

# **Exercise measurements and interventions for children with childhood cancer**

**Master of Science Thesis**

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16 July 2010

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**ONDERGETEKENDE**

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# Content

## **Systematic Review**

- *Exercise Interventions for children and young adults during and after treatment for childhood cancer*.....1
  - Abstract.....2
  - Background.....3
  - Objectives.....5
  - Methods.....5
  - Results .....10
  - Discussion .....16
  - Authors' conclusion .....18
- Characteristics of included studies .....20
- Characteristics of excluded studies .....24
- References.....26
- Appendix
  - Search strategy.....33
  - Data extraction form.....41

## **Article**

- *Steep Ramp Testing in children with childhood cancer; an alternative for the cardio-pulmonary exercise test?*.....45
  - Abstract .....46
  - Introduction.....47
  - Method.....48
  - Results.....50
  - Discussion.....55
  - Conclusion .....57
  - References.....58

# **Exercise interventions for children and young adults during and after treatment for childhood cancer**

## **Systematic Review**

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## Abstract

### Background

Over the years improvements in childhood cancer treatment regimes led to a considerable increase in survival rates within the childhood cancer population. This growing population of survivors is at risk for several adverse effects of both the cancer and its treatment. Many studies have reported a decreased physical fitness (aerobic capacity and muscle strength) and social functioning, due to deconditioning in patients and survivors of childhood cancer. Cancer and cancer treatment induces lean tissue degeneration and potentially induces abnormalities in the cardiac and skeletal muscle. The effect of an exercise intervention during, or after cancer treatment has mainly been investigated in adults. The intervention of interest is physical exercise therapy within the first five years of childhood cancer diagnosis. The exercise training must be aimed at increasing physical fitness, by aerobic, anaerobic, strength or mixed fitness training.

### Objectives

#### Primary objective:

The aim of this review is to evaluate the effect of exercise on physical fitness (e.g. aerobic capacity, muscle strength or functional performance), of children who received an exercise intervention within the first five years of diagnosis of cancer, compared to a control group of childhood cancer patients who did not receive an exercise intervention.

#### Secondary objectives:

In addition, we will determine whether exercise within the first five years of diagnosis has a positive effect on fatigue, anxiety, depression, self-efficacy and/or HrQoL. This will also be evaluated by comparing childhood cancer patients receiving an exercise intervention to childhood cancer patients who did not receive an exercise intervention.

### Search methods

We searched the following electronic databases until April first 2010: MEDLINE/PubMed, EMBASE/Ovid, the Cochrane Central Library of Controlled Trials, CINAHL, and Physiotherapy Evidence Database (PEDro).

### Results

Out of 897 publications a total of 4 randomised clinical trials were being identified for inclusion in this review. In total 119 patients participated in the studies, 56 in the intervention group and 63 in the control group. There was a wide variety in mode and intensity between the investigated studies. The duration of the follow-up differed greatly. The shortest duration of follow-up lasted 2-4 days while the longest follow-up was more than 3 years. The control arm varied from no intervention at all, standard activity recommendations to an equivalent amount of time spent with patients who were randomized to the standard care arm doing social activities.

Several physiological outcome measures (knee strength, aerobic fitness and activity questionnaires) improved after the exercise intervention. None of the psychological outcomes differed significantly compared to the control group. No adverse effects of the training are reported.

### Authors' conclusions

Exercise interventions for children and young adults during and after treatment for childhood cancer show promising results for physiological outcomes like muscle strength and joint mobility. None of the investigated studies showed any effect in psychological outcomes. None of the studies have reported adverse effects, indicating that it is probably safe to perform exercise interventions for children during their treatment for ALL. However due to several forms of bias we are very uncertain about the estimate of effect and further research is very likely to have an important impact on the investigated outcome measures.

## Background

Childhood cancer is defined as cancer developed among children aged 0 to 19 years old ([Jemal 2006](#)). Statistically the occurrence of cancer during childhood is uncommon, despite that it is the most common cause of death in children ([Jemal 2006](#)). The incidence of childhood cancer is almost similar worldwide ([Jemal 2006](#)). The latest epidemiology study of Linabery and Ross describes the overall age-adjusted incidence rate (IR) of childhood cancer to be 158 per 1,000,000 person-years (PY) of which leukemia (IR: 41.9 per 1,000,000 PY) and central nervous system (CNS) tumors (27.6 per 1,000,000 PY) are the two most common ([Linabery 2008](#)).

Over the past 35 years, improvements in childhood cancer treatment regimens have led to a considerable increase in survival rates within the childhood cancer population. This growing population of survivors is at risk for several adverse effects of both the cancer and its treatment. When childhood cancer is diagnosed, it is primarily treated with chemotherapy, radiotherapy or surgery. Especially chemotherapy and radiotherapy are known to have damaging effects which can result in adverse childhood cancer late effects. Approximately seventy-five percent of the childhood cancer survivors face at least one or more late effects. ([Geenen 2007](#)) A wide variety of late effects can occur, such as cardiac dysfunction, sub- or infertility, obesity, hearing problems, second malignant neoplasms, pulmonary dysfunction, or osteoporosis ([Dickerman 2007](#); [Geenen 2007](#); [Mulrooney 2008](#); [Ness 2005](#); [Oeffinger 2006](#); [Robison 2005](#); [Skinner 2007](#)). In addition, a considerable number of survivors of (childhood) cancer suffer from a poor physical fitness level and motor function disability ([van Brussel 2005](#); [Liu 2009](#)). Motor function disability in patients or survivors of childhood cancer is mostly thought to be related with negative motor signs, such as insufficient muscle activity, or muscle weakness ([Wright 1998](#)).

Indeed, over the years many studies have reported a decreased physical fitness (aerobic capacity and muscle strength) and social functioning, due to deconditioning in patients and survivors of childhood Acute Lymphoblastic Leukemia ([Aznar 2006](#); [San Juan 2008](#); [Warner 2008](#); [Wright 1998](#)), or childhood cancer in general ([Arroyave 2008](#); [De Caro 2006](#); [Ness 2005](#); [Ness 2009](#); [Winter 2010](#)). Physical fitness refers to a set of qualities that people have, or achieve, that relate to the ability to perform physical activity. These obtained attributes include several health related components such as cardiorespiratory fitness, muscular endurance, muscular strength, body composition and flexibility ([Caspersen 1985](#)). Reduced daily energy expenditure and lower levels of physical activity have been described as the most important cause of this reduced state of physical fitness ([Warner 2008](#)). Factors contributing to a reduced physical activity include disease and treatment-related limitations in

exercise capacity, such as cytostatic toxicity and negative effects on healthy tissue, duration of chemotherapy and radiotherapy, and a sedentary life-style ([Warner 2008](#)). Furthermore, psychosocial effects of disease and treatment might also play a role since they may affect motivational drive and/or result in a poorer self-perception of one's adequacy to perform physical activity ([Warner 2008](#); [Wright 1998](#)).

Since physical fitness represents the functional status of most of the body functions involved in the performance of daily physical activities and/or physical exercise it is considered one of the most important health markers. Physical inactivity with subsequent muscle atrophy and reduced strength is probably the most prominent cause of this reduced state of physical fitness ([Dickerman 2007](#); [Schneider 2007a](#); [Tisdale 2009](#)). It may lead to obesity, fatigue, and a poor skeletal and/or mental health ([Durstine 2000](#); [Meeske 2005](#); [Von Essen 2000](#); [Warner 2008](#)). In turn, these factors may further reduce physical activity and physical fitness making these health outcomes into a self-perpetuating condition if the cycle is not broken. Clearly, all these health outcomes (separately or simultaneously) may negatively impact both short and long-term health and health-related quality of life (HrQOL) ([Odame 2006](#), [Varni 2007](#)). Therefore, prevention of inactivity-related health problems by increasing physical fitness both during and following treatment is essential.

The effects of a exercise intervention during, or after cancer treatment are primarily been tested in adults ([Cramp 2008](#); [Dimeo 2001](#); [May 2009](#)). These interventions indicate that cancer patients can both physically and mentally benefit from exercise in combating the (late) side effects of the treatment ([Irwin 2009](#)). However, as a preventive tool for late-occurring health problems an exercise intervention is advised to be introduced early, which is at least within the first five years after cancer diagnosis ([Han 2009](#), [Oeffinger 2004](#)). Next to an increased physical fitness, a physical exercise intervention in adult cancer patients also showed a positive impact on cancer-related fatigue, anxiety and depression, self-efficacy and ultimately on (health-related) quality of life ([Cramp 2008](#); [Franklin 2006](#); [Korstjens 2008](#); [Lucia 2005](#); [Monga 2007](#); [Pinto 2005](#); [Winningham 2001](#)).

Despite positive results of exercise therapy in adult cancer patients, the evidence of benefits in patients with childhood cancer is still limited. Studies within this population and its survivors have been initiated and the first data have been published ([Aznar 2006](#); [Hinds 2007](#); [Lucia 2005](#)). However, the study populations in these studies are small. For crafting decisions in healthcare management, patients and clinicians have to consider the benefits and drawbacks of supportive care such as costs and effectiveness.

Therefore, pooling of outcome measures from multiple studies is necessary for evidence based statements concerning the value of exercise therapy during, or after childhood cancer to prevent, or recover from physical or psychosocial side effects.

The purpose of this Cochrane review was to summarize the existing literature on the efficacy of exercise therapy which started during childhood cancer treatment, or within the first five years after childhood cancer diagnosis, and to provide a best-evidence synthesis or meta-analysis of the reported results.

## **Objectives**

### *Primary objective:*

The aim of this review was to evaluate the efficacy of exercise on physical fitness (e.g. aerobic capacity, muscle strength or functional performance), in children who received an exercise intervention within the first five years of diagnosis of cancer, compared with a control group of childhood cancer patients which did not receive an exercise intervention.

### *Secondary objectives:*

In addition, we determined whether exercise within the first five years of diagnosis had a positive effect on fatigue, anxiety, depression, self-efficacy and/or HrQOL in the same patient category.

## **Methods**

The intervention of interest was physical exercise therapy within the first five years of childhood cancer diagnosis. The exercise training must be aimed at increasing physical fitness, by aerobic, anaerobic, strength or mixed fitness training.

The exercise therapy could be offered as additional treatment or as rehabilitation to the standard cancer therapy. The exercise therapy could take place in any setting or location. It can either be a group intervention or be performed individually. The duration of the intervention may differ, as well as the daily time spent on activities or sports, and the sports locations (in-, or outside the hospital).

### *Types of studies*

Randomized controlled trials (RCTs) and clinical controlled trials (CCTs) were eligible for inclusion in this systematic review. For CCTs being included in the review a strong equivalent comparable control group was required.



### *Types of participants*

Study participants were <19 years old at the time of diagnosis of childhood cancer. Participants of the exercise program are actively receiving treatment, or were within 5 years follow-up of diagnosis.

Studies with a combination of childhood and adult cancer participants could only be included when results of the two populations are separately reported.

### *Types of interventions*

The studies compared an exercise intervention with a control group receiving usual care (i.e. no specific exercise program prescribed, or an alternative treatment to increase physical fitness or HrQOL) in patients with childhood cancer. Different types of physical training or exercise programs could be included in the intervention; for instance muscle strength or stretching exercises, aerobic exercises, or sports such as gymnastics, swimming, running or bicycling. The intervention could have taken place in any setting, such as a hospital, local health club or sports institute, school or home setting and could be delivered to a group or an individual participant.

### *Types of outcome measures*

The review included studies evaluating the effect of exercise on physical fitness, HrQOL, fatigue, self-efficacy, anxiety and depression. All adverse events (due to, or not clear to be related to the intervention) will be described.

### *Primary outcomes*

Physical fitness, which can be measured by:

1. Cardiorespiratory fitness (e.g. peak oxygen uptake ( $VO_{2peak}$ ), peak work rate ( $W_{max}$ ), endurance time)
2. Muscle endurance / strength
3. Body composition
4. Flexibility
5. Activity energy expenditure
6. Level of daily activity
7. Time spent exercising (more than daily activity)

Methods: (1) Test of aerobic or anaerobic exercise capacity, using the following test methodology: ergometry on cycle ergometer or treadmill, Wingate anaerobic test, steep-ramp-test, maximal anaerobic running/cycling test, Shuttle Run test, Coopertest; (2) Muscle endurance/ strength, using: hand-held dynamometer, the spring scale, the Lateral Step-up test, Sit-to-Stand test, ten repetition maximum, Sit-to-Stand test, minimum chair height test, Muscle Power Sprint Test, 10 x 5 meter sprint test, or 6 minute walk test or incremental shuttle walking test; (3) Body composition, using: Body Mass Index, skin fold measurement, DEXA scan, waist circumference, waist-hip-ratio; (4) Flexibility, using the sit-and-reach test.

#### *Secondary outcomes*

1. Health-related quality of life
2. Fatigue
3. Anxiety and depression
4. Self-efficacy

Methods: (questionnaire) instruments to investigate are for instance (1) (health-related) quality of life are: the Pediatric Quality of Life Inventory (PedsQL), CHQ, and DISABKIDS. (2) Fatigue: PedsQL Multidimensional Fatigue Scale, Childhood cancer fatigue scale (CCFS), Fatigue scale Child (FS-C), Fatigue scale adolescents (FS-A), Fatigue scale Parents (FC-P), (3) Depression: Childhood depression inventory (CDI), and the center of epidemiological studies depression scale (CES-D). (4) Self-efficacy can be measured by the confidence scale, Self-Efficacy Questionnaire for Children (SEQ-C), or the Children's Self-Efficacy Scale.

#### *Search methods for identification of studies*

##### *Electronic searches*

We searched the following electronic databases: MEDLINE/PubMed (from 1945 to 1 April 2010), EMBASE/Ovid (from 1980 to 1 April 2010), the Cochrane Central Library of Controlled Trials (CENTRAL) (The Cochrane Library, issue 2 2010), CINAHL (from 1982 to 1 April 2010, and Physiotherapy Evidence Database (PEDro) (until 1 April 2010) (<http://www.pedro.fhs.usyd.edu.au/index.html>) The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in Appendix 1.

### *Searching other resources*

Information about trials not registered in MEDLINE, EMBASE, CENTRAL, CINAHL, and PEDro, either published or unpublished, were located by searching the reference lists of relevant articles and reviews.

Additionally, we searched the ISRCTN register and the register of the National Institute of Health (<http://www.controlled-trials.com>) for ongoing trials. Only studies in the English, French, German and Dutch language were eligible for inclusion.

## **Data collection and analysis**

### *Selection of studies*

After employing the search strategy described previously, the reviewer (PT) undertook identification of studies meeting the inclusion criteria. Eligible studies, which seem to meet the inclusion criteria on grounds of the title, and abstract were obtained in full. Details for exclusion were clearly stated for the eligible studies.

### *Data extraction and management*

Data extraction was performed using standardised forms (Appendix 2) with information regarding: the study design, participant baseline characteristics, setting, sample size, number of participants in each study arm, type of intervention(s), duration of intervention, randomizations and blinding procedure, type of control group, type of treatment and stage of treatment (for example during or after treatment), duration of patient follow-up, outcome measures extracted will include: changes in cardiorespiratory fitness, muscle strength/endurance, body composition, body flexibility, energy expenditure per time period (for example day, week or month), changes in level of daily activity and time spent exercising.

In addition, psychosocial outcomes such as questionnaire outcome data on Quality of Life, fatigue, anxiety and depression and the child's self-efficacy were extracted and occurring adverse events were noted.

When necessary attempts were made by emailing authors to obtain data that have not been included into published reports.

### Assessment of risk of bias in included studies

Risk of bias of the included studies was assessed according to the following criteria: concealment of treatment allocation (selection bias), blinding of the care provider and blinding of the patients (performance bias), blinding of the outcome assessor (detection bias), intention-to-treat analysis and completeness of follow up (attrition bias). For all risk of bias items the definitions as described in the module of the Cochrane Childhood Cancer Group were used ([Kremer 2009](#)).

The quality of the studies was rated by using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) criteria ([Guyatt 2008a](#); [Guyatt 2008](#)).

For purposes of systematic reviews, GRADE defines the quality of a body of evidence ('High', 'Moderate', 'Low', or 'Very Low') as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest [Table 1](#). The GRADE system entails an assessment of the quality of a body of evidence for each individual outcome ([Guyatt 2008](#)). Factors that may decrease the quality of evidence: (i) Study limitations; (ii) inconsistency of results; (iii) indirectness of evidence; (iv) imprecision; (v) publication bias. Factors that may increase the quality of evidence: (i) large magnitude of effect; (ii) plausible confounding, which would reduce a demonstrated effect; (iii) dose-response gradient ([Guyatt 2008a](#)). GRADE suggests the terms *strong* and *weak* recommendations, considering the desirable and undesirable effects, quality of the evidence, values and preferences and costs of an intervention ([Guyatt 2008](#)).

**Table 1 GRADE Quality Assessment Criteria ([Guyatt 2008a](#); [Guyatt 2008](#))**

| Quality of evidence | Study design           | Lower if <sup>x</sup>   | Higher if <sup>x</sup>   |
|---------------------|------------------------|---|--|
| High                | Randomised Trail       | <i>Study quality</i><br>-1 - serious limitations<br>-2 - very serious limitations     | <i>Strong association</i><br>+1 - strong, no possible confounders, consistent and direct evidence<br>+2 - very strong, no major threats to validity and direct evidence<br>+1 - evidence of a dose response gradient<br>+1 - all plausible confounders would have reduced the effect |
| Moderate            | Quasi-randomised Trail | -1 - important inconsistency<br><i>Directness</i>                                     |  |
| Low                 | Observational Study    | -1 - some uncertainty   |  |
| Very low            | Any other evidence     | -2 - major uncertainty<br>-1 - sparse data<br>-1 - high probability of reporting bias |  |

#### Footnotes

x: 1 or 2: move up one/two grade/s.

### *Measures of treatment effect*

Continuous outcomes: The main outcomes will comprise changes in physical fitness and movement disorders. Where the same measurement scale has been used across studies, the weighted mean difference (WMD) method will be employed to pool post-treatment mean scores, with the weight given to each study determined by the precision of its estimate of effect. When the studies use different scales to measure outcome the standardized mean difference method will be used. For the interpretation of the Cohen's standardized mean difference the following criteria will be used ([Higgins 2008](#)).

- <0.41 represents a small effect
- 0.40 to 0.70 represents a moderate effect
- >0.70 represents a large effect

Dichotomous outcomes: For variables with two possible outcomes relative risk / risk ratio (RR) or odds ratio (OR) analyses will be calculated, with a 95% confidence interval.

### *Assessment of heterogeneity*

Heterogeneity was assessed both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, i.e. the  $I^2$  statistic. Significant heterogeneity was defined as  $I^2 < 50\%$  ([Higgins 2008](#)) Potential sources of clinical heterogeneity were assessed by: (i) patient characteristics (ii) treatment setting; (iii) stratification methods within studies.

## **Results**

The literature search yielded a total of 897 studies. After reading title and abstracts, 32 intervention studies published between 2001 and 2010 met our inclusion criteria. One additional study ([Hinds 2007](#)) was identified by reference tracking and a second study was found at <http://www.controlled-trials.com> under registration number NCT00902213 which is currently recruiting patients. Therefore no data is available from that study.

### *Included studies*

A total of 4 randomised clinical trials RCT's were being identified for inclusion in this review ([Hartman 2009](#); [Hinds 2007](#); [Marchese 2004](#); [Moyer-Mileur 2009](#)). In total 119 patients (age range: 1-18) participated in the four studies, 56 in the intervention group and 63 in the control group. For trial characteristics and outcome see the 'Characteristics of included studies' table.

### *Excluded studies*

Twenty eight studies were excluded for the following reasons: four studies were not RCTs or CCTs, 17 studies did not include the interested age group and 6 studies did not include exercise as an intervention. One study was written in Polish and therefore excluded due to language restrictions. Details of the excluded studies can be found in the 'Characteristics of excluded studies' table.

### *Participants*

Three out of four studies investigated the effect of exercise therapy in children with acute lymphoblastic leukemia (ALL) ([Hartman 2009](#); [Marchese 2004](#); [Moyer-Mileur 2009](#)). In all three studies the children were during maintenance therapy for their ALL. A total of 92 patients (44 intervention and 48 control) were included in these studies. The mean age of the participants of the study was ranged from 1 until 18 years. The study of Hinds et al. investigated patients with a solid tumor (n=25) or acute myeloblastic leukemia (n=4) who were scheduled for chemotherapy or clinical care guidelines and had ([Hinds 2007](#)). In this study the mean age of the participants was 12.48 years with a range from 7.36 - 18.16 years.

### *Interventions*

There was a wide variety in mode and intensity between the investigated studies. [Hinds 2007](#) investigated the effect of an supervised 'enhanced physical activity' (EPA) program on a stationary bicycle for 30 minutes twice daily for 2-4 days during hospitalization. No monitoring of vital signs such as heart frequency were recorded during this activity. The study outcomes were measured by the use of: questionnaires concerning sleep and fatigue. [Hartman 2009](#) and [Moyer-Mileur 2009](#) investigated the physical effects of an advice for more moderate to vigorous activities per week. Suggestions for moderate to vigorous activities were given, such as jumping and running. Hartman et al were additionally interested in the effects of stretching exercises on the ankle mobility. While [Moyer-Mileur 2009](#) used physical performance tests and dietary questionnaires to investigate the effect of appropriate nutrition education in combination with activities. The fourth study ([Marchese 2004](#)) studied a combination of advices and supervised training and the effect on physical performance and ankle mobility on children with ALL.

The duration of follow-up differed greatly between the four studies. The shortest intervention period and follow-up lasted 2-4 days ([Hinds 2007](#)), while the longest follow-up was over 3 years ([Hartman 2009](#)). The other two studies had an intervention time and follow-up period of respectively 16 weeks ([Marchese 2004](#)) and 12 months ([Moyer-Mileur 2009](#)).

The control study-arm varied from no intervention ([Hartman 2009](#); [Marchese 2004](#)), to standard recommendations ([Moyer-Mileur 2009](#)) or an equivalent amount of time talking with patients. ([Hinds 2007](#))

*Risk of bias in included studies*

Methodological quality of the included studies was by the use of the Cochrane quality assessment. All studies had an adequate sequence generation and allocation concealment, except [Moyer-Mileur 2009](#) who were unclear about the concealment. So it is likely there is no selection bias. Three studies ([Hinds 2007](#); [Marchese 2004](#); [Moyer-Mileur 2009](#)) were unclear over there blinding of the care provider and blinding of the patients this can lead to performance bias. Hartman et al blinded the outcome assessor to minimize detection bias. They did not report over their primary outcome variables at the end of their study. Moyer-Mileur et al reported several outcomes incompletely. No other ways of bias were detected by the authors. More information is given in the risk of bias section of the 'Characteristics of included studies' table. A summary of the review authors' judgements about each methodological quality item for each included study is given in figure 1.

|                   | Adequate sequence generation? | Allocation concealment? | Blinding? | Incomplete outcome data addressed? | Free of selective reporting? | Free of other bias? |
|-------------------|-------------------------------|-------------------------|-----------|------------------------------------|------------------------------|---------------------|
| Hartman 2009      | +                             | +                       | +         | ?                                  | -                            | +                   |
| Hinds 2007        | +                             | +                       | ?         | ?                                  | +                            | +                   |
| Marchese 2004     | +                             | +                       | ?         | +                                  | +                            | +                   |
| Moyer-Mileur 2009 | +                             | ?                       | ?         | +                                  | ?                            | +                   |

**Figure 1:** Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Two authors ([Hartman 2009](#); [Moyer-Mileur 2009](#)) were contacted for additional information concerning post test information which they did not address in their article. Hartman provided post test mean data +/- SD. The other author unfortunately did not respond to the request.

## **Effects of interventions**

### *Physiological outcome*

The included studies all used different physiological outcome measurements, except for the outcome variable passive ankle range of motion. ([Summary of findings table 2](#))

[Hartman 2009](#) et al used Body Mass Index, Bone Mineral Density and ankle dorsiflexion Passive Range of Motion to evaluate the physiological effects of their intervention in patients with ALL. Their intervention consisted of an initial session and follow-up sessions every 6 weeks. The pediatric physical therapist gave education regarding possible motor problems resulting from chemotherapy. An exercise program was introduced after the initial session, consisting of exercises to maintain hand and leg function (once a day), stretching exercises to maintain ankle dorsiflexion mobility and short-burst high-intensity exercises (both twice daily). The control group received neither a initial session nor any prescheduled follow-up sessions. The outcome measures of their study showed no statistical differences between childhood ALL patients who received the exercise program and those who received standard care.

[Marchese 2004](#) investigated the effect of a 16 week training program on range of motion (ROM), muscle strength, walking distance and stair climbing for children with ALL. Twenty-eight children were randomly assigned to either a 16 weeks training program or the control group. Knee extension strength tested with the hand held dynamometer improved significantly after the training program. All other outcome measures did not differ significantly.

[Moyer-Mileur 2009](#) studied the amount of push-ups (knees positioned on the ground), the results on the PACER (Progressive Aerobic Cardiovascular Endurance Run) and the results of the pedometer and Sit and Reach test, added with the ACTIVITY GRAM questionnaire (physical activity) to measure the differences in outcome of their intervention. The intervention consists of a (1) minimum of three 15 to 20 minute sessions of moderate to vigorous activity per week. (2) Appropriate nutrition education materials on the basis of the US DAFGP. Nutrition related activities were also provided and reviewed monthly by a registered dietitian with expertise in both exercise and pediatric nutrition.



Children in the control group were provided with standard recommendations to eat a well-balanced diet, take a multivitamin with low or no folic acid, and to perform activity as tolerated. The duration of the intervention was 12 months. Outcomes of the tests used in the study were not presented and can therefore not be displayed in the summary of findings table 2.

**Table 2: Summary of findings table on physiological outcome measures**

| Physiological outcomes after exercise intervention for children and adolescent during or after childhood cancer. |  |   |                              |  |
|--|--|---|------------------------------|--|
| Outcomes   | Illustrative comparative risks* (95% CI)   |   | No of Participants (studies) | Quality of the evidence (GRADE)          |
|  | Assumed risk   | Corresponding risk  |                              |  |
|  | Control  | exercise intervention   |                              |  |
| <b>Bone Mineral Density</b><br>DEXA scan<br>Follow-up: mean 2 years  | The mean bone mineral density in the control groups was<br><b>-1.14 standard deviation score</b> | The mean Bone Mineral Density in the intervention groups was<br><b>1.07 standard deviations higher</b><br>(0.48 to 1.66 higher)           | 51<br>(1 study)              | ⊕⊕⊕⊕<br><b>very low</b> <sup>1,2,3</sup> |
| <b>Passive Ankle Range of Motion</b><br>Goniometry   | The mean passive ankle range of motion in the control groups was<br><b>6.75 degrees</b>          | The mean Passive Ankle Range of Motion in the intervention groups was<br><b>1.26 standard deviations higher</b><br>(0.76 to 1.76 higher)  | 79<br>(2 studies)            | ⊕⊕⊕⊖<br><b>low</b> <sup>3,4</sup>        |
| <b>Body Mass Index</b><br>Quetelet index<br>Follow-up: mean 2 years  | The mean body mass index in the control groups was<br><b>1.00 standard deviation score</b>       | The mean Body Mass Index in the intervention groups was<br><b>0.88 standard deviations higher</b><br>(0.3 to 1.46 higher)                 | 51<br>(1 study)              | ⊕⊕⊕⊖<br><b>very low</b> <sup>1,2,3</sup> |
| <b>Strength</b><br>Strength normalized by patients weight  | The mean strength in the control groups was<br><b>0.22 standard deviation score</b>              | The mean Strength in the intervention groups was<br><b>0.27 standard deviations higher</b><br>(0.26 lower to 0.8 higher)                  | 56<br>(1 study)              | ⊕⊕⊕⊖<br><b>low</b> <sup>2,3</sup>        |
| <b>Timed Up and Down Stairs</b><br>seconds   | The mean timed up and down stairs in the control groups was<br><b>8.6 seconds</b>                | The mean Timed Up and Down Stairs in the intervention groups was<br><b>0.11 standard deviations higher</b><br>(0.64 lower to 0.85 higher) | 28<br>(1 study)              | ⊕⊕⊕⊖<br><b>low</b> <sup>2,3</sup>        |
| <b>9 minute Run - Walk</b><br>9 minute Run - Walk  | The mean 9 minute run - walk in the control groups was<br><b>1.01 kilometre</b>                  | The mean 9 minute Run - Walk in the intervention groups was<br><b>0.33 standard deviations higher</b><br>(0.42 lower to 1.07 higher)      | 28<br>(1 study)              | ⊕⊕⊕⊖<br><b>low</b> <sup>2,3</sup>        |

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Not free of selective reporting

<sup>2</sup> The upper or lower confidence limit crosses an effect size of 0.5 in either direction.

<sup>3</sup> Published evidence is limited to a small number of trials

<sup>4</sup> Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.

## Psychological outcome

Two out of four studies investigated changes in items of physiological functioning as a result of the intervention ([Summary of findings table 3](#)). The study of [Marchese 2004](#) used the PedsQL to evaluate the effect of the intervention on Quality of Life. Their 16 week training program did not show significant differences between the control and the intervention group on health related quality of life. [Hinds 2007](#) used a questionnaire to assess the observed level of fatigue (Daily Sleep Diary-Parent, Fatigue Scale) to assess the effect of the intervention on the child's sleep pattern and level of fatigue. The authors found no score differences on the fatigue questionnaire and concluded that an inpatient intervention of EPA can be delivered to children and adolescents receiving chemotherapy, but no statistical differences could be identified. Both studies reported no statistically significant difference in post test analyses.

## Adverse effects

No adverse effects were reported in the investigated studies.

**Table 3: Summary of findings table on psychological outcome measures**

| Psychological outcomes after exercise intervention for children and adolescents during or after childhood cancer |  |   |                              |  |
|--|--|---|------------------------------|--|
| Outcomes   | Illustrative comparative risks* (95% CI) |   | No of Participants (studies) | Quality of the evidence (GRADE)          |
|  | Assumed risk                             | Corresponding risk  |                              |  |
|  | Control                                  | exercise intervention for psychological outcomes  |                              |  |
| <b>Quality of life</b><br>PedsQoL  | Not mentioned                            | The mean Quality of life in the intervention groups was <b>0.03 standard deviations lower</b> (0.56 lower to 0.49 higher) | 56<br>(1 study)              | ⊕⊕⊕⊖<br><b>low</b> <sup>1,2</sup>        |
| <b>Sleep</b><br>The Daily Sleep Diary  | Not mentioned                            | The mean Sleep in the intervention groups was <b>0.21 standard deviations higher</b> (0.33 lower to 0.75 higher)          | 54<br>(1 study)              | ⊕⊖⊖⊖<br><b>very low</b> <sup>1,2,3</sup> |
| <b>Fatigue</b><br>The Fatigue Scale  | Not mentioned                            | The mean Fatigue in the intervention groups was <b>0.1 standard deviations lower</b> (0.53 lower to 0.32 higher)          | 86<br>(1 study)              | ⊕⊖⊖⊖<br><b>very low</b> <sup>1,3</sup>   |

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> The upper or lower confidence limit crosses an effect size of 0.5 in either direction.

<sup>2</sup> Published evidence is limited to a small number of trials

<sup>3</sup> Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.

## Discussion

### *Intervention*

The results of this review concerning the effects of an exercise intervention in children and adolescents during or after treatment for childhood cancer show that there are only four studies performed with mixed methodology and quality. These studies suggest that an exercise intervention has positive effects on functional activities such as walking stairs or running, but also on body composition, joint mobility and bone mineral density. The effect sizes of these outcomes indicate a positive trend for physical fitness and motor functioning. These findings correspond with results from exercise interventions performed in adult patients with cancer ([De Backer 2007a](#); [May 2008](#); [Martin 2009](#)).

Although positive psychological effects are described for adults with cancer after an exercise program ([Burnham 2002](#); [Oldervoll 2004](#); [De Backer 2007](#)) none of the included studies showed significant effects on the psychological outcome measures. [van Weert 2008](#) et al. showed positive effect of self-management programmes and self-efficacy enhancing programmes on health outcomes, exercise adherence and later exercise behaviour. These findings are still to be investigated in children and adolescents during or after childhood cancer.

It seems that supervised training ([Hinds 2007](#); [Marchese 2004](#)) reveals the best physiological and psychological improvements for children with cancer following an exercise program during or after their treatment. Their exercise protocols consisted of longer duration per session and a higher intensity compared to the other studies ([Hartman 2009](#); [Moyer-Mileur 2009](#)). By the experiences in adult cancer patients and survivors and according to the theoretical framework of physical training to increase physical fitness ([Faigenbaum 1999](#)) it can be hypothesised that under professional supervision exercise sessions will give better results. Therefore, supervised exercise can theoretically be seen as the most successful training intervention for children. This can be affirmed by several other non randomised studies which also show significant increase after an supervised exercise program in children during and after their cancer treatment ([Lucia 2005](#); [San Juan 2008a](#)). But according to the four randomized studies included in this review this can not be confirmed.

Furthermore, strength and endurance training might contribute to the effect of health and should have an intensity of 3-5 times a week ([Faigenbaum 1999](#)). In adults with cancer the study of De Backer et al. showed in their systematic review that resistance training resulted in significant training effects for cardiopulmonary and muscle function. In this study no adverse effects as result of the resistance training were reported ([De Backer 2007](#)). For adults a positive dose-response relationship between the amount of exercise performed and

improvements in physiological and psychological measures is described ([Martin 2009](#)). This review can not confirm this relationship between frequency and effect. Maybe the intensity in the studies of [Hartman 2009](#) and [Moyer-Mileur 2009](#) was not high enough to retain any results.

Survivors of childhood cancer are less physically active compared to their healthy peers ([Warner 2008](#)). Less than one third of this population participates in an activity that caused them to “work up a sweat” ([Demark-Wahnefried 2005](#)). Furthermore, only 48% of the American childhood cancer survivors met the American exercise guidelines (i.e., 1 hour a day on most days of the week for adolescents and 30 minutes a day on most days of the week for adults) ([Surgeon General 2007](#)).

The evidence that exercise interventions are valuable for children during and after chemotherapy is still sparse. However, given that survivors of childhood cancers have an increased risk of secondary cancers, cardiovascular disease, osteoporosis and diabetes it should be important to provide lifestyle interventions for this vulnerable group. The optimal distribution of type, intensity, duration, and frequency of physical activity across the lifespan is unclear, but it should be gender, age, and site specific and supports moderate activity (>4.5 MET) more than light activities (<4.5 MET) ([Thune 2001](#)).

#### *Outcome measures*

Different outcome measures were used in the studies of this review. Therefore comparing the outcome measures was not possible. The methodological quality of outcome measures differed also widely. For instance bone mineral density was measured with the "gold standard" a DEXA scan. However physical fitness assessment was in none of the included studies performed with the "gold standard", which is a cardiopulmonary exercise test with gasanalyses. Two of the excluded studies used a cardiopulmonary exercise test, indicating that this test is feasible in this population ([San Juan 2007](#); [San Juan 2008](#)).

#### *Limitations of this review*

Although we tried to identify all trials in the area of interest, there is always a possibility that we have missed some studies. This could have led to a selection bias. The comprehensive search was carried out but revealed only studies published in the English language. The excluded studies due to language barriers could have diminish the selective publication. Only one reviewer performed the search and rated the quality of the evidence. This could have led to bias. A wide variety of studies was incorporated in this review with all small numbers of participants.

Between the studies there is a considerable degree of clinical heterogeneity in terms of adjuvant therapy, mode and intensity of exercise. Statistical heterogeneity could not be detected due to the various outcome measures.

#### *Quality of the evidence*

The methodological quality of the studies was rated using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) criteria. For each outcome the strength of the evidence is given in an overview shown in the [Summary of findings table 2](#) and [Summary of findings table 3](#). Due to the small study populations and measurements with non-gold standard instruments it can be concluded that the overall quality of the evidence is low to very low. We therefore are very uncertain about the estimated effect and further research is very likely to have an important impact on our confidence in the estimate effect.

### **Authors' conclusions**

#### *Implications for practice*

Exercise interventions for children and young adults during and after treatment for childhood cancer show promising results for physiological outcomes like muscle strength and joint mobility. None of the investigated studies showed any effect in psychological outcomes. None of the studies have reported adverse effects, so it is probably with low risk to perform exercise training interventions for children during their treatment for ALL. However due to several forms of bias we are very uncertain about the estimate of effect and further research is very likely to have an important impact on the investigated outcome measures.

#### *Implications for research*

Further research in this field should be thoroughly planned according to well-recognized guidelines for training protocols. Outcome assessment should be performed with the best and for children accepted instruments available, such as a cardiopulmonary exercise test with gasanalyses. In addition it would be interesting to find out if more training leads to better results in children with cancer, as presented in the dose response relation shown in adults. For now almost only randomised controlled trials for children with ALL are studied, in practice it would be useful to know whether exercise interventions are beneficial for children with other types of cancer.

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## Characteristics of included studies

### Hartman 2009

|                      |  |
|----------------------|--|
| <b>Methods</b>       | Randomized Controlled Trial  |
| <b>Participants</b>  | Patients during treatment for ALL.<br>Inclusion: (1) ALL treated according DCOG ALL-9 protocol, (2) 1-18 yr.<br>n= 51 (25 intervention, 26 control)  |
| <b>Interventions</b> | <i>Intervention:</i><br>An initial session and follow-up sessions every 6 weeks with the pediatric physical therapist comprised of education regarding possible motor problems resulting from chemotherapy. An exercise program was introduced, consisting of exercises to maintain hand and leg function (once a day), stretching exercises to maintain ankle dorsiflexion mobility and short-burst high-intensity exercises (both twice daily).<br><i>Control:</i><br>Neither a initial session nor any prescheduled follow-up sessions<br><i>Duration:</i><br>3 years |
| <b>Outcomes</b>      | Motor performance (M-ABC), BMI, body composition, Bone Mineral Density, Ankle dorsiflexion passive range of motion   |
| <b>Notes</b>         |  |

### Risk of bias table

| Item                               | Judgement | Description   |
|------------------------------------|-----------|---|
| Adequate sequence generation?      | Yes       | Quote: "...randomization into the intervention or the control group was carried out in randomly permuted blocks of randomly chosen size"  |
| Allocation concealment?            | Yes       | Quote: "...using sealed envelopes prepared by the statistician."  |
| Blinding?                          | Yes       | Quote: "The investigators and treating physicians were blinded for the randomization."  |
| Incomplete outcome data addressed? | Unclear   | The study did not address this outcome  |
| Free of selective reporting?       | No        | One or more outcomes (no sd are given on primary outcome variables, BMD and motor performance) of interest in the review are reported incompletely so that they can not be entered in meta-analysis |
| Free of other bias?                | Yes       | The study appears to be free of other sources of bias.  |

## Hinds 2007

|                      |   |
|----------------------|---|
| <b>Methods</b>       | Randomized Controlled Trial   |
| <b>Participants</b>  | <p>Patients scheduled for chemotherapy or clinical care guidelines for a solid tumor (m=25) or AML (n=4).</p> <p>Inclusion: (1) 7-18 yr, (2) admitted for a 2-4 day inpatient stay for scheduled chemotherapy or clinical care guidelines.</p> <p>n= 29 (14 intervention, 15 control) 2 patients excluded in the intervention group due to missing data (n =1) and abnormal findings of the actigraph. (n =1)</p> |
| <b>Interventions</b> | <p><i>Intervention:</i></p> <p>Supervised Enhanced Physical Activity on a stationary bicycle for 30 minutes twice daily for 2-4 days of hospitalization.</p> <p><i>Control:</i></p> <p>A team member spent an equivalent amount of time with patients who were randomized to the standard care arm.</p> <p><i>Duration:</i></p> <p>2-4 days</p>   |
| <b>Outcomes</b>      | Wrist-Actigraph, Fatigue measurements (Daily Sleep Diary-Parent, Fatigue Scale)   |
| <b>Notes</b>         |   |

### Risk of bias table

| Item                               | Judgement | Description  |
|------------------------------------|-----------|--|
| Adequate sequence generation?      | Yes       | Quote: "Patients were randomly assigned to study arms by a computer-generated program..."  |
| Allocation concealment?            | Yes       | Quote: "The randomization procedure established by the study biostatistician was based on Zelen's methodology."  |
| Blinding?                          | Unclear   | The study did not address this outcome   |
| Incomplete outcome data addressed? | Unclear   | No reasons for missing data reported   |
| Free of selective reporting?       | Yes       | The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified. |
| Free of other bias?                | Yes       | The study appears to be free of other sources of bias.   |



## Marchese 2004

|                      |   |
|----------------------|---|
| <b>Methods</b>       | Randomized Controlled Trial   |
| <b>Participants</b>  | <p>Patients receiving maintenance therapy for ALL.</p> <p>Inclusion: (1) ALL, (2) 4-18 yr, (3) time of maintenance (First- or second half) and (4) risk Group (low, standard or high)</p> <p>n= 28 (13 intervention, 15 control)</p>  |
| <b>Interventions</b> | <p><i>Intervention:</i></p> <p>Five sessions (20 min to 1h; immediately after initial testing and 2,4,6,8 and 12 weeks later)of physical therapy (stretching and strengthening exercises, supervised) and an individualized home-based exercise program ( bilateral ankle dorsiflexion stretching held for 30s 5 days a wee, bilateral lower extremity strengthening 3 sets fo 10 repetitions 3x/week and aerobic exercises (i.e. walking, biking or swimming).</p> <p><i>Control:</i></p> <p>No instructions related to physical fitness and no physical therapy.</p> <p><i>Duration:</i></p> <p>16 weeks during treatment</p> |
| <b>Outcomes</b>      | Ankle dorsiflexion strength, <b>knee extension strength</b> , TUDS (Timed up and down stairs), 9 min run-walk, PedsQL (health related QOL measure), Ankle dorsiflexion active range of motion   |
| <b>Notes</b>         | Significant differences ( $P < 0.05$ ) between group differences are printed in bold  |

## Risk of bias table

| Item                               | Judgement | Description  |
|------------------------------------|-----------|--|
| Adequate sequence generation?      | Yes       | Quote: "stratified by their CCG standard risk or high-risk treatment groups and by ... first or second half of maintenance therapy."                   |
| Allocation concealment?            | Yes       | Quote: "... an envelop to select assignment into the intervention or control group"  |
| Blinding?                          | Unclear   | The study did not address this outcome.  |
| Incomplete outcome data addressed? | Yes       | No missing outcome data  |
| Free of selective reporting?       | Yes       | The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified. |
| Free of other bias?                | Yes       | The study appears to be free of other sources of bias.   |

## Moyer-Mileur 2009

|                      |  |
|----------------------|--|
| <b>Methods</b>       | Randomized Controlled Trial  |
| <b>Participants</b>  | Patients with standard risk ALL during maintenance therapy.<br>Inclusion: (1) ALL treated with CCG 1991 protocol, (2) 4-10 yr.<br>Inclusion: (1) ALL treated with CCG 1991 protocol, (2) 4-10 yr.<br>n= 13 (6 intervention, 7 control)   |
| <b>Interventions</b> | <i>Intervention:</i><br>(1) A minimum of three 15 to 20 minute sessions of moderate to vigorous activity per week. (2) Appropriate nutrition education materials on the basis of the US DAFGP and nutrition related activities were also provided and reviewed monthly by a registered dietitian with expertise in both exercise and pediatric nutrition.<br><i>Control:</i><br>Children were provided standard recommendations to eat a well-balanced diet, take a multivitamin with low or no folic acid, and to perform activity as tolerated.<br><i>Duration:</i><br>12 months |
| <b>Outcomes</b>      | Push-ups (knees positioned on the ground), PACER (Progressive Aerobic Cardiovascular Endurance Run), <b>Pedometer</b> , Sit and Reach test, <b>ACTIVITY GRAM questionnaire (physical activity)</b> , Three-day food intake record  |
| <b>Notes</b>         | Significant differences ( $P < 0.05$ ) between group differences are printed in bold   |

### Risk of bias table

| Item                               | Judgement | Description  |
|------------------------------------|-----------|--|
| Adequate sequence generation?      | Yes       | Quote: "Subjects were randomized..."   |
| Allocation concealment?            | Unclear   | The study did not address this outcome.  |
| Blinding?                          | Unclear   | The study did not address this outcome.  |
| Incomplete outcome data addressed? | Yes       | Plausible effect size among missing outcomes (n=1) not enough to have a clinically relevant impact on observed effect size |
| Free of selective reporting?       | Unclear   | One or more outcomes of interest in the review are reported incompletely so that they can not be entered in meta-analysis. |
| Free of other bias?                | Yes       | The study appears to be free of other sources of bias.   |

#### Footnotes

## Characteristics of excluded studies

*Bird 2010*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Burnham 2002*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Chang 2008*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Coleman 2003*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Coleman 2003a*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Coleman 2008*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Courneya 2003*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Courneya 2009*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Doorenbos 2006*

|                      |                          |
|----------------------|--------------------------|
| Reason for exclusion | No exercise intervention |
|----------------------|--------------------------|

*Gocha 2001*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Hayes 2004*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Kato 2008*

|                      |                          |
|----------------------|--------------------------|
| Reason for exclusion | No exercise intervention |
|----------------------|--------------------------|

*Kim 2008*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Ladha 2006*

|                      |   |
|----------------------|---|
| Reason for exclusion | No RCT or CCT with comparable control group |
|----------------------|---|

*Lee 2003*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Maddocks 2006*

|                      |   |
|----------------------|---|
| Reason for exclusion | No RCT or CCT with comparable control group |
|----------------------|---|

*Marinovic 2005*

|                      |                          |
|----------------------|--------------------------|
| Reason for exclusion | No exercise intervention |
|----------------------|--------------------------|

*May 2008*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Nagwa 2007*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Oh 2008*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Ostanski 2001*

|                      |                      |
|----------------------|----------------------|
| Reason for exclusion | Language restriction |
|----------------------|----------------------|

*Prieto 2005*

|                      |                          |
|----------------------|--------------------------|
| Reason for exclusion | No exercise intervention |
|----------------------|--------------------------|

*Quist 2006*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Rai 2008*

|                      |                          |
|----------------------|--------------------------|
| Reason for exclusion | No exercise intervention |
|----------------------|--------------------------|

*San Juan 2007*

|                      |   |
|----------------------|---|
| Reason for exclusion | No RCT or CCT with comparable control group |
|----------------------|---|

*San Juan 2008*

|                      |   |
|----------------------|---|
| Reason for exclusion | No RCT or CCT with comparable control group |
|----------------------|---|

*Shelton 2009*

|                      |                                    |
|----------------------|------------------------------------|
| Reason for exclusion | Age of participants above 18 years |
|----------------------|------------------------------------|

*Syczewska 2006*

|                      |                          |
|----------------------|--------------------------|
| Reason for exclusion | No exercise intervention |
|----------------------|--------------------------|

## References to studies

### *Included studies*

#### **Hartman 2009**

Hartman A, te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SM, Kemper HC, Hop WC, et al. A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia. *Pediatr.Blood Cancer* 2009;53(1545-5017 (Electronic), 1545-5017 (Linking), 1):64-71.

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Moyer-Mileur LJ, Ransdell L, Bruggers CS. Fitness of children with standard-risk acute lymphoblastic leukemia during maintenance therapy: response to a home-based exercise and nutrition program. *J.Pediatr.Hematol.Oncol.* 2009;31(1536-3678 (Electronic), 1536-3678 (Linking), 4):259-66.

### *Excluded studies*

#### **Bird 2010**

Bird L, Arthur A, Niblock T, Stone R, Watson L, Cox K. Rehabilitation programme after stem cell transplantation: randomized controlled trial. *Journal of Advanced Nursing* 2010;66(3):607-15.

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## *Appendix 1*

### *Search strategy*

## Search strategy for MEDLINE/PubMed

1. For **children** the following MeSH headings and text words will be used:

infant OR infan\* OR newborn OR newborn\* OR new-born\* OR baby OR baby\* OR babies OR neonat\* OR perinat\* OR postnat\* OR child OR child\* OR schoolchild\* OR schoolchild OR school child OR school child\* OR kid OR kids OR toddler\* OR adolescent OR adoles\* OR teen\* OR boy\* OR girl\* OR minors OR minors\* OR underag\* OR under ag\* OR juvenil\* OR youth\* OR kindergar\* OR puberty OR puber\* OR pubescen\* OR prepubescen\* OR prepuberty\* OR pediatrics OR pediatric\* OR paediatric\* OR peadiatric\* OR schools OR nursery school\* OR preschool\* OR pre school\* OR primary school\* OR secondary school\* OR elementary school\* OR elementary school OR high school\* OR highschool\* OR school age OR schoolage OR school age\* OR schoolage\* OR infancy OR schools, nursery OR infant, newborn

2. For **cancer and childhood cancer** the following MeSH headings and text words will be used:

cancer OR oncology OR oncolog\* OR neoplasms OR neoplas\* OR carcinoma OR carcinom\* OR tumor OR tumour OR tumor\* OR tumour\* OR cancer\* OR malignan\* OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo\* OR bone marrow transplantation OR bone marrow transplant\* OR lymphoma OR ((leukemia OR leukemi\* OR leukaemi\* OR (childhood ALL) OR AML OR lymphoma OR lymphom\* OR hodgkin OR hodgkin\* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom\* OR sarcoma, Ewing's OR Ewing\* OR osteosarcoma OR osteosarcom\* OR wilms tumor OR wilms\* OR neuroblastom\* OR neuroblastoma OR neuroblastom\* OR rhabdomyosarcoma OR rhabdomyosarcom\* OR teratoma OR teratom\* OR hepatoma OR hepatom\* OR hepatoblastoma OR hepatoblastom\* OR PNET OR medulloblastoma OR medulloblastom\* OR PNET\* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom\* OR meningioma OR meningiom\* OR glioma OR gliom\*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor\* OR brain tumour\* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor\* OR central nervous system tumour\* OR brain cancer\* OR brain neoplasm\* OR intracranial neoplasm\*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])

3. For **exercise therapy** the following MeSH headings and text words will be used:

exercise OR exercises OR exercis\* OR Exercise, Physical OR Exercises, Physical OR Physical Exercise OR Physical Exercises OR Exercise, Isometric OR Exercises, Isometric OR Isometric Exercises OR Isometric Exercise OR Warm-Up Exercise OR Exercise, Warm-Up OR Exercises, Warm-Up OR Warm Up Exercise OR Warm-Up Exercises OR Exercise, Aerobic OR Aerobic Exercises OR Exercises, Aerobic OR Aerobic Exercise OR exercise therapy OR Therapy, Exercise OR Exercise Therapies OR Therapies, Exercise OR physical therapy modalities OR Modalities, Physical Therapy OR Modality, Physical Therapy OR Physical Therapy Modality OR Physiotherapy (Techniques) OR Physiotherapies (Techniques) OR Physical Therapy Techniques OR Physical Therapy Technique OR Techniques, Physical Therapy OR exercise test OR exercise tests OR muscle stretching exercise OR muscle stretching exercises OR physical therapy OR physical therapies OR strengthen\* OR stretch\* OR physiotherapy[text] OR physiotherap\*[text] OR stability training OR training\* OR exercise movement technique OR exercise movement techniques OR Movement Techniques, Exercise OR exercise movement technic OR Exercise Movement Technics OR pilates based exercise OR pilates-based exercise OR Pilates Based Exercises OR Pilates-Based Exercises OR Exercises, Pilates-Based OR pilates OR physical exercise OR gymnastics OR gymnastic OR gymnastic\* OR swimming OR locomotion OR locomotions OR locomotion\* OR treadmill OR walking OR running OR aerobic OR aerobics OR aerobic\* OR cycling OR jogging OR Exertion OR disability of function[text] OR occupational therapy OR occupational therapies OR functional therapy[text] OR functional therapies[text] OR training program OR physical education and training OR Physical Education, Training OR Physical Education OR Education, Physical OR fitness OR cardio training OR weight lifting OR power training OR muscle training OR rowing OR sports OR jump OR jumping

4. For the **outcome** the following MeSH headings and text words will be used:

quality of life OR Qol OR condition\* OR physical fitness OR Fitness, Physical OR Physical Conditioning, Human OR Conditioning, Human Physical OR Conditionings, Human Physical OR Human Physical Conditioning OR Human Physical Conditionings OR Physical Conditionings, Human OR physical effort OR physical skill OR physical activity OR muscle strength OR muscular strength OR lung function OR pulmonary function OR vital capacity OR Depression OR Depressive Disorder OR Depression, involuntary OR fear OR recovery of function OR physical endurance OR range of motion OR VO2 OR VO(2peak) OR ventilatory threshold OR heart rate OR endurance OR activity energy expenditure OR DXA scan OR activity participation OR mets score OR DeltaMetS OR Wingate anaerobic test OR steep ramp test OR dynamometer OR Six Minute Walk Distance OR 6MWD OR lateral step up OR Sit-to-Stand OR ten repetition maximum OR minimum chair height OR muscle power OR gross motor function OR GMFCS OR GMFM OR incremental shuttle walking OR sit-and-reach

5. for **RCTs and CCTs** the following MeSH headings and text words will be used:

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans[mh] ([Higgins 2008](#))

Final search:

1 AND 2 AND 3 AND 4 AND 5

[pt]=publication type

[tiab]=title or abstract

[sh]=subject heading

[mh]=MeSH term

[text]=text word

[\*]=1+ more characters

[RCT]= randomised controlled trial

[CCT]= controlled clinical trial

## 2 Search strategy for Embase/OVID

1. For **children** the following Emtree terms and text words will be used:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant\$ or newborn\$ or (new adj born\$) or baby or baby\$ or babies or neonate\$ or perinat\$ or postnat\$).mp.
6. (child\$ or (school adj child\$) or schoolchild\$ or (school adj age\$) or schoolage\$ or (pre adj school\$) or preschool\$).mp.
7. (kid or kids or toddler\$ or adoles\$ or teen\$ or boy\$ or girl\$).mp.
8. (minors\$ or (under adj ag\$) or underage\$ or juvenil\$ or youth\$).mp.
9. (puber\$ or pubescen\$ or prepubescen\$ or prepubert\$).mp.
10. (pediatric\$ or paediatric\$ or peadiatric\$).mp.
11. (school or schools or (high adj school\$) or highschool\$ or (primary adj school\$) or (nursery adj school\$) or (elementary adj school) or (secondary adj school\$) or kindergar\$).mp.
12. or/5-11
13. 4 or 12

2. For **childhood cancer** the following Emtree terms and text words will be used:

1. (leukemia or leukemi\$ or leukaemi\$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom\$ or hodgkin or hodgkin\$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom\$ or Ewing\$ or osteosarcoma or osteosarcom\$ or wilms tumor or wilms\$).mp.
4. (nephroblastom\$ or neuroblastoma or neuroblastom\$ or rhabdomyosarcoma or rhabdomyosarcom\$ or teratoma or teratom\$ or hepatoma or hepatom\$ or hepatoblastoma or hepatoblastom\$).mp.
5. (PNET or medulloblastoma or medulloblastom\$ or PNET\$ or neuroectodermal tumors or primitive neuroectodermal tumor\$ or retinoblastoma or retinoblastom\$ or meningioma or meningiom\$ or glioma or gliom\$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm\$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor\$) or (brain adj tumour\$) or (brain adj neoplasms) or (brain adj cancer\$) or brain neoplasm\$).mp.
10. (central nervous system tumor\$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour\$).mp.
11. intracranial neoplasm\$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

3. For **cancer** the following Emtree terms and text words will be used:

1. (cancer or cancers or cancer\$).mp.
2. (oncology or oncolog\$).mp. or exp oncology/
3. (neoplasm or neoplasms or neoplasm\$).mp. or exp neoplasm/
4. (carcinoma or carcinom\$).mp. or exp carcinoma/

5. (tumor or tumour or tumor\$ or tumour\$ or tumors or tumours).mp. or exp tumor/
6. (malignan\$ or malignant).mp.
7. (hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo\$).mp. or exp hematologic malignancy/
8. or/1-7

4. For **physical therapy** the following Emtree terms and text words will be used:

1. (exercise or exercises or exercis\$).mp.
2. exp exercise/
3. (physical exercise or physical exercises).mp.
4. exp isometric exercise/
5. (isometric exercise or isometric exercises).mp.
6. (warm up exercise or warm up exercises or warm-up exercise or warm-up exercises).mp.
7. exp aerobic exercise/
8. (aerobic exercise or aerobic exercises).mp.
9. exp kinesiotherapy/
10. (exercise therapy or exercise therapies).mp.
11. (physical therapy modality or physical therapy modalities).mp.
12. exp pediatric physiotherapy/ or exp physiotherapy/
13. (physiotherapy or physiotherapies).mp.
14. (physical therapy technique or physical therapy techniques or physical therapy or physical therapies).mp.
15. exp exercise test/
16. (exercise test or exercise tests).mp.
17. exp stretching exercise/
18. (muscle stretching exercise or muscle stretching exercises).mp.
19. (strengthen\$ or stretch\$).mp.
20. exp muscle exercise/ or stability training.mp. or exp muscle training/
21. training\$.mp.
22. (exercise movement technique or exercise movement techniques).mp.
23. (exercise movement technic or exercise movement technics).mp.
24. (pilates-based exercise or pilates based exercise or pilates-based exercises ot pilates based exercises).mp.
25. pilates.mp. or exp pilates/
26. physical exercise.mp.
27. (gymnastic or gymnastics or gymnastic\$).mp.
28. exp swimming/ or swimming.mp.
29. exp locomotion/
30. (locomotion or locomotions or locomotion\$).mp.
31. exp treadmill/ or exp treadmill exercise/
32. treadmill.mp.
33. walking.mp. or exp walking/
34. exp running/ or running.mp.
35. cycling.mp. or exp cycling/
36. jogging.mp. or exp jogging/
37. (aerobic or aerobics or aerobic\$).mp.
38. exertion.mp.
39. disability of function.mp.
40. exp occupational therapy/
41. (occupational therapy or occupational therapies).mp.
42. (functional therapy or functional therapies).mp.
43. training program.mp.
44. (physical education and training).mp.
45. physical education.mp. or exp physical education/
46. fitness.mp. or exp fitness/
47. cardio training.mp.
48. weight lifting.mp. or exp weight lifting/
49. power training.mp.
50. muscle training.mp.
51. rowing.mp. or exp rowing/
52. sports.mp. or exp sport/
53. exp jumping/ or (jump or jumping).mp.
54. or/1-53

5. For **outcome** the following Emtree terms and text words will be used:

1. exp "quality of life"/
2. (quality of life or QoL).mp.
3. general condition improvement/

4. condition\$.mp.
5. physical fitness.mp. or exp fitness/
6. (human physical conditioning or human physical conditionings).mp.
7. physical effort.mp.
8. physical skill.mp.
9. physical activity.mp. or exp physical activity/
10. (muscle strength or muscular strength).mp. or exp muscle strength/
11. lung function.mp. or exp lung function/
12. pulmonary function.mp.
13. vital capacity.mp. or exp vital capacity/
14. depression.mp. or exp depression/
15. depressive disorder.mp.
16. involuntal depression.mp. or exp involuntal depression/
17. fear.mp. or exp fear/
18. recovery of function.mp. or exp convalescence/
19. physical endurance.mp. or exp endurance/
20. range of motion.mp. or exp "range of motion"/
21. (VO2 or VO2peak).mp.
22. (VO adj 2peak).mp.
23. ventilatory threshold.mp.
24. heart rate.mp. or exp heart rate/
25. exp endurance/ or endurance.mp.
26. exp energy expenditure/ or activity energy expenditure.mp.
27. exp dual energy X ray absorptiometry/ or DXA scan.mp.
28. activity participation.mp.
29. mets score.mp.
30. (mets or DeltaMetS).mp.
31. Wingate anaerobic test.mp.
32. exp Steep Ramp Test/ or steep ramp test.mp.
33. dynamometer.mp. or exp dynamometer/
34. (Six Minute Walk Distance or 6MWD).mp.
35. lateral step up.mp.
36. Sit-to-Stand.mp.
37. ten repetition maximum.mp.
38. minimum chair height.mp.
39. muscle power.mp.
40. (gross motor function or GMFCS or GMFM).mp.
41. incremental shuttle walking.mp.
42. sit-and-reach.mp.
43. or/1-42

6. For **RCTs and CCTs** the following Emtree terms and text words will be used:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. randomized.ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8
10. Human/
11. 9 and 10

#### **Final search**

1 and (2 or 3) and 4 and 5 and 6

[mp]=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

[ti,ab]=title, abstract

[sh]=subject heading

[/]=Emtree term

[\$]=1+more characters

[RCT]= randomised controlled trial

[CCT]= controlled clinical trial



### 3 Search strategy for Central Register of Controlled Trials (CENTRAL)

1. For **children** the following text words will be used for searching Title, Abstract, or Keywords:

infant OR infan\* OR newborn OR newborn\* OR new-born\* OR baby OR baby\* OR babies OR neonat\* OR perinat\* OR postnat\* OR child OR child\* OR schoolchild\* OR schoolchild OR school child OR school child\* OR kid OR kids OR toddler\* OR adolescent OR adoles\* OR teen\* OR boy\* OR girl\* OR minors OR minors\* OR underag\* OR under ag\* OR juvenil\* OR youth\* OR kindergar\* OR puberty OR puber\* OR pubescen\* OR prepubescen\* OR prepuberty\* OR pediatrics OR pediatric\* OR paediatric\* OR peadiatric\* OR schools OR nursery school\* OR preschool\* OR pre school\* OR primary school\* OR secondary school\* OR elementary school\* OR elementary school OR high school\* OR highschool\* OR school age OR schoolage OR school age\* OR schoolage\* OR infancy

2. For **childhood cancer** the following text words will be used for searching Title, Abstract, or Keywords:

(leukemia OR leukemi\* OR leukaemi\* OR (childhood ALL) OR AML OR lymphoma OR lymphom\* OR hodgkin\* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom\* OR Ewing\* OR osteosarcoma OR osteosarcom\* OR wilms tumor OR wilms\* OR nephroblastom\* OR neuroblastoma OR neuroblastom\* OR rhabdomyosarcoma OR rhabdomyosarcom\* OR teratoma OR teratom\* OR hepatoma OR hepatom\* OR hepatoblastoma OR hepatoblastom\* OR PNET OR medulloblastoma OR medulloblastom\* OR PNET\* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom\* OR meningioma OR meningiom\* OR glioma OR gliom\* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR cancer or neoplasms or tumor or cancers or neoplasm or tumors)

3. For **cancer** the following text words will be used for searching Title, Abstract, or Keywords:

cancer OR oncology OR oncolog\* OR neoplasms OR neoplas\* OR carcinoma OR carcinom\* OR tumor OR tumour OR tumor\* OR tumour\* OR cancer\* OR malignan\* OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo\* OR bone marrow transplantation OR bone marrow transplant\* OR leukaemia OR lymphoma

4. For **physical therapy** the following text words will be used for searching Title, Abstract, or Keywords:

exercise OR exercises OR exercis\* OR Physical Exercise OR Physical Exercises OR Isometric Exercises OR Isometric Exercise OR Warm-Up Exercise OR Warm Up Exercise OR Warm-Up Exercises OR Aerobic Exercises OR Aerobic Exercise OR exercise therapy OR Exercise Therapies OR physical therapy modalities OR Physical Therapy Modality OR Physiotherapy (Techniques) OR Physiotherapies (Techniques) OR Physical Therapy Techniques OR Physical Therapy Technique OR exercise test OR exercise tests OR muscle stretching exercise OR muscle stretching exercises OR physical therapy OR physical therapies OR strengthen\* OR stretch\* OR physiotherapy OR physiotherap\* OR stability training OR training\* OR exercise movement technique OR exercise movement techniques OR exercise movement technic OR Exercise Movement Technics OR pilates based exercise OR pilates-based exercise OR Pilates Based Exercises OR Pilates-Based Exercises OR pilates OR physical exercise OR gymnastics OR gymnastic OR gymnastic\* OR swimming OR locomotion OR locomotions OR locomotion\* OR treadmill OR walking OR running OR aerobic OR aerobics OR aerobic\* OR cycling OR jogging OR Exertion OR disability of function OR occupational therapy OR occupational therapies OR functional therapy OR functional therapies OR training program OR physical education and training OR Physical Education OR fitness OR cardio training OR weight lifting OR power training OR muscle training OR rowing OR sports OR jump OR jumping

5. For **outcome** the following text words will be used for searching Title, Abstract, or Keywords:

quality of life OR Qol OR condition\* OR physical fitness OR Human Physical Conditioning OR Human Physical Conditionings OR physical effort OR physical skill OR physical activity OR muscle strength OR muscular strength OR lung function OR pulmonary function OR vital capacity OR Depression OR Depressive Disorder OR involuntional depression OR fear OR recovery of function OR physical endurance OR range of motion OR VO<sub>2</sub> OR VO<sub>2</sub>(peak) OR ventilatory threshold OR heart rate OR endurance OR activity energy expenditure OR DXA scan OR activity participation OR mets score OR DeltaMetS OR Wingate anaerobic test OR steep ramp test OR dynamometer OR Six Minute Walk Distance OR 6MWD OR lateral step up OR Sit-to-Stand OR ten repetition maximum OR minimum chair height OR muscle power OR gross motor function OR GMFCS OR GMFM OR incremental shuttle walking OR sit-and-reach

#### Final search:

1 and (2 or 3) and 4 and 5

[\*]=1+ more characters

#### 4 Search strategy for CINAHL

[MH] MeSH headings: exploding retrieves all documents containing any of the subject terms below the term selected.

[+] related terms are also taken into the search: In case of a plus sign (+) next to a narrower or related term, there are narrow terms below the term.

1. For **children** the following the following MeSH headings (MH) and text words will be used for searching Title, Abstract, or Keywords:

"schoolage" OR (MH "Schools+") OR "peadiatric" OR "paediatric" OR "pediatric" OR (MH "Puberty+") OR "juvenile" OR "underage" OR "under age" OR ("teenager") or (MH "Adolescence+") OR "adolescent" OR "kids" OR "kid" OR "schoolchild" OR ("child\*") or (MH "Child") ("newborn") or (MH "Infant, Newborn+") OR ("infant") or (MH "Infant+")

2. For **cancer** the following the following MeSH headings (MH) and text words will be used for searching Title, Abstract, or Keywords:

(MH "Central Nervous System Neoplasms+") OR "childhood tumour" OR "childhood tumor" "childhood cancer" OR (MH "Meningioma") OR (MH "Retinoblastoma") OR (MH "Neuroectodermal Tumors+") OR (MH "Ameloblastoma") OR (MH "Teratoma") OR (MH "Rhabdomyosarcoma") OR (MH "Neuroblastoma") OR (MH "Nephroblastoma") OR (MH "Osteosarcoma+") OR (MH "Sarcoma, Ewing's") OR (MH "Sarcoma+") or (MH "Osteosarcoma") OR (MH "Lymphoma+") OR (MH "Leukemia+") OR (MH "Bone Marrow Transplantation+") or (MH "Bone Marrow Neoplasms") OR "hemato oncological" OR ("malignancy") or (MH "Hematologic Neoplasms+") OR "tumour" OR "tumor" OR (MH "Carcinoma+") OR (MH "Neoplasms+") OR ("oncology") or (MH "Oncology+") or (MH "Pediatric Oncology Nursing") or (MH "Oncologic Care") OR ("cancer") or (MH "Neoplasms")

3. For **exercise intervention** the following the following MeSH headings (MH) and text words will be used for searching Title, Abstract, or Keywords:

("sports") or (MH "Sports+") or (MH "Amateur Sports") or (MH "Aquatic Sports") (MH "Rowing") or (MH "Ergometry") OR ("muscle training") or (MH "Muscle Strengthening") OR "power training" OR (MH "Weight Lifting") OR ("cardio training") or (MH "Athletic Training") or (MH "Athletic Training Programs") OR ("fitness") or (MH "Physical Fitness") OR (MH "Physical Education and Training+") OR "training program" "functional therapies" OR "functional therapy" OR (MH "Occupational Therapy+") or (MH "Pediatric Occupational Therapy") OR "disability of function" OR (MH "Exertion") OR (MH "Cycling") or (MH "Ergometry") OR (MH "Running") or (MH "Running, Distance") OR (MH "Walking") or (MH "Sports") OR (MH "Treadmills") OR (MH "Locomotion") or (MH "Movement") OR (MH "Swimming") OR (MH "Gymnastics") OR ("pilates") or (MH "Pilates") OR (MH "Therapeutic Exercise+") or (MH "Aerobic Exercises") or (MH "Arm Exercises") or (MH "Back Exercises") OR (MH "Stretching") OR (MH "Exercise Test+") or (MH "Exercise Test, Cardiopulmonary") or (MH "Exercise Test, Muscular+") OR "physiotherapy" OR ("exercise therapy") or (MH "Therapeutic Exercise+") or (MH "Exercise Therapy: Ambulation (Iowa NIC)") or (MH "Exercise Therapy: Balance (Iowa NIC)") or (MH "Exercise Therapy: Joint Mobility (Iowa NIC)") or (MH "Exercise Therapy: Muscle Control (Iowa NIC)") OR ("physical therapy") or (MH "Physical Therapy+") or (MH "Pediatric Physical Therapy") or (MH "Physical Therapy Practice, Evidence-Based") or (MH "Physical Therapy Practice, Research-Based") OR "therapies" OR (MH "Aerobic Exercises+") or (MH "Therapeutic Exercise+") OR (MH "Warm-Up Exercise") (MH "Isometric Contraction") or (MH "Isometric Exercises") OR ("physical") or (MH "Education, Physical Therapy") or (MH "Home Physical Therapy") or (MH "Pediatric Physical Therapy") or (MH "Physical Activity") OR ("exercise") or (MH "Exercise+") or (MH "Abdominal Exercises") or (MH "Aerobic Exercises+") or (MH "Anaerobic Exercises") or (MH "Aquatic Exercises") or (MH "Arm Exercises") or (MH "Back Exercises")

4. For **outcome** the following the following MeSH headings (MH) and text words will be used for searching Title, Abstract, or Keywords:

"shuttle walking test" or ("repetition maximum") or (MH "Anaerobic Threshold") (MH "Rising") OR("lateral step up") or (MH "Step") OR ("six minute walking distance") or (MH "Running, Distance") or (MH "Walking+") OR(MH "Dynamometry") OR "steep ramp test" OR ("anaerobic test") or (MH "Achievement Tests") OR "wingate" OR (MH "Basal Metabolism") or (MH "Glucose Metabolism Disorders") OR (MH "Leisure Participation (Iowa NOC)") or (MH "Play Participation (Iowa NOC)") OR ("DXA scan") or (MH "Biometrics") OR (MH "Energy Metabolism+") or (MH "Activities of Daily Living+") or (MH "Human Activities+") OR ("endurance") OR (MH "Heart Rate+") or (MH "Heart Rate Variability") OR (MH "Respiratory Muscles") OR "VO2" OR "Vo2 peak" OR (MH "Range of Motion") or (MH "Range of Motion (Saba CCC)") or (MH "Motion Therapy, Continuous Passive") or (MH "Motion") OR (MH "Physical Endurance+") OR (MH "Recovery") or (MH "Functional Assessment") OR (MH "Fear+") OR (MH "Depression+") OR ("lung function") or (MH "Respiratory Function Tests+") or (MH "Functional Status") OR ("muscle strength") or (MH "Muscle Strength+") or (MH "Muscle Strengthening+") or (MH "Exercise Test, Muscular+") OR ("physical skill") or (MH "Exercise Test") or (MH "Motor Skills") or (MH "Social Skills") or (MH "Social Skills Training") OR (MH "Exertion") or (MH "Education, Physical Therapy") or (MH "Home Physical

Therapy") OR (MH "Physical Fitness+") or (MH "Fitness Centers") OR (MH "Conditioning (Psychology)") or (MH "Conditioning, Cardiopulmonary") OR (MH "Quality of Life+") or (MH "Health and Life Quality (Iowa NOC) (Non-Cinahl)+")

5. For **RCTs and CCTs** the following MeSH headings and text words will be used: (MH "randomized controlled trial") or (MH "controlled clinical trial") or (MH "randomized") or (MH "placebo") or ("drug therapy") or (MH "randomly+") or (MH "trial") or (MH "groups+") and (MH "human")

#### **Final search**

1 and 2 and 3 and 4 and 5

[MH] = MeSH headings: exploding retrieves all documents containing any of the subject terms below the term selected.

[+] = related terms are also taken into the search: In case of a plus sign (+) next to a narrower or related term, there are narrow terms below the term.

[RCT]= randomised controlled trial

[CCT]= controlled clinical trial

### **5 Search strategy for PEDro**

1. For children

"paediatrics" in <Subdiscipline> field

2. For cancer and childhood cancer

"cancer" OR "oncolog" OR "neoplasm" OR "carcinom" or "tumor" OR "malignan" in the <Abstract & Title> field

3. For exercise therapy

"exercis" in the <Abstract & Title> field OR "fitness training" OR "hydrotherapy, balneotherapy" OR

"neurodevelopmental therapy, neurofacilitation" OR "skill training" OR "strength training" in the <Therapy> field

4. For outcome

No search terms defined

5. for RCTs and CCTs

"clinical trial" in the <Method> field

#### **Final search**

1 and 2 and 3 and 4 and 5.

## *Appendix 2*

### *Data extraction form*

Review Title: Exercise interventions for children and young adults with childhood cancer  
 Date: ..... Reviewer: Patrick van der Torre / Katja Braam

RefmanID:                      First Author:                      Pub date:

Study Title:

.....  
 .....  
 .....

**Study Eligibility / Characteristics**

|                           | Review Inclusion Criteria   | Study                       |
|---------------------------|---|-----------------------------|
| Type of Study             | RCT or CCT  | Yes / No / Unclear<br>WHERE |
| Participants              | Childhood cancers (except<br>Braintumors)                                   |                             |
| Types of Intervention     | Exercise Therapy<br>Physical Therapy<br>Physical Training<br>Rehabilitation |                             |
| Types of Outcome Measures | Exercise parameters /<br>QOL  |                             |

Include    Exclude

Reason for exclusion:

.....  
 .....  
 .....

| <b>Method Section</b>           |  |
|---------------------------------|--|
| Study design                    |  |
| Total study duration            |  |
| Sequence generation             |  |
| Allocation sequence concealment |  |
| Blinding                        |  |
| Other concerns about bias       |  |

**Participant Section**

|                     | Total | Intervention | Control |
|---------------------|-------|--------------|---------|
| Total number        |       |              |         |
| Male / female       |       |              |         |
| Age                 |       |              |         |
| Setting             |       |              |         |
| Diagnostic criteria |       |              |         |

**Intervention**

|                          |  |
|--------------------------|--|
| Type of intervention     |  |
| Duration of intervention |  |
| Duration of follow-up    |  |
| Main outcome             |  |
| Time point collected     |  |
| Secondary outcomes       |  |
| Time points              |  |

**Control**

|                              |  |
|------------------------------|--|
| Type of control intervention |  |
| Duration of intervention     |  |
| Duration of follow-up        |  |
| Main outcome                 |  |
| Time points collected        |  |
| Secondary outcomes           |  |
| Time points                  |  |

## Results

Comparison:

---

**MAIN Outcome:**

---

Subcategory:

---

| Experimental |           | Control      |           |
|--------------|-----------|--------------|-----------|
| Observed (n) | Total (n) | Observed (n) | Total (n) |
|              |           |              |           |

|                  | Experiment | Control |
|------------------|------------|---------|
| Total randomized |            |         |
| Mean / Median    |            |         |
| SD               |            |         |
| Range            |            |         |

Reasons for loss/exclusion:

---

Results

Comparison:

---

Outcome:

---

Subcategory:

---

| Experimental |           | Control      |           |
|--------------|-----------|--------------|-----------|
| Observed (n) | Total (n) | Observed (n) | Total (n) |
|              |           |              |           |

|                  | Experiment | Control |
|------------------|------------|---------|
| Total randomized |            |         |
| Mean / Median    |            |         |
| SD               |            |         |
| Range            |            |         |

Reasons for loss/exclusion:

---

# Steep Ramp Testing in children with childhood cancer; an alternative for the cardio-pulmonary exercise test?

**Master of Science Thesis**

## **Author**

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Studentnumber: 3272907

16 July 2010

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UMC Utrecht, Utrecht



## **Abstract**

### **Background**

Despite the remarkable treatment advances of the past three decades, cancer remains the leading cause of death by disease in young persons. Nowhere else in the area of cancer control are medical advances as dramatic as in childhood cancer. However, medical progress is only one part of the equation.

Both childhood cancer and its treatment have enormous impact on the child's wellbeing. The side effects of the treatment may occur during, shortly, or many years following the therapy. These effects are seen in different organ systems and body functions. Recently, childhood cancer studies on physical fitness of have been presented to evaluate the impact of cancer treatment on physical health outcomes such as aerobic capacity and muscle strength. Exercise testing provides a unique technique to observe deficiencies or abnormalities which are not, or hardly detectable in the resting state. However these Cardio-pulmonary exercise tests (CPET's) are also a burden for the patient as far as exercise time concerned and the cost of healthcare due to the cost of expensive equipment and qualified personnel.

### **Objectives**

Therefore the aim of the present study is to investigate the validity of the Steep Ramp Test (SRT); a novel short exercise protocol compared to a CPET performed on a cycle-ergometer in children with cancer. In addition we will assess whether the  $VO_{2peak}$  on the CPET can be predicted from SRT variables.

### **Methods**

This study is part of a larger study (Quality of Life In Motion study) which studies the effects of a combined physical and psychosocial intervention program on physical fitness and quality of life in patients with childhood cancer. Children aged of 8 years old or above, were included in the study. Subjects performed a SRT and a CPET by using an electronically braked cycle ergometer while wearing a facemask to measure gas exchange.

### **Results**

Nineteen participants were tested (10 girls and 9 boys; age  $13.5 \pm 3.0$  years). A linear regression model equation revealed an excellent prediction for a subjects  $VO_{2peak}$  with the variables of  $W_{peak}$  achieved on the SRT and body weight.  $VO_{2peak}$  (L/min) on a CPET =  $-0.276 + 0.013*(W_{peak} \text{ SRT}) - 0.012*(\text{body weight in kg})$  [SEE: 0.194;  $R^2$ : 0.934]

The data presented in this article showed good to excellent correlations (.804 - .971) between the variables of  $HR_{peak}$ ,  $W_{peak}$ ,  $VO_{2peak}$  (L/min) and  $VO_{2peak}$  (ml/kg/min) of the SRT and the CPET. There were no significance differences between the achieved  $VO_{2peak}$  (L/min) and  $VO_{2peak}$  (ml/kg/min) on both tests.

### **Conclusion**

The SRT is a safe and valid novel short maximal exercise test to estimate the  $VO_{2peak}$  for a child with cancer. The obtained  $W_{peak}$  on the SRT can give the daily practitioner indications for training intensity for this patient group.

## Introduction

Despite the remarkable treatment advances of the past three decades, cancer remains the leading cause of death by disease in children between the ages of one and 14 years.<sup>1</sup> The American Cancer Society estimates that in 2009, over 10,000 children (~15 per 100,000) will be newly diagnosed with cancer and 1,400 will die.<sup>1</sup> In the Netherlands approximately 500 children a year are being diagnosed with childhood cancer. The risk to develop childhood cancer in the Netherlands is approximately 0.7%.<sup>2</sup> However, medical progress is only one part of the equation. Equivalent advances are needed in dealing with the psychosocial, emotional, and economic aspects of these cancers, as well as with their late effects.<sup>3</sup>

Adverse effects of childhood cancer are widely described and affect most of the human organs and structures, eg. heart, lung, liver, bone and muscle.<sup>4</sup> In a study conducted by Geenen et al the total burden of adverse health outcomes following childhood cancer was assessed. In this retrospective cohort study they showed that almost 75% had at least 1 or more adverse events, and 24.6% had 5 or more adverse events. Furthermore, 40% of survivors had at least 1 severe or life-threatening or disabling adverse events.<sup>5</sup> Therefore it is not surprising that a malignant disease or its treatment may cause long-term impairments in intellectual, emotional and physical domains that diminish functioning.<sup>6</sup> Ness et al reported restrictions in performance limitations, personal care skills, routine activities and the ability to attend school or work.<sup>6</sup> Furthermore survivors of childhood cancer are less likely than siblings to meet physical activity guidelines and were more likely than siblings to report an inactive lifestyle.<sup>7</sup>

In the recent past, studies on physical fitness of childhood cancer patients and survivors have been presented to evaluate the impact of cancer treatment on physical health outcomes such as aerobic capacity and muscle strength.<sup>8-11</sup> These studies presented data, concluding that physical fitness is often reduced in survivors of childhood Acute Lymphoblastic Leukemia (ALL) and therefore cancer health care should be completed by regular physical activities, or (adapted) sports programs to increase functional capacity.<sup>12</sup>

Exercise testing provides a unique insight by uncovering deficiencies or abnormalities not detectable in the resting state. Inadequate conditioning of the cardio-pulmonary or muscular system either from chronic illness or sedentary living also potentially impairs performance. Aerobic capacity can be measured in a variety of ways. Several equipments and protocols are described to measure a subjects aerobic capacity.<sup>13</sup> The gold standard is the exercise test to measure maximum oxygen uptake ( $VO_{2peak}$ ) of a person during a cardiopulmonary exercise test (CPET) using respiratory gas analyses.<sup>13</sup>

However these CPETs are also a serious burden on the patient as far as exercise time concerned and the cost of healthcare due to the high cost of expensive equipment and qualified personnel.

An other way to determine a person's aerobic capacity is the Steep Ramp Test (SRT). This is a steep graded maximum exercise protocol on a bicycle. The SRT has several advantages compared to the CPET such as the duration of the exercise on the SRT is much shorter. In addition there is no need for performing respiratory gas analysis, and in adults it has shown to give a good prediction of a persons  $VO_{2peak}$  with the achieved peak work rate ( $W_{peak}$ ).<sup>14</sup> The SRT test has proven to be a reliable and valid method to measure the oxygen uptake in patients with chronic heart failure<sup>15, 16</sup> and adult survivors of cancer<sup>14, 17</sup>. However it has not been investigated whether the SRT is a safe and valid exercise test for children with cancer.

Therefore the aim of the present study is to investigate the validity of the SRT compared to the goldstandard CPET performed on a cycle-ergometer in children with cancer. The hypothesis is that there are no significant differences between the exercise variables,  $VO_{2peak}$  (L/min) or mL/kg/min, maximum ventilation (VE L/min), peak heart rate ( $HR_{peak}$ ) and peak respiratory exchange ratio ( $RER_{peak}$ ), with significant differences in  $W_{peak}$  between the SRT and the CPET. Such as seen in adults, we also hypothesised that the  $VO_{2peak}$  on the CPET is predictable from the results of the SRT ( $W_{peak}$ ).

## **Methods**

### **Study population**

This study is part of a larger study (Quality of Life In Motion study) which studies the effects of a combined physical and psychosocial intervention program on physical fitness and quality of life in patients with childhood cancer. Patient selection, inclusion and testing took place at the Child Development and Exercise Centre of the University Children's Hospital in Utrecht and at the VU Medical Centre, Amsterdam, the Netherlands. This study was approved by both Medical Ethical Committees.

Children aged of 8 years old or above, having any type of cancer treated with chemotherapy and/or radiotherapy could be included. Exclusion criteria were bone marrow transplantation needed during treatment, growth hormone use, wheelchair use and mental retardation

## Measurements

### *Steep Ramp Test*

Subjects performed a SRT by using an electronically braked cycle ergometer (Lode Corival, Lode BV, Groningen, the Netherlands). A modified protocol of the SRT<sup>15</sup> was used. After one minute of resting measurement and one minute of unloaded cycling, the test started and work rate was increased every 10 seconds. Work rate was increased with a constant increment of 15 or 20 Watt based on the subject's height according to the Godfrey protocol.<sup>18</sup> The test ended when the pedal frequency fell below 60 rpm despite verbal encouragement. The same exercise parameters as during CPET were measured and were defined as the values achieved during the last 10 seconds before stopping.  $W_{\text{peak}}$  was defined as the highest achieved work rate prior to stopping.

### *Cardiopulmonary Exercise Test*

CPET was performed after 10 minutes passive recovery following the SRT and was performed on the same electronically braked cycle ergometer. The test started with 1 minute of unloaded cycling before the application of resistance to the ergometer. Every minute work rate was increased as in the SRT. This protocol continued until the patient stopped because of voluntary exhaustion, despite strong verbal encouragement of the test-leader. The  $HR_{\text{peak}}$ ,  $RER_{\text{peak}}$ ,  $W_{\text{peak}}$  and  $VO_{2\text{peak}}$  were defined as the mean of the values achieved during the last 30 seconds.

During the SRT and CPET, subjects breathed through a facemask connected to a calibrated respiratory gas analysis system (Cortex Metamax B3, Cortex Medical, Leipzig, Germany). Expired gas was passed through a flowmeter (Triple V volume transducer), an oxygen ( $O_2$ ) analyzer, and a carbon dioxide ( $CO_2$ ) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation ( $VE$ ), oxygen uptake ( $VO_2$ ), carbon dioxide output ( $VCO_2$ ), and the RER ( $=VCO_2/VO_2$ ) from conventional equations. Heart rate was measured continuously during both tests by using a heart rate monitor (Polar, Kempele, Finland). Maximal effort occurred when 1 of the 2 criteria were met:  $HR_{\text{peak}} > 180$  beats per minute or  $RER_{\text{peak}} > 1.0$ .  $VO_{2\text{peak}}$  was taken as the average value for the last 30 seconds during the maximal exercise test. Relative  $VO_{2\text{peak}}$  was calculated as absolute  $VO_{2\text{peak}}$  divided by body weight.

## Data processing and Statistical Analysis

Data was checked for normality and heteroscedasticity, the latter referring to the degree of variability depending on the outcome of the measurement.<sup>19</sup> A visual interpretation of Bland and Altman plots was performed to check for heteroscedasticity.

Descriptive data for physical fitness characteristics and test results were calculated and expressed as mean  $\pm$  SD. Student t-test for paired samples were applied to compare the differences between the outcomes of the CPET and the SRT with significance set at  $p < 0.05$ . Associations were examined by Pearson correlation coefficient ( $r$ ) and the intra-class correlation with a 95% confidence interval. Correlations were categorized according to Portney and Watkins in which .25 to .50 is a fair correlation, .50 to .75 is moderate to good relationship and above .75 there is a good to excellent relationship.<sup>20</sup> Agreement between the CPET and the SRT was verified and visualised with the Bland and Altman method.<sup>21</sup> Multivariate linear regression analyses (backward and forward method) to predict the  $VO_{2peak}$  using SRT performance was done with patient characteristics and SRT outcome variables. All statistical analyses were performed in SPSS 15.0.

## Results:

From March 2009 until March 2010 19 participants were tested (10 girls and 9 boys; age  $13,5 \pm 3.0$  years). (Table 1) Informed consent was obtained from all patients and their parents. Participants were diagnosed with a variety of childhood cancers, most children suffered from ALL ( $n= 5$ ). Several other types of childhood cancer were present: AML ( $n=2$ ), CML ( $n=2$ ), Hodgkin's lymphoma ( $n=3$ ), braintumor ( $n=3$ ) and solid tumors ( $n=4$ ). All participants were treated with chemotherapy, three participants received adjuvant radiotherapy. One girl refused to perform both exercise tests due to a therapy related infection in here mouth and therewith the fear for pain when using the face mask during the test. In total there were 18 valid test series, due to the design of the study, one participant was tested three times, 4 participants were tested twice and 8 participants were tested once.. No adverse effects were reported by the participants.

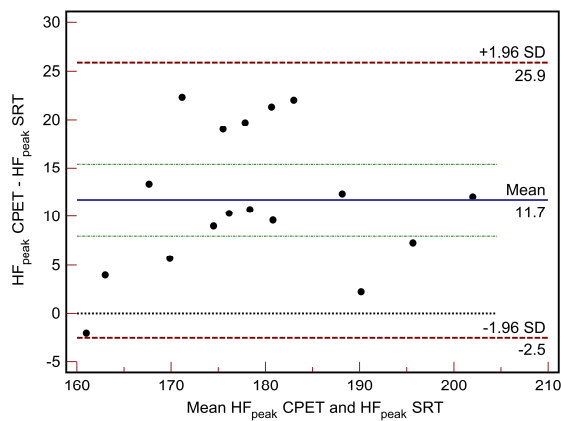
**Table 1: Subject characteristics (N=19)**

| Characteristics                          | Value             | %    |
|--|-------------------|------|
| Sex (n)                                  |                   |      |
| Male                                     | 10                | 52.6 |
| Female                                   | 9                 | 47.4 |
| Age (y)                                  |                   |      |
| Mean $\pm$ SD                            | 13.5 $\pm$ 2.96   |      |
| Range                                    | 8.1 – 17.3        |      |
| Anthropometrics                          |                   |      |
| Height (cm) (mean $\pm$ SD)              | 160.1 $\pm$ 19.30 |      |
| Range                                    | 126.0 – 185.0     |      |
| Weight (kg) (mean $\pm$ SD)              | 56.4 $\pm$ 23.05  |      |
| Range                                    | 25.0 – 95.0       |      |
| Height for age (z-score) (mean $\pm$ SD) | -0.24 $\pm$ 1.15  |      |
| Range                                    | -2.1 – 1.9        |      |
| BMI (kg/m <sup>2</sup> ) (mean $\pm$ SD) | 20.9 $\pm$ 4.92   |      |
| Range                                    | 14.5 – 29.7       |      |
| Cancer type (n)                          |                   |      |
| ALL                                      | 5                 | 26.3 |
| AML                                      | 2                 | 10.5 |
| CML                                      | 2                 | 10.5 |
| Hodgkin's lymphoma                       | 3                 | 15.8 |
| Brain tumors                             | 3                 | 15.8 |
| Solid tumors                             | 4                 | 21.1 |
| Treatment protocol (n)                   |                   |      |
| Chemotherapy                             | 16                | 84.2 |
| Chemotherapy and radiotherapy            | 3                 | 15.8 |

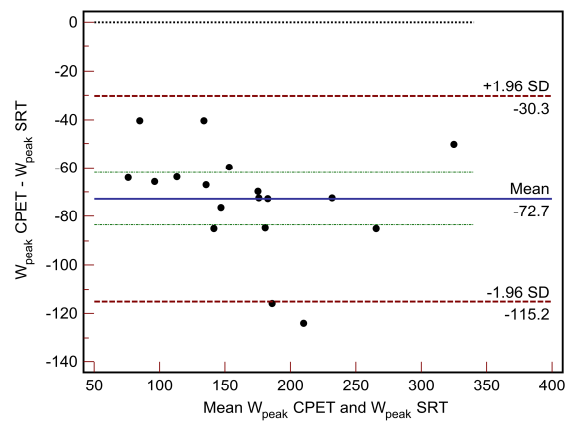
Abbreviations: y, years; sd, standard deviation; BMI, Body Mass Index; ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myoblastic Leukaemia; CML, Chronic Myoblastic Leukaemia

### Comparison of peak exercise variables between CPET and SRT

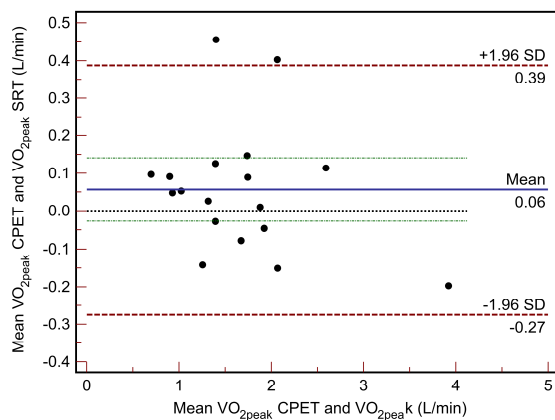
The Shapiro-Wilk Test showed normal distribution of the exercise variables in the two tests. No systemic bias was noted for CPET and SRT measurements of  $VO_{2peak/kg}$  values. Bland and Altman plots for  $HR_{peak}$  showed a higher achieved heart rate of 12 beats per minute during the CPET. (Figure 1) The mean  $W_{peak}$  during the CPET was 72 Watts lower compared to the  $W_{peak}$  on the SRT. (Figure2) The Bland-Altman concordance analysis for  $VO_{2peak}$  (L/min) and  $VO_{2peak/kg}$  (mL/kg/min) during the SRT demonstrated a relatively small dispersion compared with  $RER_{peak}$ ,  $VO_{2peak}$  (L/min) and  $VO_{2peak/kg}$  (mL/kg/min) during the CPET (Figure 3-4).



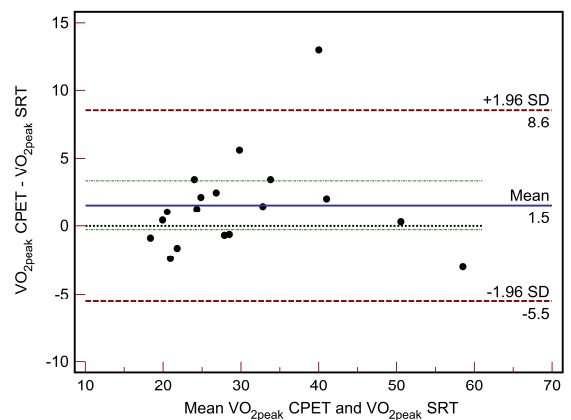
**Figure 1:** Bland and Altman plot heart rate peak



**Figure 2:** Bland and Altman plot Work rate peak



**Figure 3:** Bland and Altman plot  $VO_{2peak}$  (L/min)



**Figure 4:** Bland and Altman plot  $VO_{2peak/kg}$  (ml/kg/min)

The paired t-test showed no significant differences between the  $RER_{peak}$ ,  $VO_{2peak}$  (L/min) and  $VO_{2peak}$  (ml/kg/min). The mean difference in  $VO_{2peak}$  was -0.06 L/min and  $VO_{2peak}$  (mL/kg/min) -1.2 mL and did not revealed any significance findings ( $p > 0.05$ ). Mean maximum ventilation achieved on the SRT was roughly 8 L/min less compared to the mean 61.0 L/min value on the CPET. Participants mean  $VO_{2peak}$  (L/min) measured during the SRT was 5% lower compared to the  $VO_{2peak}$  (L/min) measured during the CPET. Corrected for kilograms the difference becomes only 3% in the advantage of a higher  $VO_{2peak}$  kg/mL/min during the CPET. The  $W_{peak}$  achieved during the SRT was 51% higher compared to the  $W_{peak}$  achieved during the CPET. The duration of the SRT was one minute and 45 seconds, the mean exercise time of the CPET was 6 minutes and 50 seconds. (Table 2)

**Table 2: Exercise variables obtained during the SRT and CPET**

|  | Mean $\pm$ SD     | Range        | Mean diff. $\pm$ SD | p-value |
|--|-------------------|--------------|---------------------|---------|
| HR <sub>peak</sub> SRT (beats/min)       | 173 $\pm$ 11      | 160 – 196    | - 12 $\pm$ 7        | .001*   |
| HR <sub>peak</sub> CPET (beats/min)      | 184 $\pm$ 12      | 160 – 208    |                     |         |
| RER <sub>peak</sub> SRT                  | 1.24 $\pm$ 0.18   | 1.06 – 1.68  | .06 $\pm$ .05       | .19     |
| RER <sub>peak</sub> CPET                 | 1.18 $\pm$ 0.10   | .92 – 1.39   |                     |         |
| VE SRT (L/min)                           | 52.8 $\pm$ 19.9   | 27.1 – 111.1 | -8.2 $\pm$ 14.8     | .03*    |
| VE CPET (L/min)                          | 61.0 $\pm$ 25.8   | 29.1 – 128.6 |                     |         |
| VO <sub>2peak</sub> SRT (L/min)          | 1.63 $\pm$ 0.77   | .65 – 4.02   | -.06 $\pm$ .17      | .17     |
| VO <sub>2peak</sub> CPET (L/min)         | 1.69 $\pm$ 0.72   | .75 – 3.82   |                     |         |
| VO <sub>2peak</sub> /kg SRT (mL/kg/min)  | 29.5 $\pm$ 11.0   | 18.8 – 60.0  | -1.5 $\pm$ 3.6      | .09     |
| VO <sub>2peak</sub> /kg CPET (mL/kg/min) | 31.0 $\pm$ 11.4   | 17.9 – 57.0  |                     |         |
| W <sub>peak</sub> SRT Work rate peak     | 203.8 $\pm$ 67.0  | 105 – 350    | 72.7 $\pm$ 21.7     | .001*   |
| W <sub>peak</sub> CPET Work rate peak    | 131.0 $\pm$ 61.2  | 44 – 300     |                     |         |
| Exercise time SRT (seconds)              | 104.9 $\pm$ 29.9  | 70 – 175     | -302.8 $\pm$ 146.1  | .001*   |
| Exercise time CPET (seconds)             | 409.5 $\pm$ 173.6 | 176 – 899.1  |                     |         |

Abbreviations: SRT; Steep Ramp Test, CPET; Cardio Pulmonary Exercise Test, sd; standard deviation, Mean diff; mean difference SRT and CPET, HR; Heart rate, RER; Respiratory Exchange Ratio, VE; minute ventilation, VO<sub>2</sub>; oxygen uptake, W; Work rate

The Pearson correlations and the Intra-class correlation (ICC) between the scores on the SRT and the scores on the reference test CPET, indicating the concurrent validity of scores for the scales, are shown in Table 3. A good to excellent correlation was seen in all exercise variables. The strongest relationship ( $r = .976$ ;  $p < .001$ ) was found between the VO<sub>2peak</sub> L/min achieved in both tests. The ICC results were comparable with the outcomes of the Pearson's correlation with good to excellent correlations. The confidence interval revealed small dispersion with exception of HR<sub>peak</sub>. All correlations were significant at the .01 level.



**Table 3: Associations between SRT and CPET exercise variables**

|  | Pearson Correlation | Intraclass correlation <sup>a</sup> | 95%CI        |
|--|---------------------|-------------------------------------|--------------|
| $W_{peak}$ SRT – $W_{peak}$ CPET                                   | .947**              | .943 <sup>b</sup>                   | .854 - .978  |
| $VO_{2peak}$ L/min SRT - $VO_{2peak}$ L/min CPET                   | .976**              | .974 <sup>b</sup>                   | .933 - .990  |
| $VO_{2peak/kg}$ (ml/kg/min) SRT - CPET $VO_{2peak/kg}$ (kg/mL/min) | .949**              | .948 <sup>b</sup>                   | .867 - .980  |
| $W_{peak}$ SRT - $VO_{2peak}$ L/min CPET                           | .937**              | .020 <sup>b</sup>                   | -.439 - .471 |
| $HR_{peak}$ SRT – $HR_{peak}$ CPET                                 | .808**              | .804 <sup>b</sup>                   | .539 - .924  |
| VE SRT(L/min) – VE CPET (L/min)                                    | .821**              | .794 <sup>b</sup>                   | .530 - .918  |

Abbreviations: SRT; Steep Ramp Test; CPET; Cardio Pulmonary Exercise Test; sd standard deviation; Mean diff; mean difference SRT and CPET; CI, Confidence Interval, HR; Heart rate, VE; minute ventilation,  $VO_2$ ; oxygen uptake, W; Work rate

a. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

b. The estimator is the same, whether the interaction effect is present or not.

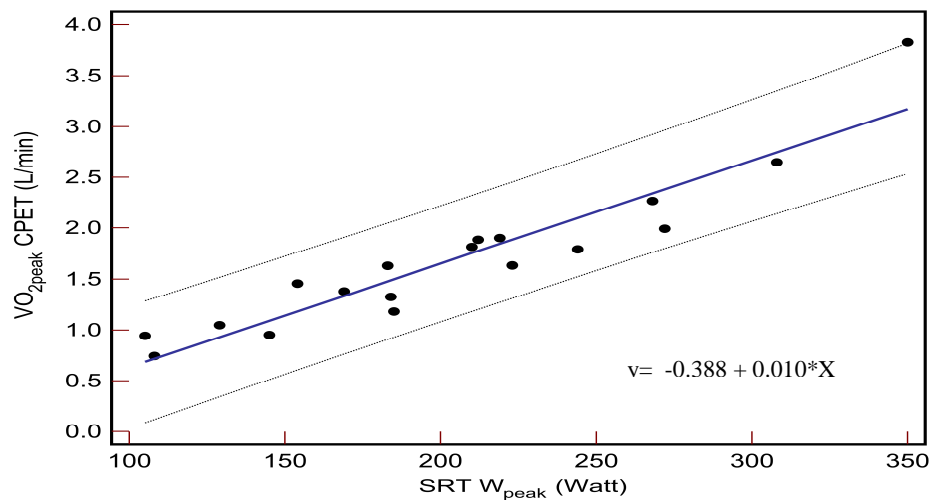
\*\* . Correlation is significant at the 0.01 level (2-tailed).

### Prediction of $VO_{2peak}$ from the SRT performance

A multiple linear regression model (forward and backward method) was used to develop a prediction of  $VO_{2peak}$  CPET from the measurements of the SRT. The best predictor of a persons  $VO_{2peak}$  (L/min) was the  $W_{peak}$  on the SRT (Figure 5 ). After including a person anthropometrics the prediction model even fitted better. The resulting regression equation to estimate  $VO_{2peak}$  was as follows:

$$VO_{2peak} (L/min) \text{ on a CPET} = -0.276 + 0.013*(W_{peak} \text{ SRT}) - 0.012*(body \text{ weight in kg}) [SEE: 0.194; R^2: 0.934]$$

The Standard Error of the Estimate (SEE) was 0.194 litre, implying a prediction margin of  $\pm 2SDs$  of 0.388 L/min.



**Figure 5: Linear regression between  $VO_{2peak}$  on CPET and  $W_{peak}$  achieved on SRT**

Abbreviations: SRT; Steep Ramp Test; CPET; Cardio Pulmonary Exercise Test;  $VO_2$ ; oxygen uptake, W; Wattage

## Discussion

This study showed the possibility to make a prediction of a persons  $VO_{2peak}$  achieved on the CPET from outcomes on the SRT; a novel short maximum exercise capacity test. A linear regression model equation revealed an excellent prediction for a persons  $VO_{2peak}$  with the variables of  $W_{peak}$  achieved on the SRT and body weight.

The SRT has several other advantages compared to the CPET such as less time-consuming and reduced costs. The average exercise time of the SRT was almost 4 times shorter compared to the CPET. The reduction in exercise time together with the possibility to estimate  $VO_{2peak}$  from the  $W_{peak}$  on SRT provides a significant reduction in costs, because no expensive personnel and equipment is needed to determine a persons  $VO_{2peak}$ . Therefore it can be performed in physical therapy settings without a movement laboratory.

The data presented in this article showed good to excellent correlations (.804 - .971) between the variables of  $HR_{peak}$ ,  $W_{peak}$ ,  $VO_{2peak}$  (L/min) and  $VO_{2peak}$  (ml/kg/min) of the SRT and the CPET. There were no significance differences between the achieved  $VO_{2peak}$  (L/min) and  $VO_{2peak}$  (ml/kg/min) on both tests. However there were differences between the peak work rate and the  $HR_{peak}$ .

$W_{peak}$  depends on the chosen protocol, during a short intensive protocol children can achieve higher work rates compared to a longer, less intensive protocol.<sup>22</sup> Therefore it is not surprisingly that the  $W_{peak}$  on the SRT was over 50% higher to the outcome on the CPET.

The higher  $HR_{peak}$  on the CPET can also rely on the longer duration of the CPET, but a warm-up effect from the SRT can not be excluded.

To evaluate whether an exercise test in children yields "true" maximum values, Bar-Or and Rowland described guidelines regarding subjective values as signs of intense effort, as unsteady running or biking, sweating and clear unwillingness to continue and objective criteria, as  $HR_{peak} > 95\%$  of predicted,  $RER_{peak} > 1.00$  and  $VO_2$  plateau in last minute.<sup>23</sup> All participants reached 3 out of 4 features during the CPET. The plateau phase in the last minute was not considered appropriate during the SRT. Taken that into account all participants reached 2 out of 3 features during the SRT. All participants had to execute their effort because of fatigue in their muscles.

The main purpose of this study was to develop a prediction model of  $VO_{2peak}$  on outcomes of the SRT. De Backer investigated this prediction model for adults with cancer. They found a prediction model of  $VO_{2peak} (L/min)$  on a CPET =  $0.356 + 6.7 * (W_{peak} SRT)$  with a SEE of 616 mL. Indicating a higher intersection with the x-axis resulting in a higher achieved workload, which is plausible for the physiological differences between children and adults. These differences occur due to growth and development but also because of changes in metabolic responses in children.<sup>23</sup> The SEE in our population is almost 50% less which contributes positively to the certainty of the prediction.

In addition to the possibility to receive the  $VO_{2peak}$  by the use of SRT results and a multivariate regression model, the SRT has several other advantages for the use in daily clinical practice. The peak work rate outcome can be used to tailor exercise training programs.<sup>17</sup> De Backer et al showed that this way of training gives practitioners the possibility to prescribe individualised training protocols based on a person's outcome on the SRT. They showed that this high-intensity, individualised protocols attribute to a higher quality of life in patients with cancer. Pediatric training programs need to be well-designed as well as supervised by qualified professionals who understand the physical and psychosocial uniqueness of children and adolescents. The SRT gives the practitioner the possibility to do so.<sup>24</sup> Hopefully this training program can also contribute in the quality of life for children with cancer.

Further research should investigate the reliability of the SRT in children with cancer. It is important to know the reliability of a measurement because of the consistency of a set of measurements. Considering the small sample size of this study, these results should be interpreted with caution, this gives opportunities for future research.

This study has several limitations that have to be taken into account when interpreting these outcomes. The study population was not homogenous. Children were included between age 8 and 18 years old and therefore growth and development phase and before or after puberty might have had influences on the study results. In addition, being on or of cancer treatment as well has his impact. On the contrary both tests were performed in the same person on the same day and therefore comparing the results of both tests was possible.

We did not randomize the order of tests. The test always started with the SRT and ended with the CPET. Therefore the fixed order could contribute to a systemic bias. Because this study was part of a larger study this could not be changed. However in a similar study in adolescents with cystic fibrosis by Werkman et al they performed the different protocols in the opposite way.<sup>25</sup> They found comparable outcomes as seen in this study. Therefore we do not think the systemic bias interferes with the outcomes of this study. The findings of this study can only be addressed to children with cancer other patient categories have to be investigated in the near future.

## **Conclusion**

The SRT is a safe and valid, novel short time maximal exercise test to estimate the  $VO_{2peak}$  for a child with cancer. The obtained  $W_{peak}$  on the SRT can give the daily practitioner indications for training intensity for this patient group and thereby contribute to a well-designed support to accomplish better results for exercise training in the near future.

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