.4 (21.9)	73.7 (20.4)	76.8 (18.6)	70.4 (17.1)	80.3 (16.0)	84.8 (16.3)	-2.8 (-10.3; 4.7)	-2.9 (-12.3; 6.6)				
Emotional functioning	75.2 (17.9)	75.6 (19.0)	77.5 (18.7)	75.8 (17.7)	79.1 (19.1)	85.0 (15.4)	-2.6 (-10.7; 5.6)	-6.2 (-13.7; 1.2)				
Social functioning	78.3 (19.3)	78.8 (16.5)	84.5 (17.0)	82.8 (14.0)	84.4 (15.0)	89.0 (12.8)	-2.5 (-8.1; 3.2)	1.5 (-9.1; 6.2)				
School functioning	61.5 (23.8)	65.4 (18.8)	70.1 (24.3)	67.6 (19.7)	75.3 (17.9)	79.0 (15.7)	-4.4 (-11.1; 2.4)	-2.7 (-11.8; 6.4)				
Psychosocial health status	70.3 (17.8)	73.1 (15.0)	79.0 (16.7)	75.4 (13.9)	79.1 (13.9)	82.0 (19.5)	-2.1 (-7.0; 2.9)	1.2 (-7.1; 9.6)				
Total score	68.4 (18.2)	70.1 (15.7)	77.2 (16.4)	73.8 (14.1)	73.8 (17.6)	84.5 (13.1)	2.0 (-4.6; 8.6)	-2.3 (-9.0; 4.2)				
PedsQL cancer - parent-report^e												
Pain and hurt	55.1 (22.8)	70.2 (22.1)	73.9 (24.7)	70.7 (21.6)	65.2 (21.6)	69.6 (27.1)	13.4 (3.0; 23.8) [*]	13.0 (1.6; 24.4) [*]				
Nausea	73.5 (25.0)	76.1 (20.7)	80.2 (20.0)	76.4 (19.1)	82.7 (20.2)	91.3 (12.6)	-4.1 (-12.0; 3.9)	-8.8 (-16.3; -1.4) [*]				
Procedural anxiety	69.4 (28.1)	77.7 (25.5)	79.4 (22.4)	72.1 (35.9)	71.2 (32.8)	77.1 (32.3)	12.6 (1.9; 23.3) [*]	6.6 (-4.3; 17.6)				
Treatment anxiety	86.2 (20.6)	87.5 (17.0)	86.7 (18.1)	86.4 (19.1)	87.5 (19.8)	93.2 (14.7)	1.4 (-6.0; 8.7)	-5.7 (-12.9; 1.4)				
Worries	74.7 (21.4)	82.1 (18.5)	75.0 (28.7)	70.4 (26.0)	74.8 (22.0)	84.5 (17.1)	7.4 (-1.2; 16.1)	-9.4 (-21.6; 2.7)				
Cognitive problems	66.7 (19.4)	68.7 (19.4)	72.7 (22.2)	68.1 (19.9)	71.7 (22.0)	78.4 (16.9)	-2.6 (-10.6; 5.4)	-4.3 (-13.0; 4.4)				

Perceived physical appearance	67.4 (23.4)	71.3 (31.6)	78.4 (27.1)	68.4 (26.4)	74.5 (27.6)	78.6 (24.2)	-1.6 (-13.5; 10.3)	-1.3 (-11.7; 9.1)
Communication	74.9 (24.5)	74.4 (27.8)	80.3 (21.9)	73.9 (22.7)	76.8 (23.3)	79.8 (19.3)	-2.0 (-11.8; 7.9)	-2.1 (-12.7; 8.5)
Total score	72.0 (14.9)	75.3 (15.2)	78.1 (16.2)	72.5 (16.0)	74.3 (14.3)	81.8 (11.3)	2.9 (-2.0; 7.8)	-1.8 (-7.1; 3.5)
PedsQL cancer - self-report[§]								
Pain and hurt	73.9 (25.2)	80.3 (22.4)	80.7 (24.3)	79.2 (17.9)	78.8 (21.9)	84.1 (19.7)	3.5 (-5.1; 12.1)	-0.7 (-11.5; 10.1)
Nausea	71.6 (25.2)	76.3 (26.7)	83.9 (19.0)	77.0 (17.0)	78.1 (24.0)	85.9 (16.6)	4.4 (-4.1; 12.9)	0.4 (-8.3; 9.1)
Procedural anxiety	79.2 (25.4)	80.5 (24.6)	80.3 (23.9)	74.1 (30.7)	77.9 (29.8)	81.0 (27.3)	-0.5 (-8.9; 8.0)	-3.0 (-11.0; 4.9)
Treatment anxiety	86.4 (22.8)	86.5 (21.1)	89.0 (15.9)	90.5 (20.2)	90.9 (12.9)	94.0 (12.4)	-3.2 (-10.0; 3.7)	-3.8 (-11.7; 4.2)
Worries	72.4 (24.1)	77.9 (21.6)	83.3 (19.2)	73.0 (22.7)	79.5 (20.8)	85.1 (18.3)	-0.2 (-3.5; 3.1)	-0.3 (-10.2; 9.5)
Cognitive problems	72.0 (20.4)	67.3 (19.5)	69.5 (23.5)	74.2 (14.2)	74.8 (17.1)	78.6 (22.5)	-6.0 (-13.1; 1.2)	-4.5 (-15.7; 6.6)
Perceived physical appearance	76.8 (26.0)	76.6 (23.9)	84.5 (20.1)	78.3 (22.9)	78.3 (25.4)	78.7 (27.0)	-3.0 (-9.7; 4.5)	1.5 (-7.9; 10.9)
Communication	74.9 (24.5)	80.1 (18.9)	81.0 (22.5)	77.9 (21.2)	79.0 (18.4)	81.0 (22.4)	-0.3 (-7.5; 6.8)	-1.3 (-11.1; 8.5)
Total score	76.0 (15.5)	77.2 (15.1)	80.5 (13.9)	77.5 (13.1)	79.3 (13.2)	83.1 (13.4)	-1.1 (-5.0; 2.8)	-1.2 (-6.9; 4.5)
PedsQL multidimensional fatigue parent-report[§]								
General fatigue	53.6 (28.3)	61.9 (25.1)	64.0 (25.4)	58.0 (25.3)	71.7 (23.8)	74.2 (21.5)	-3.6 (-13.0; 5.8)	-5.8 (-15.5; 4.0)
Sleep-rest fatigue	64.1 (23.4)	70.6 (23.7)	68.4 (26.3)	71.0 (20.6)	76.3 (22.7)	79.9 (20.3)	1.3 (-7.3; 9.9)	-5.0 (-14.8; 4.9)
Cognitive fatigue	68.5 (23.7)	72.0 (23.6)	70.0 (23.4)	72.8 (22.4)	73.9 (19.9)	79.0 (19.4)	2.3 (-6.3; 10.8)	-6.5 (-16.1; 3.2)
Total fatigue	61.7 (22.4)	68.2 (21.9)	66.8 (22.6)	66.3 (19.5)	74.0 (19.4)	77.7 (17.8)	0.7 (-6.4; 7.8)	-5.8 (13.8; 2.2)
PedsQL multidimensional fatigue self-report[§]								
General fatigue	68.1 (24.9)	71.3 (23.0)	77.1 (21.6)	72.7 (18.6)	79.3 (19.0)	82.8 (20.6)	-4.0 (-10.8; 2.9)	-1.1 (-10.8; 8.7)
Sleep-rest fatigue	67.8 (18.6)	70.4 (18.3)	75.0 (21.3)	74.3 (15.4)	73.2 (21.6)	81.8 (18.4)	-0.3 (-9.2; 8.6)	-4.6 (-13.7; 4.4)
Cognitive fatigue	70.5 (24.3)	73.3 (19.4)	77.8 (22.7)	75.9 (20.0)	77.5 (22.0)	81.6 (20.8)	-1.3 (-8.9; 6.2)	-0.7 (-10.2; 8.7)
Total fatigue	67.7 (19.8)	71.7 (17.9)	76.6 (20.1)	74.3 (15.7)	76.7 (16.9)	82.0 (17.3)	-1.2 (-7.2; 4.7)	-1.6 (-9.6; 6.4)

Abbreviations: I, intervention group; C, control group; SD, standard deviation; N, number; CI, confidence interval; *p < 0.025; [§]Corrected for baseline scores; [§] Range 0-100 with higher scores meaning a higher level of reported HrQoL in all subscales and versions of PedsQL

DISCUSSION

A combined physical and psychosocial training for children with cancer during or shortly after treatment, showed largely no effect on HrQoL, behavioral problems, depressive symptoms and self-perception. Some small effects on the long-term were seen for HrQoL. However, this effect was reported only by the parents and not by the patients themselves. Corrected for baseline scores, at both short and long-term follow-up parents in the intervention group reported a greater improvement for their children on the Pain and Hurt scale, compared to parents in the control group. This indicates that, in their perception, their child's pain had decreased. The discrepancy between parent report and self-report could be due to a difference between (pain-related) behavior and the actual feeling of pain. Due to the intervention, children may be more willing and able to perform normal activities despite still feeling pain. Parents might perceive this improved willingness/ability to perform normal activities as their child experiencing less pain, leading to higher scores on the parent-reported Pain and Hurt scale. However, the children themselves may still indicate more pain because they perceive the same level of pain, despite that more normal daily activities are being performed. It is reported that parents and children base their evaluation of HrQoL on different types of information: parents are better in reporting observable behavior (e.g. physical functioning) whereas children are better in reporting their internal states or feeling, e.g. emotional functioning [30]. This might explain why the effect reported by the parents was not the same as that in the children's self-reports.

In contrast to our hypotheses, no differences between the two groups were found in behavioral problems, depressive symptoms and self-perception. However, we have to keep in mind that at baseline participants reported only few (internalising) behavior problems and depressive symptoms and, with exception of their perception of athletic competence, their self-perception was relatively good. Since psychosocial functioning of most participants in general was in the normal range at baseline, this raises the question whether we could have expected the children to improve significantly. Unfortunately, the small numbers of children with questionnaire scores in the clinical ranges does not allow to compare the results for children with and without clinically significant problems. In future research it would be interesting to make this distinction to determine whether specific risk groups could benefit from such an intervention.

The fact that significant effects of the intervention on psychosocial functioning were not found in contrast to what was expected, might be because natural recovery in the first year after intensive treatment overshadows the training effect, leading to only small differences in the changes between the two groups. Also, because the HrQoL of childhood cancer patients improves during treatment (although still poor compared to the norm) and continues to improve after treatment [30], more data based on an (even) longer term are needed to establish whether patients in the intervention group who receive both physical and psychosocial training actually benefit from the offered tools in this training. Another consideration may be the timing of the intervention. The program was offered immediately after the intensive phase of treatment to help promote recovery and prevent more negative effects of treatment. However, it may be relevant to start the training during the intensive phase of treatment or to start the training later, when patients have passed the phase of natural recovery and are more able to put the intervention into practice.

Although this multicenter RCT did not prove effectiveness of the intervention to improve quality of life or psychosocial functioning of childhood cancer patients by an intensive intervention combining physical and psychological training, publication of the results of this study are important. Publication bias of non-effective trials is a common problem [32], but in our opinion these largely null findings needs to be published as well, because it suggests that researchers and clinicians for the time being, need to be reluctant to offer interventions like this to individual patients. For future research we suggest to evaluate possible effects of this intervention for specific risk groups of childhood cancer patients.

To our knowledge this is the first study to evaluate the psychosocial effects of a combined psychosocial and physical intervention in childhood cancer patients in a randomized setting. Although the intervention is quite demanding, adherence rates for the psychosocial training sessions and physical training sessions were pretty good and the intervention seemed applicable. However, some limitations need to be addressed. First, at long-term follow-up the minimum number of participants required in each study arm was no longer available, mainly due to the recurrence of disease in both groups. Secondly, power calculations for this RCT were not based on psychosocial outcomes, but on improvement in physical fitness. To detect more differences between the two groups on psychosocial outcomes, more participants in each group are probably required. In retrospect,

the power calculations should also have been performed on the psychosocial outcome measures to ensure that the study had sufficient participants in each study arm to detect the psychosocial effects. Thirdly, the total study group might be biased towards a more positive attitude on physical and psychosocial training of the participants compared with the non-participants. Participants rated their physical fitness lower than the non-participants, and patients with more internalizing behavioral problems were more willing to participate [29]. In the control group, patients could choose whatever support they needed and, due to participation in this study, may have had heightened interest in the topic possibly leading to a higher consumption of support from physical therapists and/or psychologists themselves; this may have led to fewer differences than expected between the intervention and control group. Although the data are incomplete, self-reported cost diaries from 5 of 17 (29%) children in the control group revealed that they visited a psychologist or psychotherapist during the first three months of this study. Problems attaining good participations rates are mentioned often in other intervention studies in pediatric oncology; e.g. participation rates of approximately 25% are reported [33-34]. The participation rate in this study was 40%, so still about 60% of the patients did not participate despite all efforts of the research team. This leads to questions about the likelihood that patients in clinical practice are in need of such an intervention. to find enough patients willing to participate in such a demanding intervention.

The present study indicates that a combined physical and psychosocial training during or shortly after treatment in children with cancer shows no effects on HrQoL and psychosocial functioning in general, with the exception of modest positive effects on pain and procedural anxiety, as reported by the parents. Future research should determine whether this intervention warrants adaptations and/or should be offered in a different way or at different time points, in the aim to enhance the psychosocial health of childhood cancer patients.

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