The QLIM study

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CHAPTER 2

Cardiorespiratory fitness and physical activity in children with cancer

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ABSTRACT

Purpose. This study assessed cardiorespiratory fitness (CRF), physical activity (PA) and sedentary behavior (SB), as well as factors associated with these outcomes in children during or shortly after cancer treatment.

Methods. Cross-sectionally, CRF data, obtained by the cardiopulmonary-exercise-test, and PA and SB data, obtained by an accelerometer, were assessed in children with cancer (8-18 years old). Linear regression models were used to determine associations between CRF, PA or SB and patient characteristics.

Results. Among 60 children with cancer, mean age 12.6 years, 35 boys, 28% were during cancer treatment. CRF, reported as the Z-score of VO_{2peak}, showed that 32 children had a VO_{2peak} Z-score which was -2 below the predicted value. CRF was significantly associated with PA and SB: each additional activity count per min resulted in 0.05 $ml \cdot kg^{-1} \cdot min^{-1}$ VO_{2peak} increase and each additional min sedentary reduced VO_{2peak} by 0.06 $ml \cdot kg^{-1} \cdot min^{-1}$.

Multiple linear regression models of PA and SB showed that decreased activity was significantly associated with higher age, being fatigued, being during childhood cancer treatment ($p<0.001$), or having a higher percentage of fat mass. The multiple linear regression model showed that lower CRF was significantly associated with increased fatigue, being during cancer treatment, having a higher percentage of fat mass and lower belief of own athletic-competence ($p<0.001$).

Conclusion. This study revealed that children during or shortly after cancer treatment have low CRF-scores. The most inactive children had a higher fat mass, were fatigued, older and during childhood cancer treatment. Unexpectedly, treatment-related factors showed no significant association with activity behavior.

INTRODUCTION

Cardiorespiratory fitness (CRF) and muscle strength, have shown to be reduced both during and after childhood cancer treatment.[32,34,138] Both are considered important health markers, since they represent the functional status of most body functions involved in the performance of daily physical activities (PA). A reduction in CRF and muscle strength can be caused by physical inactivity.[27,28] When inactivity persists it will put the patient at risk for obesity, cardiovascular disease, reduced muscle strength, decreased bone mineral density, and subsequently, a reduced health-related quality of life (HrQoL).[28,52,94,139,140]

In childhood cancer patients, the cancer treatment may adversely interfere with the patients' physical and mental ability to engage in PA. Several determinants are known to influence motor function. Chemotherapy can result in anemia, decreased oxygen transport to the muscles, and reduced muscle function[141], the use of vincristine can result in peripheral-neuropathy with muscle weakness in hands and feet, while anthracyclines may impair cardiac function, and bleomycine may result in decreased lung function due to pulmonary fibrosis.[24] Also mechanical factors are important, such as decreased motor function after an amputation in bone tumor patients[18], or ataxia following brain tumor treatment[19]. Apart from clear physical factors, being fatigued, as well as having depressive symptoms, may also negatively influence PA.[61]

Previous studies, using an accelerometer to objectively measure PA, showed that childhood cancer patients have low PA levels.[27–30] These studies, however, were performed in small groups and did not study the association between PA and CRF.

Only recently, both in children and adults, sedentary behavior (SB) has been introduced as a new important negative factor for health.[142] SB is defined as activities that typically require low-energy expenditure, such as sitting on the couch.[143] Frequent and prolonged sitting periods puts a person at risk for obesity and other metabolic conditions that enhance the risk of chronic diseases (e.g. type 2 diabetes, cardiovascular disease, breast and colon cancer).[144–146] Children with cancer are already at increased risk for chronic diseases, and therefore assessing SB in children with cancer is important.[17] Through questionnaires, one study found that 9% of the children with cancer left their bed for less than 1-hour, while 44% of the questioned patients reported to leave their bed over 10 hours per day during home-stays.[147] Up till now no studies objectively measured SB in childhood cancer patients.

This study aimed to assess CRF in childhood cancer patients during or shortly after treatment and to evaluate the association with objectively measured PA and SB. In addition, the impact of several physical and psychosocial factors on PA and SB were assessed in order to identify targets for future interventions aimed at stimulating PA, decreasing SB to ultimately increase CRF and HrQoL.

METHODS

Study population

This study is a cross-sectional study using the baseline data of a randomized controlled trial (RCT), evaluating the effects of a combined 12-week exercise and psychosocial training program for children with cancer on physical fitness and HrQoL (The Quality of Life in Motion (QLIM)-study). Details on the design of this study had been described previously.[148]
Eligible children were 8-18 years old, diagnosed with any type of malignancy, treated with chemotherapy and/or radiotherapy, during or within the first year after cancer treatment. Patients who were not able to make self-reflections (children <8 years old, or with a mental retardation), who received growth hormones, who were planned for stem cell transplantation, and those who were not able to ride a bike, or read and write Dutch were excluded.
Patients were recruited between March 2009 and July 2013. Eligible patients were identified through patient databases by pediatric oncologists, the study-researcher or research nurse of the pediatric oncology/hematology departments within four University hospitals in the Netherlands: VU University Medical Center Amsterdam, Academic Medical Center Amsterdam, Erasmus MC Rotterdam and University Medical Center, Utrecht. Patient records and the clinic data were weekly reviewed to verify eligibility. When children needed to be hospitalized, and when clinical conditions (low blood counts, infections, or others) made participation impossible (as assessed by their treating physician), children were considered unable to start study participation, and therefore the start of the study was postponed. Both patients and their parents or legal representatives received spoken and written information and provided written informed consent as by approval of the medical ethics committees of the four participating hospitals and was performed according to the 1964 Declaration of Helsinki. Register; Dutch Trial Registry number NTR1531.

Procedure

Study data were obtained at the university hospital of the child. Children were assessed on CRF, muscle strength, and body composition. Child-report questionnaires were used to measure psychosocial functioning. In the week after the study measurements an accelerometer was used to measure PA and SB. Clinical data, such as data on cancer diagnosis, treatments, and complications, were obtained from medical records.

Measures

Cardiorespiratory fitness was assessed during a cardiopulmonary exercise test on an electronically braked cycle ergometer (Lode, Corival P, ProCare B.V. Groningen, the Netherlands) using the Godfrey protocol. During the test ventilatory gas exchange data were determined breath-by-breath. The peak oxygen uptake (VO_{2peak}) was calculated as the mean value of the final thirty seconds of the test, and expressed in milliliters per kilogram per min ($ml \cdot kg^{-1} \cdot min^{-1}$). Predicted values for VO_{2peak} were calculated from an age- and sex-based equation.[103] Measured VO_{2peak} results were compared with these predicted values.

Physical activity and sedentary behavior of each patient were measured by the Actical activity monitor (B series, Philips Respironics Actical Mini Mitter, Murrysville, PA, USA). The Actical is an accelerometer (37 x 29 X 11 mm) which has been validated in children between 7-18 years old.[109] The receiver operating characteristic curves were 0.85, 0.93 and 0.95 for a sedentary to light, light to moderate, and a moderate to vigorous activity level, respectively.[109] The Actical accelerometer was attached to an elastic waist belt, and worn on the left hip during daytime at waking-hours (between 6:00 am and 11:59 pm) on 4 consecutive days (Wednesday- Saturday). The device was removed while bathing or swimming.

When the device was worn less than 500 min/day, the measurement of that day was considered invalid. Time not wearing the accelerometer was defined as 60-min of consecutive zero's on the read-out and this time during waking hours was excluded from the analyses. The acceleration signal of the Actical is summed over a specific time interval (epoch).[149] A 15-sec epoch was used in the study.

Physical activity (PA) was expressed as mean counts-per-minute (cpm). For the present study we used the following cpm range to define the different activity intensities: sedentary status corresponds with an activity count of less than 100 cpm, light activity with 100-1599 cpm, moderate activity corresponds with 1600-4760 cpm and 4760 or more cpm was considered as a vigorous activity level.[150] Children who participated at least 60 min per day at an activity level of >1600 cpm were categorized as fulfilling the international PA recommendations.[43]

Sedentary behavior (SB), defined as a cpm below 100, was presented as mean minutes sedentary (out of 1080 measured minutes per/day) and as accelerometer-based sedentary bouts. Sedentary bouts were defined as periods of at least 5, 10, 20, 30 and 60 min of SB.[142,151]

Possible associated factors

Physical factors

For all study participants, *height and weight* were measured to the nearest millimeter (mm) and 0.1 kilogram (kg), respectively. *Body mass index* (BMI; kg/m^2) was calculated as well as the BMI-Z-scores using the growth calculator for professionals.[152]
Muscle strength was measured by the use of hand-held dynamometry (CITEC, CT 3001, Haren, the Netherlands)[153] using the break-method.[154] The highest out of three scores were used in the analyses. Lower body muscle strength was calculated as the sum of the best (left or right) upper-leg, lower-leg and foot scores. Upper body muscle strength was calculated as the sum of the best shoulder, elbow and grip strength scores.
Body fat was assessed by dual energy X-ray absorptiometry (DXA). The assessment was performed on a Hologic Delphi/ Discovery, or a Lunar Prodigy scanner. Differences in percentage of fat mass were corrected accordingly the equation of Shepherd et al. (2012).[119]
Fatigue was self-assessed by the use of the PedsQL™ Multidimensional fatigue scale (acute version)[128], with lower scores indicating more fatigue (range: 0-100); the results of the sub-scale 'general fatigue' were included in the study analyses.

Psychosocial factors

The participation in sports of the study participant before the cancer diagnosis was evaluated by the use of a questionnaire which was developed for this study.
Athletic competence, was assessed with a subscale of the Self Perception Profile questionnaire for children aged 8-11 years old (CBSK) and for adolescents aged 12-18 years old (CBSA).[155] Higher scores reflect a more positive perception of the athletic competence (range between 0-100 points).
Depressive symptoms were assessed by the use of the Children's Depression Inventory (CDI). This questionnaire for children aged 7-18 years old, contains 27 items which assesses self-reported depressive symptoms.[156] For this study we used the total scores (range: 0-54).

Statistical analysis

Normality of the data was assessed by normality plots and the Shapiro-Wilk test. When data showed a normal distribution, continuous outcomes were expressed as mean (standard deviation [SD] or range), in case of non-normal distribution, median (interquartile range [IQR]) scores were reported. Paired sample t-test was used to assess differences between the observed and predicted VO_{2peak} (ml·kg^{-1}·min^{-1}) values.[103]

Univariate regression analyses were performed to identify association between and additional associated factors for CRF (VO_{2peak}), PA (cpm) and SB (min sedentary p/d). Because the sample size (N=60) did not allow us to simultaneously include all potential variables into the multiple linear regression model, we preselected a maximum of 6 variables with $p < 0.15$ from the univariate regression analyses and include them in the multiple linear backward regression analyses. By hand factors with the highest p-value were removed until all factors were statistically significant. The coefficient of determination and the standard error of the estimate (SEE) are included to present a measure for variance and accuracy of the regression models. A 2-sided *P*-value < 0.05 was considered statistically significant in all analyses. IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp., USA) was used for the statistical analyses.

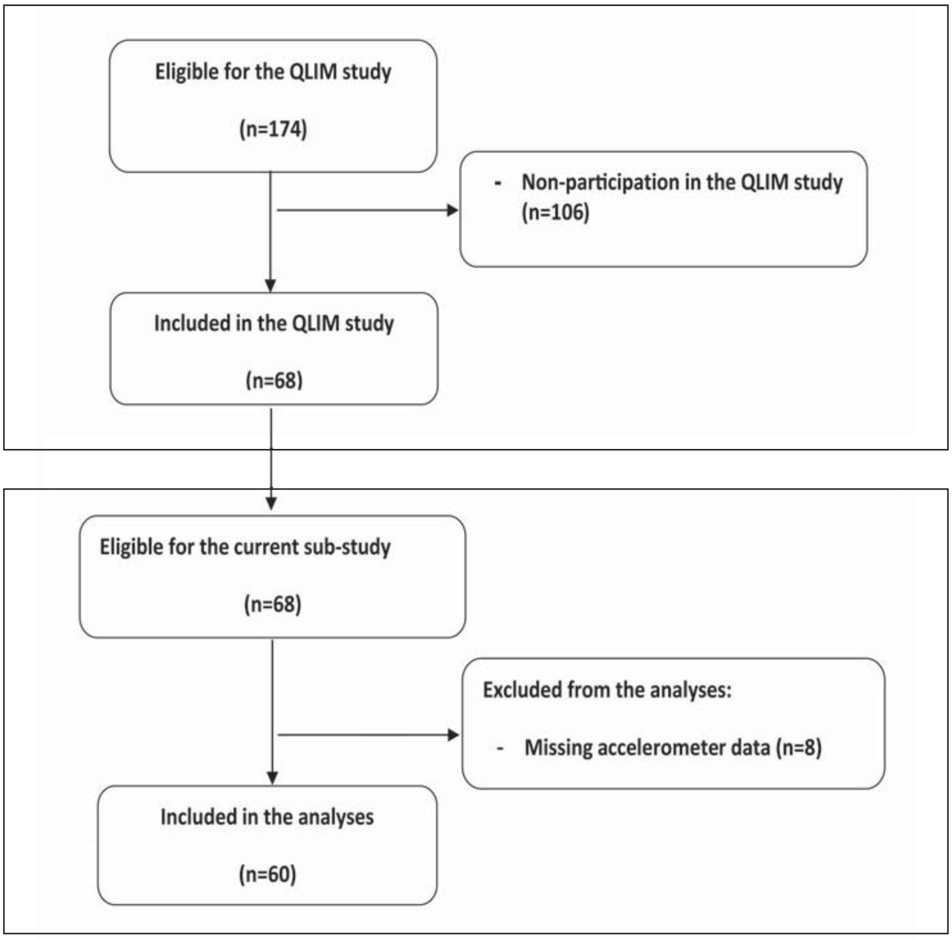


Figure 2.1: Flow chart of the Quality of Life In Motion study, a randomized controlled trail evaluating the effects of a 12-week combined physical and psychosocial training program for children with cancer.

RESULTS

General and medical characteristics

A total of 174 children were invited to participate in the QLIM study, of whom 68 (37 boys) were included (Figure 2.1). Due to missing accelerometer data in eight patients, the current study, therefore, analyzed the results of 60 children (35 boys) with a mean age of 12.6 years (SD: 3.1; range: 8.0-18.0 years). A total of 17 children (28%) were during cancer-treatment at time of the study (Table 2.1). Thirty-seven (62%) were treated with chemotherapy alone.

Both the general and medical characteristics of the eight children who were excluded from the analyses, as well as characteristics of the 106 non-participants[157], were not significantly different from the 60 children who were analyzed (data not shown).

Table 2.1: Demographic and clinical characteristics of the 60 Dutch 8-18 year old participants of the Quality of Life In Motion study

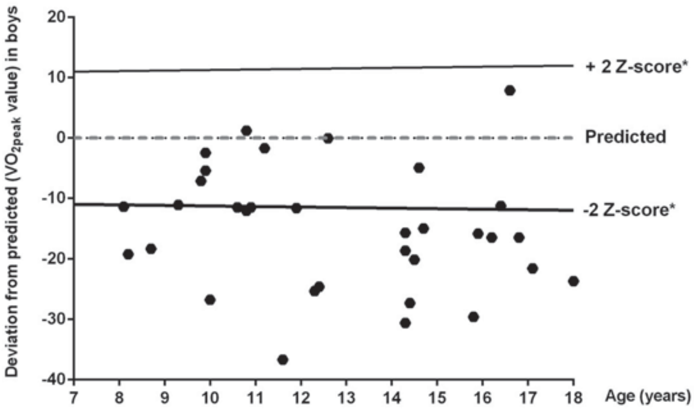
Variable	Patients included: N = 60 mean ± SD / median (IQR)
Gender (male)	35
Age, years	13.8 (10 - 16)
Height, cm	156 ± 17.3
Weight, kg	50.7 (34 – 63)
BMI SDS score (SDS)	0.4 (-0.2 – 1.4)
Fat mass SDS score (SDS)	0.8 (0.1 – 1.4)
Diagnoses:	
Acute lymphoblastic leukemia	17
Acute Myeloid Leukemia	8
Brain tumor	8
Hodgkin's lymphoma	7
Bone tumor	7
Non-Hodgkin lymphoma	5
Rhabdomyosarcoma	3
Chronic Myeloid Leukemia	2
Others	3
Treatment:	
CT	37
CT + RT	7
CT + S	8
CT + RT + S	8
Vincristine	36
Location of the bone tumor:	
Upper limp with prosthetic device	0/3
Lower limp with prosthetic device	2/3
Trunk with prosthetic device	1/1

Legend: N: number; SD: standard deviation; IQR: interquartile range; SDS: standard deviation score; cm: centimeter; kg: kilogram; CT: chemotherapy; RT: radiotherapy; S: surgery

Cardiorespiratory fitness

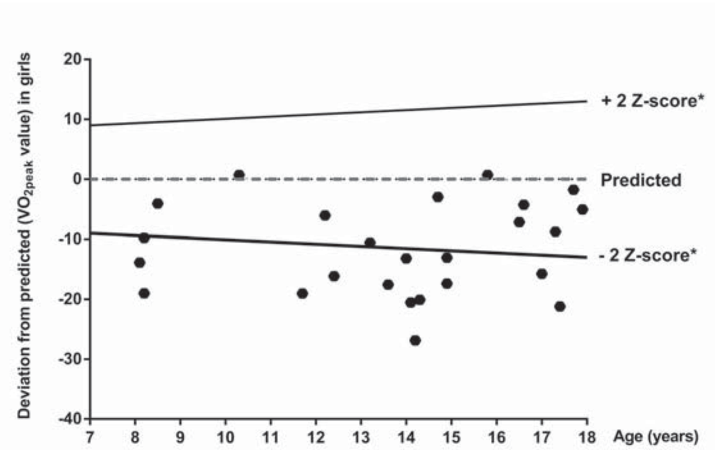
Cardiorespiratory fitness (CRF), expressed as VO_{2peak} ($ml{\cdot}kg^{-1}{\cdot}min^{-1}$), in the study population was 31.7 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (SD 9.2). The mean predicted value of the study group was 45.1 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (SD 3.6), resulting in a mean absolute difference between the measured and predicted values of -13.4 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (SD 9.2) ($p<0.001$). Results for boys and girls separately are presented in Figure 2.2A and 2.2B.

A total of 32 children (53%) had a Z-score ≤ -2; approximately 12 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ below the predicted value.[103] The 17 children who were during treatment, all belonged to the -2 Z-scores group.



Legend: VO_{2peak}: peak oxygen uptake;
Z-score: standard deviation from the mean ;
* Based on age matched norm values

Figure 2.2A: Measured versus predicted VO_{2peak} in boys (according to age and sex matched norm values) in the Quality of Life In Motion study (N=35)



Legend: VO_{2peak}: peak oxygen uptake;
Z-score: standard deviation from the mean;
* Based on age matched norm values

Figure 2.2B: Measured versus predicted VO_{2peak} in girls (according to age and sex matched norm values) in the Quality of Life In Motion study (N=25)

Physical activity and sedentary behavior

Physical activity (PA) was monitored over a median period of 4 days (IQR: 3.5 - 4 days). Overall, the median PA level was 127 cpm (IQR: 80-219) (Table 2.2). The children spent 16% of their day-time on light-activities, were 7% (SD 4.4) moderately active, and spent only 0.1% (SD 0.2) of the day on a vigorous activity level.
Evaluation of *sedentary behavior (SB)* showed that children were sedentary in 80% of all waking hours: median of 869 min (IQR: 785 - 911) of the 1080 min which were analyzed per day. Study results also showed that prolonged sitting periods without interruptions (≥ 20 or 30 min) were common (Table 2.2).

Table 2.2: Median scores on physical activity levels and time spent sedentary in childhood cancer participants of the Quality of Life In Motion study

Variables	Patients (n = 60)	
PHYSICAL ACTIVITY*	Median (IQR)/ n/total	%
Counts per minute	127 (80-219)	
Daytime minutes spent on		
Sedentary (min)	869 (785-911)	76 [a]
Light activities (min)	195 (150-263)	16 [a]
Moderate activities (min)	18 (5-39)	7 [a]
Vigorous activities (min)	0 (0 - 1)	0.1 [a]
Meeting MVPA recommendations	9/60	15 [b]
Boys	7/35	20 [b]
Girls	2/25	8 [b]
SEDENTARY BEHAVIOR*		
Sedentary period		
≥ 5 min	26 (22 - 29)	
≥ 10 min	15 (13 - 18)	
≥ 20 min	8 (6 - 10)	
≥ 30 min	4 (3 - 6)	
≥ 60 min	1 (0 – 2)	

Legend: *Assessment between 6.00 am and 23.59 pm (a total of 1080 min); N: number;
IQR: interquartile range; min: minutes; %: percentage of the day during waking-hours;
MVPA: moderate-to-vigorous physical activity
[a]: percentage of the day during waking-hours
[b]: percentage of the total group of children

Cardiorespiratory fitness, physical activity/ sedentary behavior and associated factors

In either way, CRF, PA and SB showed highly significant associations (Table 2.3). A positive association was found between CRF (VO_{2peak}) and PA (cpm) (β 0.05; 95% CI: 0.0;0.1; $p<0.001$): every additional cpm resulted in a 0.05 $ml \cdot kg^{-1} \cdot min^{-1}$ increase in CRF. SB had a negative association with CRF (β -0.06; 95% CI: -0.1;-0.0; $p< 0.001$): every additional minute of sedentary time per day decreased the CRF by 0.06 $ml \cdot kg^{-1} \cdot min^{-1}$ (Table 2.3).

Table 2.3: Results of univariate and multiple linear regression analyses for cardiorespiratory fitness, physical activity and sedentary behavior in children with cancer

	Physical activity (activity counts per minute)		Sedentary behavior (min sedentary)		Cardiorespiratory fitness (VO2peak; ml·kg-1·min-1)	
	Univariate regression	Multiple regression Model 1	Univariate regression	Multiple regression Model 2	Univariate regression	Multiple regression Model 3
Independent variables	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Age (years)	-15.4 (-23.6 to -7.2)***	-11.9 (-19.8 to -4.0)**	14.6 (7.8 to 21.5)***	10.0 (3.5 to 16.5)**	-0.1 (-0.9 to 0.6)	
Sex [a] (0/1)	-43.5 (-99.7 to 12.8)		28.4 (-20.5 to 77.2)		-4.0 (-8.7 to 0.8)	
Muscle strength						
* Upper body strength	-0.1 (-0.3 to 0.2)		0.1 (-0.1 to 0.3)		0.0 (-0.0 to 0.0)	
* Lower body strength	-0.0 (-0.2 to 0.1)		0.1 (-0.1 to 0.2)		0.0 (0.0 to 0.0)	
Percentage of fat mass	-5.4 (-9.0 to -1.7)**		4.9 (1.8 to 7.9)**	3.7 (1.1 to 6.3)**	-0.8 (-1.0 to -0.5)***	-0.5 (-0.7 to -0.2)***
Lean body mass	-0.0 (-0.0 to 0.0)		0.0 (0.0 to 0.0)*		0.0 (0.0 to 0.0)	
Cancer [b] (0/1)	-18.6 (-77.7 to 40.5)		10.4 (-40.6 to 61.4)		-3.6 (-8.5 to 1.3)	
Treatment [c] (0/1)	-15.9 (-73.9 to 42.1)		3.4 (-46.7 to 53.5)		- 3.1 (-8.0 to 1.8)	
Amputation [d] (0/1)	-34.6 (-122.2 to 53.0)		25.9 (-49.7 to 101.5)		-3.3 (-10.7 to 4.1)	
VCR use [d] (0/1)	-38.2 (-95.4 to 19.0)		35.0 (-14.8 to 84.8)		-4.7 (-9.7 to 0.2)	
Glucocorticoid use [d] (0/1)	3.6 (-53.0 to 60.2)		6.7 (-42.0 to 55.4)		1.1 (-3.7 to 6.0)	
During/after cancer treatment [e] (0/1)	63.9 (3.4 to 124.3)*	68.0 (18.1 to 118.0)**	-47.9 (-100.4 to 4.7)		7.4 (2.4 to 12.3)**	3.9 (0.3 to 7.5)*
Sports part before DX [f] (0/ 1)	27.2 (-41.8 to 96.1)		-14.5 (-74.5 to 45.5)		1.5 (-4.2 to 7.2)	
Fatigue [g]	2.6 (1.5 to 3.7)***	1.8 (0.7 to 2.9)**	-2.1 (-3.1 to -1.1)***	-1.2 (-2.2 to -0.2)*	0.2 (0.1 to 0.3)***	0.2 (0.1 to 0.3)***
Depressive symptoms	-6.2 (-11.9 to -0.5)*		5.8 (0.9 to 10.7)*		-0.8 (-1.3 to -0.4)**	
Athletic competence	0.9 (-0.1 to 1.8)		-0.6 (-1.4 to 0.2)		0.2 (0.1 to 0.2)***	0.1 (0.0 to 0.1)*
Physical activity	—		-0.73 (-0.9 to -0.6)***		0.05 (0.0 to 0.1)***	
Sedentary behavior	-0.99 (-1.1 to -0.8)***		—		-0.06 (-0.1 to -0.0)***	
Cardiorespiratory fitness	6.99 (4.4 to 9.6)***		-5.87 (-8.0 to -3.7)***		—	

P-value: * <0.05; **<0.01; *** <0.001; CI: confidence interval; B: regression coefficient; VCR: vincristine; DX: diagnosis; [a]0: boys; [a]1: girls; [b]0; hematological malignancy [b]1: solid tumor; [c]0: chemotherapy [c]1: chemotherapy in combination with one or more other treatment modalities; [d]0: no; [d]1: yes; [e]0: during treatment; [e]1: after treatment; [f]0: no sport before diagnosis; [f]1: did sport before cancer diagnosis; [g] higher scores indicate less fatigue; R2: r-squared; SEE: standard error of the mean
Model 1: factors before backward selection: 1) age, 2) percentage of fat mass, 3) lean body mass, 4) being during/after cancer treatment, 5) fatigue, and 6) depressive symptoms
Model 2: factors before backward selection: 1) age, 2) percentage of fat mass, 3) lean body mass, 4) being during/after cancer treatment, 5) fatigue, and 6) depressive symptoms
Model 3: factors before backward selection: 1) lower body muscle strength 2) percentage of fat mass, 3) being during/after cancer treatment, 4) fatigue, 5) depressive symptoms, and 6) athletic competence

Physical activity

Single factor associations showed that PA was significantly associated with: age (β -15.4; 95% CI: -23.6;-7.2; p<0.001), percentage of fat mass (β -5.4; 95% CI: -9.0;-1.7; p=0.005), being during (0)/after (1) cancer treatment (β 63.9; 95% CI: 3.4;124.3; p=0.039), fatigue (β 2.6; 95% CI: 1.5;3.7; p<0.001), and depressive symptoms (β -6.2; 95% CI: -11.9;-0.5; p=0.034) (Table 2.3). For the multivariate analysis a 6th factor was added: lean body mass (β 0.0; 95% CI: -0.0;0.0; p=0.056).

The multiple linear regression analysis for PA showed that age (β -11.9; 95%CI: -19.8;-4.0; p=0.004), being during (0)/after (1) cancer treatment (β 68.0; 95% CI: 18.1;118.0; p=0.008), and fatigue (β 1.8; 95%CI: 0.7;2.9; p=0.002; i.e. higher scores indicate less fatigue) were significantly associated with PA (Table 2.3). Thus, younger children who were following cancer treatment and who were less fatigued were more active. These factors explained 41.8% of the variance in PA; SEE = 85.0 (model P<0.001).

Sedentary behavior

Significant univariate associated factors for SB (min sedentary p/d) were age (β 14.6; 95% CI: 7.8; 21.5; p<0.001), percentage of fat mass (β 4.9; 95% CI: 1.8;7.9; p= 0.002), lean body mass (β 0.0; 95%CI: 0.0; 0.0; p=0.016), fatigue (β -2.1; 95%CI: -3.1; -1.1; p<0.001), and depressive symptoms (β 5.8; 95% CI: 0.9; 10.7; p=0.021) (see Table 2.3). For the multiple regression analyses also being during/after treatment (β -47.9; 95% CI: -100.4; 4.7; p=0.074) was added as an independent variable.

After backward elimination the final multiple regression model for SB included age (β10.0; 95% CI: 3.5;16.5; p=0.003), percentage of fat mass (β 3.7; 95% CI: 1.1;6.3; p=0.007), and fatigue (β -1.2; 95% CI: -2.2;-0.2; p=0.015) (Table 2.3). Older age, being fatigued and having an increased percentage of fat mass was associated with more minutes of SB per day. The three factors together explained 43.0% of the variance in SB; SEE = 71.0 (model P<0.001).

Cardiorespiratory fitness

Univariate, CRF furthermore was significant associated with percentage of fat mass (β -0.8; 95% CI: -1.0;-0.5; p<0.001), being during (0)/after (1) cancer treatment (β 7.4; 95% CI: 2.4;12.3; p=0.004), fatigue (β 0.2; 95% CI: 0.1;0.3; p<0.001), depressive symptoms (β -0.8; 95% CI: -1.3;-0.4; p=0.001), and athletic competence (β 0.2; 95% CI: 0.1; 0.2; p<0.001) (Table 2.3). For the multiple regression analyses also lower body muscle strength (β 0.0; 95% CI: 0.0;0.0; p=0.055) was added as an independent variable.

The multiple linear regression analysis for CRF showed that fat mass (β -0.5; 95% CI: -0.7; -0.2; p<0.001), being during/after treatment (β 3.9; 95% CI: 0.3;7.5; p=0.035), fatigue (β 0.2; 95% CI: 0.1;0.3; p<0.001), and beliefs of athletic competence (β 0.1; 95% CI: 0.0;0.1; p=0.034) were significantly associated with CRF. Thus, fatigued children with increased fat mass, and reduced beliefs in athletic competence, and those during cancer-treatment had the lowest CRF. These four factors explained 64.8% of the variance in CRF; SEE = 5.7 (model $P<0.001$).

DISCUSSION

The present study shows that the CRF is low in the majority of children during as well as after cancer treatment when compared to healthy Dutch children. Furthermore, this is the first study performed in children with cancer that clearly demonstrates that decreased CRF is significantly associated with objectively assessed low PA and high SB. Children at risk for reduced PA had the highest percentage of fat mass, were older and fatigued and were during childhood cancer treatment. Unexpectedly treatment related factors did not significantly influence activity behavior. These results indicate that intervention studies should focus on preventing or reducing fatigue and overweight, in order to improve PA behavior and ultimately increase CRF. The most sedentary children of the study were older and during childhood cancer treatment, pointing out an important target population.

Our finding that older age and fatigue were significantly associated with reduced PA, is in line with previous findings among healthy children.[61,158,159] In children with cancer however, next to an older age and being fatigued, Hooke et al. (2011) also found that children who exhibit emotional dysfunction were more sedentary.[61] The latter could not be confirmed with our data. Psychological factors in our study did not show a clear association pattern with PA and SB. In univariate models, depressive symptoms showed a significant associated with the two outcomes; however, in multiple regression models, this factor did not remain significant. This indicates that this association was weak, or possibly mediated by other factors.[51]

International recommendations for children advice 60 min of moderate-to-vigorous physical activity per day.[43] The current study showed that 20% of the boys and 7% of the girls, during or shortly after childhood cancer treatment, met the activity recommendations. Which, however, is in line with the worrisome results of the normal Dutch population.[67] This indicates that only a small percentage of all children, with or without cancer, reach the international PA recommendation. Yet, related to the given cancer treatment and possible late-complications and diseases, the impact of inactivity in children with cancer may be worse than in healthy children.[17]

Despite positive attitudes towards PA[160], the current study showed that children with cancer were highly sedentary. Especially the prolonged periods of SB are striking, i.e. the sitting periods of 20 min or more were approximately four times higher in this study population, compared to reported data of healthy children.[161] The activity cpm were also considered lower than those reported in healthy children.[39] We found a median cpm score of 127 (IQR: 80-219 cpm) equally distributed among sex, whereas a meta-analysis among 20,871 healthy children reported that girls had a mean PA of 540 cpm (193 SD) and boys a mean PA of 642 cpm (226 SD).[39] However, such as for PA data, the SB data of the study among healthy children were obtained with a different accelerometer (Actigraph) using different cut-off points for activity intensities, decreasing comparability.[39]

Strength and Limitations of this study

The strength of this study is the number of included children; 60 is a relatively large population compared to patient numbers used in the four earlier studies which reported PA accelerometer data (range: 7 to 38 patients).[27–30] Furthermore, this study is the first in children with cancer to combine CRF data with activity data and to show associations between activity behavior and patient characteristics. Finally, most of the data were obtained during a visit to the hospital for study purpose, increasing quality of the measurements.

This study also had some limitations that should be noted. First, the cross-sectional design does not allow for the assessment of the causal relation between study outcomes and factors. Longitudinal data of the QLIM RCT will provide further information regarding the relation between increased PA and CRF, and possible confounding or mediating factors.

Secondly, in this study accelerometer data were obtained for a period of 4 days instead of 7. The memory-capacity of the accelerometer did not allow assessment of PA by 15-s epoch for a length of 7-days. It was possible to use 15-s epochs when we limited the assessment period to four days. The use of a short epoch in children is important because children are known to perform short and intermitted actions.[149] Missing data of three days within the measurement week is a limitation. However, accelerometer data were obtained from Wednesdays until Saturdays, which are the most common days in the week in the Netherlands to participate in (team) sports during childhood. Sport participation before diagnosis was questioned retrospectively. However, the time period at which they participated in sports was not specified. This led to unclear information. To increase validity of the data we dichotomized sport participation before diagnosis (yes/no), however thereby losing some valid information.

Finally, this study included children with any type of cancer, aged between 8-18 years old and children both during and within the first year after cancer-treatment. Therefore our study group was a heterogeneous one with potentially additional influencing factors. However, as a result of this heterogeneity, we now were able to say that children with any type of cancer had reduced CRF and PA levels.

CONCLUSION

In conclusion, the present study shows that CRF is low in children during as well as shortly after cancer treatment and that this low fitness is associated with reduced PA levels and increased SB across all cancer and treatment types. It revealed that older children, more fatigued children who were during cancer treatment were the least active. Increased SB, in addition, was significantly associated with older age, more fatigue and having a higher percentage of fat mass. This indicates that especially the fatigued, overweight or obese adolescents with cancer, and those who are during cancer treatment, need to be informed about the health risks of a prolonged sedentary lifestyle and be advised in how to increase their PA level. In the QLIM RCT we will assess the causal relation between CRF, PA, SB, fatigue, age, and treatment-related factors in children with cancer, to develop an optimal exercise intervention for this population, in order to increase PA, and CRF to ultimately decrease chronic diseases and impaired HrQoL later in life.