

Physical exercise training interventions for children and young adults during and after treatment for childhood cancer (Review)

Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJL



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For Preview Only

[Intervention Review]

Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

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ABSTRACT

Background

A decreased physical fitness and impaired social functioning has been reported in patients and survivors of childhood cancer. This is influenced by the negative effects of disease and treatment of childhood cancer and by behavioural and social elements. Exercise training for adults during or after cancer therapy has frequently been reported to improve physical fitness and social functioning. More recently, literature on this subject became available for children and young adults with cancer, both during and after treatment.

Objectives

This review aimed to evaluate the effect of a physical exercise training intervention (at home, at a physical therapy centre, or hospital based) on the physical fitness of children with cancer, in comparison with the physical fitness in a care as usual control group. The intervention needed to be offered within the first five years from diagnosis.

The second aim was to assess the effects of a physical exercise training intervention in this population on fatigue, anxiety, depression, self efficacy, and health-related quality of life and to assess the adverse effects of the intervention.

Search methods

For this review the electronic databases of CENTRAL, MEDLINE, EMBASE, CINAHL, PEDro, and ongoing trial registries were searched on 6 September 2011. In addition, a handsearch of reference lists and conference proceedings was performed in that same month.

Selection criteria

The review included randomised controlled trials (RCTs) and clinical controlled trials (CCTs) that compared the effects of physical exercise training with no training, in people who were within the first five years of their diagnosis of childhood cancer.

Data collection and analysis

By the use of standardised forms two review authors independently identified studies meeting the inclusion criteria, performed the data extraction, and assessed the risk of bias. Quality of the studies was rated by using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) criteria.

Main results

Five articles were included in this review: four RCTs (14, 14, 28, and 51 participants) and one CCT (24 participants). In total 131 participants (74 boys, 54 girls, three unknown) were included in the analysis, all being treated for childhood acute lymphoblastic leukaemia (ALL). The study interventions were all implemented during chemotherapy treatment.

The duration of the training sessions ranged from 15 to 60 minutes per session. Both the type of intervention, as well as the intervention period, which ranged from 10 weeks to two years, varied in all the included studies. In all included studies the control group received care as usual.

All studies had methodological limitations, such as small numbers of participants, unclear randomisation methods, and single-blind study designs in case of an RCT.

Cardiorespiratory fitness was studied by the use of the nine-minute run-walk test, the timed up-and-down stairs test, and the 20-m shuttle run test. Only the up-and-down stairs test showed significant differences between the intervention and the control group, in favour of the intervention group (P value = 0.05, no further information available).

Bone mineral density was assessed in one study, in which a statistically significant difference in favour of the exercise group was identified (standardised mean difference (SMD) 1.07; 95% confidence interval (CI) 0.48 to 1.66; P value < 0.001). Body mass index was assessed in two studies. The pooled data on this item did not show a statistically significant difference between the intervention and control study group.

Flexibility was assessed in three studies. In one study the active ankle dorsiflexion method was used to assess flexibility and the second study they used the passive ankle dorsiflexion test. No statistically significant difference between the intervention and control group was identified with the active ankle dorsiflexion test, whereas with the passive test method a statistically significant difference in favour of the exercise group was found (SMD 0.69; 95% CI 0.12 to 1.25; P value = 0.02). The third study assessed body flexibility by the use of the sit-and-reach distance test; no statistically significant difference between the intervention and control group was identified.

One study assessed the effects of an inspiratory muscle training programme aimed to train the lung muscles and increase physical fitness. This study reported no significant effect on either inspiratory or expiratory muscle strength. Two other studies using either knee and ankle strength changes by hand-held dynamometry or the number of completed push-ups (with knees on the ground) and a peripheral quantitative computed tomography of the tibia to determine the muscle mass did not identify statistically significant differences in muscle strength/endurance.

The level of daily activity, health-related quality of life, fatigue, and adverse events were assessed in one study only; for all these items no statistically significant differences between the intervention and control group were found.

None of the included studies evaluated the outcomes activity energy expenditure, time spent exercising, anxiety and depression, or self efficacy.

Authors' conclusions

The effects of physical exercise training interventions for childhood cancer participants are not yet convincing due to small numbers of participants and insufficient study methodology. Despite that, first results show a trend towards an improved physical fitness in the intervention group compared to the control group. Changes in physical fitness were seen by improved body composition, flexibility, and cardiorespiratory fitness. However, the evidence is limited and these positive effects were not found for the other assessed outcomes, such as muscle strength/endurance, the level of daily activity, health-related quality of life, and fatigue. There is a need for more studies with comparable aims and interventions, using higher numbers of participants and for studies with another childhood cancer population than ALL only.

PLAIN LANGUAGE SUMMARY

Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Physical exercise training interventions for children and young adults during and after treatment for childhood cancer (Review)
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Childhood cancer is much less common than adult cancer at around 144 to 148 cases per one million children ([Cancer Research UK 2011](#); [National Cancer Institute 2012](#)). An intensive treatment, including combined treatment modalities such as surgery, chemotherapy, radiotherapy, or a combination, is often needed for cure. These treatment modalities are frequently accompanied by adverse events, such as nausea, serious infections, organ damage (heart, lung, kidney, liver), decreased bone density, but also decreased muscle strength and physical fitness.

In the past, children were advised to recover in bed, and to take as much rest as needed. Nowadays, it is considered that too much immobility may result in a further decrease of physical fitness and physical functioning. These adverse effects might be prevented or minimised by introducing a physical exercise training intervention during, or shortly after, childhood cancer treatment.

This review includes four randomised controlled trials and one clinical controlled trial that evaluated the effects of a physical exercise training programme in children during cancer treatment. Childhood acute lymphoblastic leukaemia (ALL) is the most common type of childhood cancer. For that reason, researchers often focus on this type of cancer. In total 131 participants with ALL were included in the analysis. The results of the review show that physical exercise training interventions can be performed in children with this type of cancer and that there are some small benefits on body composition (percentage of fat mass, muscles, and bones), flexibility, and cardiorespiratory fitness (endurance capacity). However, the evidence for a benefit on physical fitness of these interventions is limited due to methodological limitations of the included studies. More studies assessing the effects of exercise on body composition, muscle functioning, daily activity, psychological functioning, or a combination of these, are needed. Furthermore, the current findings do not provide enough evidence to identify the optimal physical exercise training programme for children with cancer, neither do they provide information on the characteristics of people who will, or will not, benefit from such a programme. These important issues still need to be clarified.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Patient or population: children and young adults during and after treatment for childhood cancer
Intervention: cardiorespiratory fitness outcomes after exercise intervention for children and adolescents during or after childhood cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cardiorespiratory fitness outcomes after exercise intervention for children and adolescents during or after childhood cancer				
9-minute run-walk test wheeled distance counter Follow-up: mean 4 months	The mean 9-minute run-walk test in the control groups was 3304.5 feet (1007.2 m)	The mean 9-minute run-walk test in the intervention groups was 0.33 standard deviations higher (0.42 lower to 1.07 higher)		28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.33 (-0.42 to 1.07)
Timed up-and-down stairs test stopwatch Follow-up: mean 4 months	The mean timed up-and-down stairs in the control groups was 8.6 seconds	The mean timed up-and-down stairs in the intervention groups was 0.11 standard deviations higher (0.64 lower to 0.85 higher)		28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.11 (-0.64 to 0.85)

*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; **SMD:** standardised mean difference

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.

¹ Total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect).

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

³ Published evidence is limited to a small number of trials.

BACKGROUND

Description of the condition

Only a small percentage of the total population suffer from childhood cancer; approximately 144 to 148 cases per million children (Cancer Research UK 2011; National Cancer Institute 2012). However the impact of childhood cancer is significant. Many studies report a decreased physical fitness (aerobic capacity and muscle strength) and a poor social functioning, in patients and survivors of acute lymphoblastic leukaemia (ALL), which is the most common type of childhood cancer (Aznar 2006; Hartman 2009; Hovi 1993; Marchese 2004; Moyer-Mileur 2009; San Juan 2008; Warner 1998; Warner 2008; Wright 1998; Wright 2005) and also in childhood cancer patients in general (Arroyave 2008; Cox 2008; De Caro 2006; Hartman 2008; Ness 2005; Ness 2009; Winter 2009). In addition, a considerable number of survivors of childhood cancer suffer from motor function disability (Geenen 2007; Van Brussel 2006). Motor function disability in patients or survivors of childhood cancer is mostly related to negative motor signs, such as insufficient muscle activity, or muscle weakness (Hartman 2008; Wright 2005). A 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 in childhood cancer patients (Warner 2008).

Positive effects of exercise training on physical fitness have been reported in studies with adult cancer patients (Cramp 2008; Oldervoll 2004; Schmitz 2005; Watson 2004). It is hypothesised that similar results are possible in children with cancer, or survivors of childhood cancer (Moyer-Mileur 2009).

Description of the intervention

The intervention under consideration was a physical exercise training programme, introduced within the first five years following the diagnosis of childhood cancer. The exercise training should aim to increase physical fitness by aerobic, anaerobic, strength, or mixed fitness training.

How the intervention might work

Cancer and cancer treatment induce lean tissue degeneration and can, therefore, potentially cause abnormalities in the cardiac and skeletal muscle (Schneider 2007). A decline in protein synthesis and protein degeneration by cancer and its treatment, can reduce muscle mass, the muscle fibre cross-section, and muscle extensibility. This can result in a decreased oxidative enzyme activity and a decreased number of proteins necessary for metabolism (Schneider 2007). Cancer patients often experience muscle weakness, a decreased functional capacity, decreased flexibility, reduced mobility, and diminished health-related quality of life (HRQoL)

(Hartman 2008; Schneider 2007). In addition, a decreased psychosocial functioning and HRQoL as a result of cancer has impact on a person's motivational drive and can result in a poorer self-perception of one's ability to perform physical activity (Warner 2008; Wright 1998).

Physical activity can prevent or diminish the negative effects of a sedentary life-style such as obesity, poor skeletal health, fatigue, and poor mental health, thereby increasing HRQoL of the individual. Increasing physical activity is possible by adopting a less inactive life-style and increasing sports participation. Beneficial effects of physical activity during or shortly after cancer therapy are an increase in muscle mass and plasma volume, improved lung ventilation and lung perfusion, and also an increased cardiac reserve, which can lead to a higher concentration of oxidative muscle enzymes.

This was seen in the study by Dimeo et al (2001); the children with cancer who received cancer treatment with glucocorticoids in combination with resistance exercises, showed less muscle mass loss than the children who did not receive the additional physical exercise training intervention (Dimeo 2001).

Why it is important to do this review

Despite the positive results of exercise interventions in adult cancer patients, the evidence for benefits in childhood cancer patients is limited. Studies within the population of childhood cancer patients and survivors have been initiated and the first data have been published. However, the number of participants in the various publications is small and the variety in type of cancer limited, making it difficult to draw conclusions. In making healthcare management decisions, participants and clinicians must weigh the benefits and drawbacks of supportive care. Pooled data can help in this decision-making process.

The purpose of this Cochrane review is to summarise the existing literature on the effectiveness of physical exercise training interventions in children with cancer, implemented within the first five years from diagnosis and to provide a best-evidence synthesis or meta-analysis of the reported results.

OBJECTIVES

Primary objective

To evaluate the effect of a physical exercise training intervention on the physical fitness (e.g. aerobic capacity, muscle strength, or functional performance) of children with cancer within the first five years from their diagnosis (performed either during or after cancer treatment), compared to a control group of childhood cancer patients who did not receive an exercise intervention.

Secondary objectives

To determine whether physical exercise within the first five years of diagnosis has an effect on fatigue, anxiety, depression, self efficacy, and HRQoL and to determine whether there are any adverse effects of the intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing the effects of physical exercise training within the first five years following the diagnosis of childhood cancer with no training.

A CCT was included in the review when the study included a well-defined and comparable control group. Factors that were taken into account regarding comparability were: being childhood cancer patients or survivors, age, sex, and country of origin.

We included cluster-randomised trials when the intervention and control groups were comparable in each aspect except for the location of cancer treatment and study recruitment.

We included cross-over trials when the study results were available for each separate intervention period. The data of the first randomisation period were then used.

Reviews were not included but were assessed for relevant references. In addition, we excluded observational studies (including case reports, case-control studies) and surveys from this review.

Types of participants

Study participants were under 19 years of age at diagnosis of any type of childhood cancer. Participants in the physical exercise training programme needed to be no more than five years from diagnosis. We only included studies that also included adult cancer participants when the results of the childhood and adult study populations were reported separately.

Types of interventions

Studies that were included compared a physical exercise training intervention for childhood cancer patients or survivors with a control group receiving care as usual. Care as usual is defined as care when needed, but no specific exercise programme or alternative intervention prescribed to increase physical fitness, HRQoL, self perception, or a combination of these, or to decrease adverse events, fatigue, anxiety, depression, or a combination of these in childhood cancer patients.

The physical exercise training interventions that were offered included different types of training or exercise programmes. For instance, muscle strength or stretching exercises, aerobic exercises, or sports such as gymnastics, swimming, running, or bicycling.

The exercise training intervention could have been additional care during therapy or could have been offered after the standard cancer therapy in a form of rehabilitation. The goals of this exercise training intervention were preventing motor disabilities and a decline in physical fitness, or treating motor function problems which developed during childhood cancer therapy.

The exercise training intervention could have taken place in any setting or location: at home, at a physical therapy centre, in a hospital, or elsewhere. It could either have been a group intervention, or an individual programme.

The duration of the exercise training intervention needed to be at least four weeks, in order to be able to report on exercise training effects. The upper limit of the training duration was not fixed for this review. In addition, the duration of physical activities (daily time spent on activities or sports) could differ per protocol.

Types of outcome measures

We included studies evaluating the effect of physical exercise training interventions on physical fitness, HRQoL, fatigue, self efficacy, anxiety and depression. Furthermore adverse effects of the intervention programme were studied.

Primary outcomes

The primary outcome of this review was physical fitness measured by:

1. cardiorespiratory fitness (e.g. peak oxygen uptake (VO_{2peak}), peak work rate (W_{max}), endurance time): aerobic or anaerobic exercise capacity tested by ergometry on a cycle ergometer or treadmill, the Wingate anaerobic test, the steep-ramp-test, maximal anaerobic running/cycling test, the Cooper test, or another valid instrument;
2. muscle endurance/strength: assessed with a hand-held dynamometer, the Biodex, the spring scale, the lateral step-up test, the sit-to-stand test, 10 repetitions maximum, the up-and-down stairs test, the minimum chair height test, the muscle power sprint test, a 10 x 5-m sprint test, the six-minute walk test, the incremental shuttle walking test, or another valid instrument;
3. body composition: using body mass index (BMI), skin-fold measurement, a dual energy x-ray absorptiometry (DXA) scan, waist circumference, or the waist-to-hip-ratio;
4. flexibility: conducted with a goniometer, flexometer or with the sit-and-reach test, V-sit test, shoulder or trunk rotation test, straight leg raise, the passive and active ankle dorsiflexion test, or another valid instrument;
5. activity energy expenditure: for example by using an accelerometer;

6. level of daily activity: assessed by an exercise diary, questionnaire, or by accelerometry;
7. time spent exercising (more than daily activity): assessed by an exercise diary, questionnaire, or by accelerometry

Secondary outcomes

Secondary outcomes of the review were:

1. HRQoL: measured by the Paediatric Quality of Life Inventory (PedsQL), Child Health Questionnaire (CHQ), and DISABKIDS;
2. fatigue: assessed by the PedsQL Multidimensional Fatigue Scale, Childhood Cancer Fatigue Scale (CCFS), or the Fatigue Scale for a child (FS-C), the same scale for adolescents (FS-A), and for parents (FS-P);
3. anxiety and depression: measured by the Childhood Depression Inventory (CDI) and the Center of Epidemiological Studies Depression Scale (CES-D);
4. self efficacy: assessed using the Confidence Scale, the Self-Efficacy Questionnaire for Children (SEQ-C), or the Children's Self-Efficacy Scale;
5. adverse effects during the study period by collecting information on the occurrence of sport injuries, infections, fractures, heart failure, the recurrence of cancer, and fever.

Search methods for identification of studies

Electronic searches

For this review electronic databases of The Cochrane Central Library of Controlled Trials (CENTRAL) (*The Cochrane Library*, 6 September 2011, Issue 3), MEDLINE/PubMed (from 1945 to 6 September 2011), EMBASE/Ovid (from 1980 to 6 September 2011), CINAHL (from 1982 to 6 September 2011), and Physiotherapy Evidence Database (PEDro; from 1929 to 6 September 2011) (www.pedro.org.au/) were searched.

The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are stated in the appendices ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#)).

Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE, EMBASE, CINAHL, and PEDro, either published or unpublished, by searching the reference lists of relevant articles and reviews. We scanned the conference proceedings of the International Society for Paediatric Oncology (SIOP), the American College of Sports Medicine (ACSM), the International Congress on Physical Activity and Public Health (ICPAPH), and the American Physical Therapy Association (APTA) electronically, or otherwise by handsearching from 2005 to 2011.

A search was performed in the ISRCTN register, the register of the National Institute of Health (both at www.controlled-trials.com), and the clinical trial database (www.clinicaltrials.gov) for ongoing trials on the 26 September 2011. We did not impose language restrictions and will update the searches every two years.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, identification of studies meeting the inclusion criteria was undertaken by two review authors (KB, PT) independently. We obtained in full any study that seemed to meet the inclusion criteria on title and abstract, for closer inspection. Reasons for exclusion were noted on a separate form. Discrepancies between review authors were solved by reaching consensus. In one case, a third party arbitrator (TT) was needed: we required another opinion on the study of [Macedo 2010](#). This discussion resulted in inclusion of that study because the training corresponded with the described criteria of the protocol.

Data extraction and management

Data extraction was performed independently by the two review authors (KB, PT) using standardised forms. For each study we collected information on the study design, participant baseline characteristics, settings, sample size, number of participants in each study arm, type of intervention(s), duration of intervention, randomization and blinding procedure, type of control group, type and duration of cancer treatment and stage of cancer treatment (for example, during or after treatment), and duration of participant follow-up.

The extracted outcome measures included: changes in cardiorespiratory fitness, muscle strength/endurance, body composition, body flexibility, daily energy expenditure per time period (for example, day, week, or month), and changes in the level of daily activity and time spent exercising. In addition, we used a separate form to collect information on psychosocial outcomes such as HRQoL, fatigue, anxiety and depression, and the child's self efficacy. To collect data regarding any other adverse effect of the intervention, we collected all information reported on adverse events during the intervention period in the included studies. Authors of the studies of which only an abstract was available were contacted for additional study information.

In the process of data extraction consensus was reached on all items.

Assessment of risk of bias in included studies

The two review authors (KB, PT) independently assessed the risk of bias in the included RCTs and CCT. This was done according

to the following criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias, such as significant baseline imbalance between study groups in pre-score or baseline outcome data. We also looked at differential diagnostic activity to observe differences in study protocol for the intervention group and the control group.

For all 'Risk of bias' items of the included studies we used the definitions as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included a 'Risk of bias' summary figure. This figure shows whether a study had a high, low, or unclear risk of bias; a green plus symbol corresponds with a low risk of bias, a red minus symbol corresponds with a high risk of bias and the yellow question mark symbol corresponds with lack of information or uncertainty over the potential for bias. Discrepancies between review authors were discussed and solved so consensus was reached. Quality of the outcomes in the different studies was rated by using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) criteria (Guyatt 2008; Guyatt 2008a). 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 we can be confident that an estimate of effect or association is close to the quantity of specific interest. 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 are: 1) study limitations; 2) inconsistency of results; 3) indirectness of evidence; 4) imprecision; and 5) publication bias. Factors that may increase the quality of evidence are: 1) large magnitude of effect; 2) plausible confounding, which would reduce a demonstrated effect; and 3) dose-response gradient (Guyatt 2008a). The two review authors performed the quality of evidence grading simultaneously. In case of disagreement they discussed even minor aspects to reach consensus on that matter.

Measures of treatment effect

The main outcome differences between study groups and pooled data are described in the [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#); and [Summary of findings 6](#). In these tables the illustrative comparative risks (with 95% confidence interval (CI)) and differences in standardised mean difference (SMD) are provided. For the Cohen's SMD, data were taken from the post-training/control period measurement. The results of the review also include effect estimates of the intervention per outcome measure. Across the included studies different outcome assessing scales were used. However, in case of BMI we were able to combine data of two studies.

For the interpretation of the Cohen's SMD we used the following criteria (Higgins 2011):

- less than 0.41 represents a small effect;
- 0.40 to 0.70 represents a moderate effect;
- greater than 0.70 represents a large effect.

Dealing with missing data

Relevant missing data were sought by contacting the primary study author or the corresponding study author. To optimise the strategy for dealing with missing data, we used an intention-to-treat (ITT) analysis when possible. The ITT analysis includes all participants who did not receive the assigned intervention according to the protocol as well as those who were lost to follow-up. Attrition rates, for example dropouts and withdrawals, were investigated to optimize data analyses.

Assessment of heterogeneity

Heterogeneity was assessed both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, that is the I^2 statistic. Significant heterogeneity was defined as $I^2 > 50\%$ (Higgins 2011). In case of heterogeneity, we assessed the following potential sources of clinical heterogeneity: 1) participant characteristics; 2) intervention setting; and 3) stratification methods within studies. When heterogeneity was found, we assessed potential reasons for the differences by examining the study characteristics.

Assessment of reporting biases

In the protocol we had planned to perform a funnel plot, however, due to an insufficient number of studies (fewer than 10) included in this review, we were not able to do so (Higgins 2011).

Data synthesis

The data of the included studies were entered into Review Manager software (RevMan 2011). The analyses were performed according to the updated *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). By using the GRADE criteria, the quality of the included studies was taken into account when interpreting the results for the review. We used the random-effects model throughout the review. When we were unable to perform meta-analysis, we provided all available effect information from the articles.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to evaluate whether the outcome was influenced by differences in the age of the participant, the delivered type of physical exercise training intervention, the duration of the exercise training intervention, the exercise training intervention location, type of childhood cancer, and cancer treatment. However, only a meta-analysis on BMI could be performed

and for this outcome it was not possible to perform subgroup analysis. Apart from the intervention and control groups, BMI data were not available per subgroup (Hartman 2009; Moyer-Mileur 2009).

Sensitivity analysis

For those studies that assessed similar outcomes and of which data could be pooled, we performed sensitivity analyses. We assessed whether the outcome would have been different when a study with high or unclear risk of bias would have been excluded from the analyses. This method aimed to assess whether the findings were robust to the decisions made in the process of obtaining them.

RESULTS

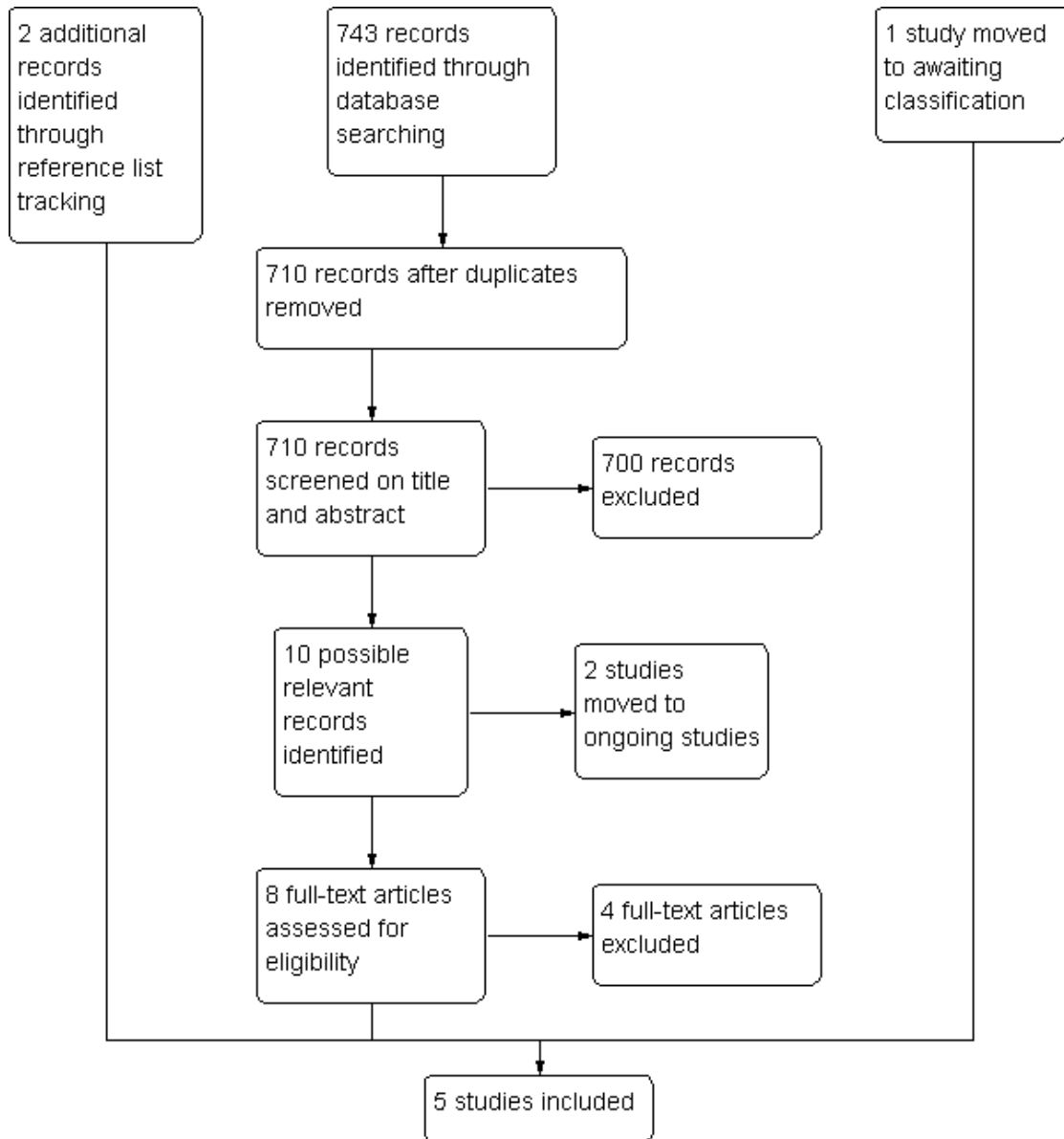
Description of studies

Results of the search

Running the searches in the electronic databases of CENTRAL, MEDLINE, EMBASE, CINAHL, and PEDro; searching the ongoing trial registries; plus searching the abstract books from SIOB, ACSM, ICPAPH, and APTA yielded 743 references.

After removal of duplicates, this search resulted in 710 potentially relevant articles. Initial screening of titles and abstracts excluded a further 700 references that did not meet the criteria for inclusion. The 10 remaining references were read in full text. Two of these 10 studies were ongoing trials, four studies did not meet all eligibility criteria and were thus excluded and four studies were included. Reference list tracking led to two additional articles that could potentially be included: one of these studies met all eligibility criteria and was thus included, whereas it was not possible to decide if the second study was eligible for inclusion based on the currently available information (Figure 1).

Figure 1. Study flow diagram.



Five studies were included, we also identified two ongoing trials (see [Characteristics of ongoing studies](#)) and one study is awaiting classification (see [Characteristics of studies awaiting classification table](#)).

Included studies

Methods

Five articles were included in this review ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)). Four of these studies were RCTs, and one study used a quasi-experimental study design, making it a CCT ([Yeh 2011](#)). One study performed a power calculation ([Hartman 2009](#)). For trial characteristics and outcomes see the '[Characteristics of included studies](#)' table.

Participants

From the five included articles 131 participants were included in the analysis. All were children diagnosed with ALL and studied during chemotherapy for childhood ALL ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)). Of the 131 children, 74 were boys, 54 girls ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)), and the sex of the three children who dropped-out was not reported. The numbers of children per study were small. [Hartman 2009](#) included the most children (n = 51) in their study, with 26 children in the usual care group and 25 in the intervention group. The 14 children in the study of [Macedo 2010](#) were divided in nine children who received care as usual and five who received the intervention. [Marchese 2004](#) included 13 children that performed the exercise intervention and 15 who had care as usual. The 13 children analysed in the study of [Moyer-Mileur 2009](#) were divided in seven who received care as usual and six received the intervention; one child was lost to follow-up. [Yeh 2011](#) included 22 children in the analyses of which 12 children received the intervention training programme and 10 received care as usual; two children were lost to follow-up.

Four studies reported their exclusion criteria; in one study no exclusion criteria were reported ([Moyer-Mileur 2009](#)). Cognitive or mental (developmental), or both, impairment were exclusion criteria in three studies ([Hartman 2009](#); [Marchese 2004](#); [Yeh 2011](#)). Having difficulties with the national language was described in one study ([Hartman 2009](#)). Children with neurological impairment could not participate in three studies ([Macedo 2010](#); [Marchese 2004](#); [Yeh 2011](#)). [Marchese 2004](#) excluded children with a genetic disorder, as well as children who were already receiving physiotherapy. Children with a chronic lung disease, neuromuscular disease, or those treated with radiotherapy could not participate in the Brazil study of [Macedo 2010](#).

Intervention

Aimed to increase physical fitness, all five studies included a home-based exercise programme, with guidance from a therapist of the treating hospital ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)). However, the duration of the entire intervention, the duration of each training session, the timing and the type of the interventions, differed across studies. The duration of the training sessions ranged from 15 minutes up to 60 minutes. The intervention period ranged from 10 weeks ([Macedo 2010](#); [Yeh 2011](#)) to two years ([Hartman 2009](#)). Four out of five studies introduced the exercise intervention during the maintenance treatment period ([Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)) and in one study it started shortly after diagnosis ([Hartman 2009](#)). Four studies determined the effects of an exercise intervention to increase muscle strength of all muscles ([Hartman 2009](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)). The study of [Macedo 2010](#) investigated the effect of an inspiratory muscle training programme. They studied the effects of a domiciliary inspiratory muscle training, which was performed with a threshold device using a load of 30% of the maximal inspiratory pressure.

For more details see the information in the [Characteristics of included studies](#) table

Control

The control groups of all five studies received care as usual ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)). With the exception of those of the study of [Macedo 2010](#), all study participants of the control groups were measured at the same time points as the intervention group.

The control group in the study of [Macedo 2010](#) performed the study assessments during the initial evaluation and after 10 weeks, whereas the intervention group performed the measurements at the end of each training week.

Outcomes

The studied primary outcomes were: cardiorespiratory fitness, muscle endurance/strength, body composition, flexibility, and level of daily activity. Secondary outcomes of this review that were mentioned in the studies were: HRQoL, fatigue, and adverse events. The other secondary outcomes (anxiety, depression, and self efficacy) were not addressed.

Because of the different aims and study methods of the five included studies, there was little to no overlap in assessed outcomes. Only changes in BMI, which is part of the information concerning body composition, were assessed in two studies ([Hartman 2009](#);

Moyer-Mileur 2009). For further information see [Characteristics of included studies](#) table and the [Data and analyses](#) tables.

Excluded studies

Four publications had been retrieved, but were subsequently excluded. One was a non-peer-reviewed conference proceeding, presenting data of a pilot study (Te Winkel 2008). The full study data were reported by Hartman 2009 and were included in this review. The second study used a cross-over design but did not publish the between-group evaluation after the first block (Speyer 2010).

Unfortunately the corresponding author did not respond to our requests for these missing data, therefore we had to exclude this report. The last two studies assessed the effects of a training intervention with duration of less than four weeks (Chamorro-Vina 2010; Hinds 2007). Information concerning the excluded references can be found in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

See the risk of bias section of the [Characteristics of included studies](#) table and [Figure 2](#) for the exact scores per study and the support for the judgements made.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hartman 2009	+	?	-	+	-	+	+
Macedo 2010	?	?	-	?	?	+	-
Marchese 2004	+	?	-	+	?	+	?
Moyer-Mileur 2009	?	?	-	?	?	+	+
Yeh 2011	-	-	-	?	+	-	?

Allocation

The random sequence generation was adequately generated in two out of the five studies (Figure 2; Hartman 2009; Marchese 2004). These two studies used block randomisation with sealed envelopes (Hartman 2009; Marchese 2004). Macedo 2010 reported that selection and allocation were random; however, it remained unclear how the randomisation was carried out. A non-randomised design was used in the study of Yeh 2011, leading to a high risk of selection bias. No information on random sequence generation was available for the fifth study (Moyer-Mileur 2009). None of the studies described the quality of the envelopes, how the envelopes were sealed, or whether they were coded. Therefore four out of five studies were judged to have an unclear risk of bias for allocation concealment (Hartman 2009; Macedo 2010; Marchese 2004; Moyer-Mileur 2009). One study did not use a randomisation method and therefore had no allocation concealment (Yeh 2011). In summary, four studies had an unclear risk of selection bias and one study had a high risk of selection bias.

Blinding

Blinding of participants and personnel (performance bias)

Due to the nature of the interventions blinding was virtually impossible: that is when the participants need to perform an exercise intervention and the children and their parents are well informed about the study purpose, participants cannot be blinded for the study randomisation. This could be a potential performance bias in all studies (Higgins 2011). Therefore, all included studies of this review were thought to have a high risk for performance bias.

Blinding of outcome assessors (detection bias)

It is possible to minimise detection bias with blinding the outcome assessor for the randomisation. Two studies used outcome assessors who were blinded for study groups (Figure 2; Hartman 2009; Marchese 2004). In the other three studies the risk was unclear.

Incomplete outcome data

All studies reported withdrawals and drop-outs during the intervention period. However, only one study used an ITT analysis to deal with missing data and thus had a low risk of attrition bias (Yeh 2011).

In the study of Marchese 2004, the authors reported missing data for daily logs of activity and heart monitor. Yet no information was reported on methods used for data imputation. For the two other studies, it also remained unclear whether they used a (valid) method for missing data imputation (Macedo 2010;

Moyer-Mileur 2009). In all these three studies the risk of attrition bias was thus unclear.

In the final study (Hartman 2009), there was a high risk of attrition bias. The authors used a simple imputation technique to include data for those children who dropped out of the study. Yet, they included the data from prior to the elimination. This method is very simple and therefore increases the risk for bias due to incomplete outcome data.

Selective reporting

In one study serious selective reporting was detected (Yeh 2011). In this study, 'adherence' was mentioned to be an extra or a secondary outcome. Yet, in the results the authors focused on this item as if it was a primary outcome. In the four other studies the risk of reporting bias was low.

Other potential sources of bias

In this review we also looked at differences in baseline outcome data. The absence of significant differences in baseline outcome data were reported in three studies (Hartman 2009; Macedo 2010; Moyer-Mileur 2009). However, in two studies it remained unclear whether all baseline test scores were significantly different between the two study groups (Marchese 2004; Yeh 2011).

The study of Macedo 2010 had a different study measurement regimen for children in the control group compared with those in the intervention group. The control group of this study performed the study assessments during the initial evaluation and after 10 weeks, whereas the intervention group performed the measurements at the end of each training week. This could have led to differential diagnostic activity. We judged this study to be of high risk for this other type of bias. The other studies used the same number of measurements, and they were free of differential diagnostic activity (Hartman 2009; Marchese 2004; Moyer-Mileur 2009; Yeh 2011).

In summary, the combination of these two other biases showed that for two studies the risk of 'other biases' was unclear (Marchese 2004; Yeh 2011), for one study the risk was considered high (Macedo 2010), and for the other two the 'other' risk was low (Hartman 2009; Moyer-Mileur 2009).

Effects of interventions

See: [Summary of findings for the main comparison](#) [Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer](#); [Summary of findings 2](#) [Body composition outcomes after physical exercise training intervention for children](#)

and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer; **Summary of findings 3** Flexibility outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer; **Summary of findings 4** Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer; **Summary of findings 5** Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer; **Summary of findings 6** Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Because of the different aims and study methods of the five included studies there was little to no overlap in assessed outcomes. Only for one item (BMI) pooling of results was possible.

Cardiorespiratory fitness

In this review cardiorespiratory fitness could be: peak oxygen uptake (VO_2 peak), peak work rate (W_{max}), or endurance time. In the included studies physical fitness was assessed by the nine-minute run-walk test (Marchese 2004), timed up-and-down stairs test (Marchese 2004), and by the 20-m shuttle run test (Moyer-Mileur 2009).

The nine-minute run-walk test (SMD 0.33; 95% CI -0.42 to 1.07; P value = 0.39) as well as the timed up-and-down stairs test (SMD 0.11; 95% CI -0.64 to 0.85; P value = 0.78) did not show a significant difference in the SMD for the intervention (n = 13) or the control group (n = 15) (Analysis 1.1; Analysis 1.2). Marchese 2004 reported one dropped-out. Data for that child were not taken into account in the analysis, only data for children who completed the trial were used; therefore no ITT analysis was conducted.

Results of the 20-m shuttle run test showed that children who performed home-based exercises during their maintenance chemotherapy for ALL (six children) were able to perform more laps than those in the control group (seven children) (P value = 0.05) (no RevMan data available). ITT analysis was not performed (Moyer-Mileur 2009).

Body composition

Bone mineral density (BMD) (Hartman 2009) and BMI (Hartman 2009; Moyer-Mileur 2009) were assessed in order to collect data on body composition.

The study of Hartman 2009 used a DXA scan to determine BMD (lumbar spine and a whole body) changes in childhood ALL participants. The assessments were performed at diagnosis, during

chemotherapy for childhood ALL, and one year after the end of treatment. Analysis showed a significant SMD 1.07 (95% CI 0.48 to 1.66; P value < 0.001) (Analysis 2.1) indicating a large and significant positive effect on the BMD for the intervention group (n = 25) compared to the control group (n = 26). This analysis was performed according to the ITT analysis principles.

Differences in BMI between the intervention group and the control group were studied in two trials, and both studies did not find BMI differences between, or within, either study group (Hartman 2009; Moyer-Mileur 2009). Moyer-Mileur 2009 tested six children with a nutrition and exercise programme compared to seven children who received care as usual. The SMD results showed no effect (SMD 0.02; 95% CI -1.07 to 1.11). In this study the data of the child who dropped out were not taken into analyses, therefore no ITT analysis on this item was performed in this review. The study of Hartman 2009 showed a statistically significant difference on BMI in favour of the exercise group (n = 25) compared to the control group (n = 26) (SMD 0.90; 95% CI 0.32 to 1.48). These BMI analyses were performed according to ITT analysis principles (Hartman 2009).

Analysis of BMI showed a non-significant moderate effect with an SMD of 0.59 (95% CI -0.23 to 1.41; P value = 0.16) (Analysis 2.2) in favour of the intervention group. In addition, analysis also showed no substantial heterogeneity ($I^2 = 48\%$) for this item between the studies (Analysis 2.2).

Flexibility

In two studies the ankle dorsiflexion range of motion was measured. However, in one study this was done in a passive way (Hartman 2009) and in the other by active contraction (Marchese 2004). Therefore data could not be pooled.

According to the ITT analysis shown in Analysis 3.1, the passive ankle dorsiflexion showed a moderate significant positive effect for the 25 children in the intervention group compared to the 26 children in the control group (SMD 0.69; 95% CI: 0.12 to 1.25; P value = 0.02) (Hartman 2009). Analysis of the ankle dorsiflexion range of motion, measured in active contraction, showed a non-significant moderate effect in the intervention group (13 children) compared to the control group (15 children) (SMD 0.46; 95% CI -0.29 to 1.22; P value = 0.23) (Analysis 3.1) (Marchese 2004). Because Marchese 2004 only provided the data of the children who finished all measurements, no ITT analysis was performed. The study of Moyer-Mileur 2009 assessed body flexibility by the use of the sit-and-reach distance test. In this study there was no difference in the test results between the six children of the intervention and seven children of the control group. P values and ITT analysis were not stated in the text or provided by the authors.

Muscle endurance/strength

Marchese 2004 assessed the knee and ankle strength changes by hand-held dynamometry in both the intervention group (13 chil-

dren) and the control group (15 children). Over time the authors found a significant effect in favour of the intervention group. Analysis showed that differences between the end scores of the intervention group and the control group were not significantly different for both knee and ankle strength (Analysis 4.1; Analysis 4.2). The SMD of the knee strength was 0.25 (95% CI -0.49 to 1.00; P value = 0.51) and the increase of ankle strength was 0.29 (95% CI -0.46 to 1.04; P value = 0.44) (Marchese 2004).

The study of Moyer-Mileur 2009 determined differences in number of completed push-ups (with knees on the ground) and used a peripheral quantitative computed tomography of the tibia to determine the muscle mass of the participants. According to the original study data, there was no significant change in maximal number of push-ups or muscle mass, within or between the intervention (six children) and control group (seven children). The report of this study did not include the data of these results, therefore the RevMan analysis could not be done.

Respiratory muscle strength of the Brazilian ALL population was determined by measuring the maximal inspiratory pressure and maximal expiratory pressure with a digital manometer and a nozzle to dissipate additional pressure caused by the facial muscles and the oropharynx (Macedo 2010). In the intervention group (five children) the authors found a significant improvement over time compared to the control group (nine children). Yet, the end score differences were not significant between the study groups; SMD for inspiratory breathing muscle strength was 0.33 (95% CI -0.77 to 1.43; P value = 0.56), for expiratory breathing muscle strength the SMD was 0.00 (95% CI -1.09 to 1.09; P value = 1.00) (Analysis 4.3; Analysis 4.4).

Due to invalid methods used for missing data imputation, an ITT analysis could not be performed for these outcomes.

Activity energy expenditure

No information was available for activity energy expenditure as it was not assessed in the included studies.

Level of daily activity

Daily physical activity of the participants was assessed in one study (Moyer-Mileur 2009). They used both the pedometer steps-per-day and an activity questionnaire to examine physical activity behaviour. This study showed that the six children of the intervention group increased in approximately the same amount in "reported activity in minutes per day" over time. In the control group three out of seven children increased in their reported activity in minutes per day. According to the original analyses the reported activities at baseline and at six months were not statistically significantly different between the intervention group and the control group (Moyer-Mileur 2009). At 12 months from baseline a higher number of steps was recorded in the intervention group compared with the controls, but this difference was of borderline

statistical significance (P value = 0.06) (no RevMan data available) (Moyer-Mileur 2009). This analysis was not performed according to the ITT procedure.

Time spent exercising (more than daily activity)

No information was available for activity energy expenditure as it was not assessed in the included studies.

Health-related quality of life

HRQoL in general and HRQoL related to cancer were assessed by the PedsQL version 3.0 in the study of Marchese 2004. There were no significant differences on the child cancer PedsQL, child general PedsQL, the parent cancer PedsQL and the parent general PedsQL over the four-month study period between the intervention (13 children) and control group (15 children). The end scores were not significantly different between the groups. The PedsQL Generic showed a non-significant small estimate of effect with an SMD of -0.23 (95% CI -0.98 to 0.51; P value = 0.54) (Analysis 5.1) and for PedsQL Cancer there was no statistically significant effect (SMD 0.16; 95% CI -0.58 to 0.91; P value = 0.66) (Analysis 5.2). A small to moderate non-significant effect was seen on the parent Peds-QL general questionnaire (SMD 0.38; 95% CI -0.37 to 1.13; P value = 0.32) (Analysis 5.3) and for the cancer-specific PedsQL module filled in by parents no statistically significant differences were reported (SMD 0.04; 95% CI -0.70 to 0.79; P value = 0.91) (Analysis 5.4).

Due to missing data an ITT analysis could not be conducted.

Fatigue

Yeh 2011 measured the effect of the exercise intervention on fatigue. This study used the PedsQL multidimensional fatigue scale. They compared the fatigue change patterns between the intervention group (12 children) and the control group (10 children) over eight time points within 10 weeks. There were no significant differences between the intervention and control group using the PedsQL general fatigue scale (SMD -0.04; 95% CI -0.88 to 0.80; P value = 0.92) (Analysis 6.1), the sleep/rest fatigue items (SMD -0.01; 95% CI -0.85 to 0.83; P value = 0.98) (Analysis 6.2), or the assessed cognitive fatigue items (SMD 0.07; 95% CI -0.77 to 0.91; P value = 0.86) (Analysis 6.3). Fatigue was assessed by the an ITT analysis.

Anxiety and depression

No information was available for anxiety and depression as these items were not assessed in the included studies.

Self efficacy

No information was available for self efficacy as this item was not assessed in the included studies.

Adverse events (due to, or not clearly related to, the intervention)

The study of [Marchese 2004](#) reported that no children had any negative effects from the exercises or experienced complications attributed to the physical programme. The other studies did not report on this item ([Hartman 2009](#); [Macedo 2010](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)).

Sensitivity analysis

Sensitivity analyses were performed for those outcomes for which pooling was possible (i.e. BMI) ([Hartman 2009](#); [Moyer-Mileur](#)

[2009](#)). We assessed whether the outcome would have been different when a study with high or unclear risk would have been excluded in the review analyses.

For two bias items: random sequence generation (selection bias) and blinding of outcome assessors (detection bias), the study of [Hartman 2009](#) had a low risk, while for the study of [Moyer-Mileur 2009](#) the risk was unclear. For these items sensitivity analyses were possible. For all other risk of bias items the two studies scored the same (i.e. low, high, or unclear risk) or performed a combination of high and unclear risk.

The outcome of the sensitivity analysis showed the BMI data of [Hartman 2009](#) without [Moyer-Mileur 2009](#) (SMD 0.90; 95% CI 0.32 to 1.48). The results of the pooled data were SMD 0.59 (95% CI -0.23 to 1.41). The results of the sensitivity analyses thus were consistent among the trials and did not differ from the overall analyses.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Outcomes		Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Body composition outcomes after exercise intervention for children and adolescents during or after childhood cancer				
Bone mineral density DXA scan Follow-up: mean 24 months	The mean bone mineral density in the control groups was -1.1412 standard deviation	The mean bone mineral density in the intervention groups was 1.07 standard deviations higher (0.48 to 1.66 higher)		51 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 1.07 (0.48 to 1.66)
Body mass index Queitlet Index Follow-up: mean 18 months		The mean body mass index in the intervention groups was 0.59 standard deviations higher (0.23 lower to 1.41 higher)		64 (2 studies)	⊕○○○ very low ^{1,2,3,4}	SMD 0.59 (-0.23 to 1.41)

*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; **DXA**: dual-energy x-ray absorptiometry; **SMD**: standardised mean difference

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.

¹ Total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect).

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

³ Published evidence is limited to a small number of trials.

⁴ Not in all studies outcome-accessors were blinded.

Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Patient or population: children and young adults during and after treatment for childhood cancer
Intervention: flexibility outcomes after exercise intervention for children and adolescents during or after childhood cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Body composition outcomes after exercise intervention for children and adolescents during or after childhood cancer				
Flexibility - active ankle dorsiflexion Goniometry Follow-up: mean 4 months	The mean flexibility - active ankle dorsiflexion in the control groups was 9.8 degrees	The mean flexibility - active ankle dorsiflexion in the intervention groups was 0.46 standard deviations higher (0.29 lower to 1.22 higher)		28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.46 (-0.29 to 1.22)
Flexibility - passive ankle dorsiflexion Goniometry Follow-up: mean 24 months	The mean flexibility - passive ankle dorsiflexion in the control groups was 3.96 degrees	The mean flexibility - passive ankle dorsiflexion in the intervention groups was 0.69 standard deviations higher (0.12 to 1.25 higher)		51 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.69 (0.12 to 1.25)

*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; **SMD:** standardised mean difference

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.

¹ Total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect).

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

³ Published evidence is limited to a small number of trials.

Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Patient or population: children and young adults during and after treatment for childhood cancer Intervention: muscle endurance/strength outcomes after exercise intervention for children and adolescents during or after childhood cancer		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Outcomes	Illustrative comparative risks* (95% CI)				
	Assumed risk	Corresponding risk			
	Control	Muscle endurance/strength outcomes after exercise intervention for children and adolescents during or after childhood cancer			
Knee strength Hand-held dynamometer Follow-up: mean 4 months	The mean knee strength in the control groups was 0.37 standard deviation	The mean knee strength in the intervention groups was 0.25 standard deviations higher (0.49 lower to 1 higher)	28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.25 (-0.49 to 1)
Ankle Strength Hand-held dynamometer Follow-up: mean 4 months	The mean ankle dorsiflexion strength in the control groups was 0.22 standard deviation	The mean ankle dorsiflexion strength in the intervention groups was 0.29 standard deviations higher (0.46 lower to 1.04 higher)	28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.29 (-0.46 to 1.04)

<p>Inspiratory breathing muscle strength Digital manometer (GlobalMedia-MVD 300) Follow-up: mean 10 weeks</p>	<p>The mean inspiratory breathing muscle strength in the control groups was 59.8 cmH₂O</p> <p>The mean inspiratory breathing muscle strength in the intervention groups was 0.33 standard deviations higher (0.77 lower to 1.43 higher)</p>	<p>14 (1 study)</p> <p>⊕○○○ very low^{1,2,3,4}</p>	<p>SMD 0.33 (-0.77 to 1.43)</p>
<p>Expiratory breathing muscle strength Digital manometer (GlobalMedia-MVD 300)</p>	<p>The mean expiratory breathing muscle strength in the control groups was 83.4 cmH₂O</p> <p>The mean expiratory breathing muscle strength in the intervention groups was 0 standard deviations higher (1.09 lower to 1.09 higher)</p>	<p>14 (1 study)</p> <p>⊕○○○ very low^{1,2,4}</p>	<p>SMD 0 (-1.09 to 1.09)</p>

*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; **cmH₂O:** centimetres of water pressure; **SMD:** standardised mean difference

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.

¹ Total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect).

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

³ Published evidence is limited to a small number of trials.

⁴ Not in all studies outcome-assessors were blinded.

Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Patient or population: children and young adults during and after treatment for childhood cancer Intervention: health-related quality of life outcomes after exercise intervention for children and adolescents during or after childhood cancer		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Outcomes	Illustrative comparative risks* (95% CI)				
	Assumed risk	Corresponding risk			
	Control	Health-related quality of life outcomes after exercise intervention for children and adolescents during or after childhood cancer			
Health-related quality of life PedsQL - General questionnaire (version 3.0) Follow-up: mean 4 months	The mean health-related quality of life in the control groups was 17.5	The mean health-related quality of life in the intervention groups was 0.23 standard deviations lower (0.98 lower to 0.51 higher)	28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD -0.23 (-0.98 to 0.51)
Cancer-specific health-related quality of life PedsQL - Cancer questionnaire Follow-up: mean 4 months	The mean cancer-specific health-related quality of life in the control groups was 14.53	The mean cancer-specific health-related quality of life in the intervention groups was 0.16 standard deviations higher (0.58 lower to 0.91 higher)	28 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.16 (-0.58 to 0.91)

*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; **PedsQI:** Paediatric Quality of Life Inventory; **SMD:** standardised mean difference.

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.

¹ Total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect).

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

³ Published evidence is limited to a small number of trials.

Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer for children and young adults during and after treatment for childhood cancer

Patient or population: children and young adults during and after treatment for childhood cancer Intervention: fatigue outcomes after exercise intervention for children and adolescents during or after childhood cancer		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Outcomes	Illustrative comparative risks* (95% CI)				
	Assumed risk	Corresponding risk			
	Control	Fatigue outcomes after exercise intervention for children and adolescents during or after childhood cancer			
General fatigue PedsQL - fatigue questionnaire Follow-up: mean 6 weeks	The mean general fatigue in the control groups was 3.4	The mean general fatigue in the intervention group was 0.04 standard deviations lower (0.88 lower to 0.8 higher)	22 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD -0.04 (-0.88 to 0.8)
Sleep/rest fatigue PedsQL - fatigue questionnaire Follow-up: mean 6 weeks	The mean sleep/rest fatigue in the control groups was 5.7	The mean sleep/rest fatigue in the intervention group was 0.01 standard deviations lower (0.85 lower to 0.83 higher)	22 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD -0.01 (-0.85 to 0.83)
Cognitive fatigue PedsQL - fatigue questionnaire Follow-up: mean 6 weeks	The mean cognitive fatigue in the control groups was 3.5	The mean cognitive fatigue in the intervention group was 0.07 standard deviations higher	22 (1 study)	⊕⊕○○ low ^{1,2,3}	SMD 0.07 (-0.77 to 0.91)

(0.77 lower to 0.91 higher)

*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; **PedsQI:** Paediatric Quality of Life Inventory; **SMD:** standardised mean difference.

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.

¹ Total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of 0.2 SD, representing a small effect).

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

³ Published evidence is limited to a small number of trials.

DISCUSSION

Summary of main results

Several studies have investigated the effects of exercise interventions on physical fitness in adult cancer patients, showing different benefits. Less frequent are studies assessing these effects in a childhood cancer population, particularly not when looking at RCT or CCT study designs.

This review included five studies. All these studies investigated the effects of a physical exercise training intervention programme of at least four weeks' duration, in children with cancer. They all aimed to improve physical functioning or psychosocial well-being, and had enrolled children with ALL. The five included studies included limited participant numbers and some lacked a well-designed exercise intervention. Therefore the outcomes of this review should be interpreted with care.

Cardiorespiratory fitness was studied by the use of the nine-minute run-walk test, the timed up-and-down stairs test, and the 20-m shuttle run test. Only the 20-m shuttle run test showed significantly better scores in the intervention group compared with the control group (P value = 0.05, no further information available). For BMD, a statistically significant difference in favour of the exercise group was identified (SMD 1.07; 95% CI 0.48 to 1.66; P value < 0.001). BMI was assessed in two studies. In contrast with the results of one of these studies (SMD 0.90; 95% CI 0.32 to 1.48), the pooled data did not show a statistically significant difference between the combined population in the intervention and control group.

Flexibility was assessed in three studies and each study used different test methods. No (statistically significant) difference between the study groups was identified in two studies, whereas in another study a statistically significant difference in favour of the exercise group was found (SMD 0.69; 95% CI: 0.12 to 1.25; P value = 0.02).

The study of [Macedo 2010](#) focused on muscles of the lung. In this study an inspiratory muscle training programme aimed to increase inspiratory or expiratory muscle strength. No significant effects were found for either inspiratory or expiratory muscle strength. Two other studies using either the knee and ankle strength changes measured by hand-held dynamometry or the number of completed push-ups (with knees on the ground) and a peripheral quantitative computed tomography of the tibia to determine the muscle mass identified no statistically significant differences in muscle strength/endurance.

No statistically significant differences between the study groups were found for the level of daily activity, HRQoL, or fatigue. In addition, only one study reported no complications attributed to the physical exercise intervention programme, whereas the other studies did not address this item.

None of the included studies evaluated the outcomes of activity energy expenditure, time spent exercising, anxiety and depression, or self efficacy.

It should be noted that the exercise interventions were not the same and the quality and quantity of the evidence was limited. For the future it will be best to assess the effects of one type of exercise intervention in more childhood cancer subgroups. This can be done in well-designed studies with large sample sizes.

Overall completeness and applicability of evidence

This review provides evidence for modest but positive effects of physical exercise training interventions for children with cancer. These modest effects could be due to small sample sizes, various interventions, and different outcome measures that were used in the studies included in this review. As a result, only data for BMI could be pooled; therefore, the results of the analysis were unstable and weak. Although the meta-analysis and sensitivity analysis outcome on BMI were robust, the patient population was unintentionally homogeneous since ; all included children had ALL. The results of this review, therefore, are not applicable for other types of childhood cancer.

The RevMan analyses results of this review are very different to the analysis performed by the authors of some of the studies, which led to different conclusions. For [Macedo 2010](#), [Hartman 2009](#), and [Marchese 2004](#), the differences were due to different methods of analysis. In this review we assessed the final outcome differences between the study groups ([Analysis 4.1](#); [Analysis 4.3](#); [Analysis 4.4](#)) and found no changes over time.

The included studies all had supervised interventions with a duration and intensity in which it was possible to have a physiological response ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Moyer-Mileur 2009](#); [Yeh 2011](#)). From literature it is known that supervised exercise interventions in children are more effective compared to non-supervised programmes ([Faigenbaum 2010](#)). It is also known that a well-designed exercise programme consists of four parameters: mode (type of exercise), intensity, frequency, and duration ([ACSM 2010](#); [Ganley 2011](#)). It would be advisable for new studies to first determine if the planned programme includes all elements of these parameters. This will increase the quality of the trials and also increase the comparability.

Appropriate statistical methods are important. The use of incorrect statistical methods can diminish the likelihood of demonstrating the real effects, also in high-quality interventions. In this review only one of the included studies used a power calculation ([Hartman 2009](#)). In the included studies the authors used a Chi² test or the Mann-Whitney U test ([Hartman 2009](#); [Moyer-Mileur 2009](#)), the Kruskal-Wallis ([Moyer-Mileur 2009](#)), and the paired sample T-test ([Macedo 2010](#)) to assess baseline (pre-score) differences between the study groups. The baseline scores were reported as group average ([Hartman 2009](#); [Macedo 2010](#); [Marchese 2004](#); [Yeh 2011](#)), but also per study participant ([Moyer-Mileur 2009](#)). These baseline differences might have had a large impact on the results and conclusions of this review. It would have been prefer-

able for all authors to have corrected for baseline differences in their analyses. However this was not done. To increase the quality of evidence of this review we hoped to be able to pool all raw data (baseline and end of study data) in one database. This would have given us the possibility to correct for these differences. Yet, not all researchers responded to our request for additional information. To investigate changes between participants and changes over time the paired sample T-tests (Hartman 2009; Macedo 2010), Friedman two-way test (Moyer-Mileur 2009), the mixed-effects model (Yeh 2011), and repeated measure analyses (Hartman 2009; Marchese 2004) were used in the included studies. The mixed-effect model and repeated measure analyses are more specific than comparing group mean changes. Therefore, the results of the studies using the better statistical methods are possibly better than the ones using simple statistical techniques. However, in this review we were not able to use this information in the outcome.

Quality of the evidence

By grading the evidence according to the GRADE criteria (Guyatt 2008) the overall quality of the studies varied between low and very low. Due to risk of bias, inconsistency, indirectness, imprecision, possible publication bias, or a combination of these, the qualities of the studies were downgraded. None of the articles was eligible for upgrading. The quality of the evidence is summarised in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4). The small numbers of participants in the trials was the main reason for the low-quality scores. This is often the case in studies in a paediatric population, and in cases of newly introduced interventions. More and larger well-controlled studies are needed to improve the quality and the quantity of evidence. This also shows the need for a core-set of outcome measures in exercise-related research in childhood chronic conditions (Van Brussel 2011).

Potential biases in the review process

The search strategies for MEDLINE/PubMed, EMBASE/OVID, CENTRAL were formulated by the Cochrane Childhood Cancer Group. In addition, two other databases were searched by the use of a search strategy we developed ourselves: CINAHL and PEDro. The PEDro database was difficult to search. Although it is possible that we missed one or two studies from this database, due to the great overlap between results of the different databases it is very unlikely that studies were missed.

This review included five studies, all with small numbers of participants. Between the studies there is a considerable degree of heterogeneity on mode and intensity of the exercise interventions. Only BMI was assessed in two different studies with no substantial heterogeneity ($I^2 = 48\%$). None of the other more important

outcome measures were assessed in more than one study. This prevented further pooling of the data.

Agreements and disagreements with other studies or reviews

In 2010, a review on childhood cancer and physical activity was published by Winter 2010. This review included 28 studies, and almost half had an uncontrolled study design. In eight studies healthy controls were used. Of the four RCTs included in that review, one study included long-term childhood cancer survivors (mean 12 years from diagnosis). Another RCT offered a two- to four-day intervention, which therefore did not match with the inclusion criteria of this Cochrane review (Hinds 2007). The two remaining RCTs of the review by Winter 2010 are also included in this Cochrane review (Hartman 2009; Marchese 2004). A second review on exercise interventions for childhood cancer patients was performed by Huang 2011. They included many of the same studies, but also the study of Chamorro-Vina 2010, which again introduced an intervention of less than four weeks. Both reviews concluded that results are promising, but that there is a need for more and larger RCTs. Both reviews stated that only a subgroup of the childhood cancer population was tested, since almost all studies concerned children with ALL. These findings are consistent with our findings.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the currently available evidence from the included RCTs and CCTs we are not able to draw conclusions regarding the best physical exercise training intervention, neither can we provide information on the best timing of the intervention during or after cancer treatment. However, the five included studies did show that exercise training is feasible in children with ALL.

Effects of the intervention are not yet convincing due to small numbers of participants and insufficient study methodology. Despite that, first results show somewhat better outcomes in the intervention group than in the control group on physical fitness items such as body composition, flexibility, and cardiorespiratory fitness. However, no significant differences were identified for muscle strength/endurance, the level of daily activity, HRQoL, fatigue, and adverse events and the included studies did not include activity energy expenditure, time spent exercising, anxiety, depression, or self efficacy to the study outcomes.

Implications for research

The observed heterogeneity in study findings can be due to differences in the physical exercise training intervention (mode, inten-

sity, frequency, duration, as well as location), different outcome measures (quantitative, qualitative, physical, or psychosocial), and methods to assess the effects of an intervention. Consensus on these items is needed in order to facilitate comparison of results across different studies.

More and high-quality evidence is needed in order to be able to draft exercise and physical activity guidelines for this population. We urge the paediatric oncology community to design national or international multicentre studies, while local and small-scale studies must be discouraged.

In addition, since we could only include five RCTs or CCTs with a total of 131 children, there is a need for additional well-designed studies with large sample sizes. Results of ongoing trials have to be awaited, and further trials with adequate power are needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hartman 2009

Methods	<p>Design: single-centre RCT</p> <p>Setting: the Netherlands</p> <p>Department: paediatric oncology/haematology, paediatric physiotherapy, paediatric endocrinology</p> <p>Randomisation: blinded for investigators and treating physicians</p> <p>Stratification: not mentioned</p> <p>Study duration: 3 years. Duration of the intervention: 24 months. Follow-up duration: 12 months</p> <p>Timing: inclusion started directly after diagnosis, at the beginning of their chemotherapy treatment</p> <p>End point measurements: at diagnosis, 32 weeks after diagnosis, 1 year after diagnosis, at the end of treatment (and 2 years after diagnosis), 1 year after the end of treatment. There was 1 additional measurement 6 weeks after diagnosis</p>
Participants	<p>n = 51</p> <p>Diagnosis: ALL (ALL non-high risk n = 34, ALL high risk n = 17)</p> <p>Age at start study: median age: 5.4 years (range 1.3 to 17.1 years)</p> <p>Sex: 30 boys, 21 girls</p> <p>Exclusion criteria: children with low cognitive impairment and those which could not understand the Dutch language</p>
Interventions	<p>The intervention consisted of an exercise programme of 2 years. The programme consisted of a hospital-based programme performed by paediatric physiotherapists. During these sessions, the physiotherapist measured the motor function to ensure an optimal level of motor functioning. In addition, there was a home-based exercise programme. Parents were supplied with an exercise list, enabling them to select exercises most appropriate for their child's age and also to vary exercises. The exercise programme included exercises to maintain ankle dorsiflexion mobility and short-burst high-intensity exercises, to prevent reduction of BMD. In addition, there were exercises to maintain hand and leg function. The hand and leg function exercises were performed once a day; stretching and jumping exercises twice daily. The duration of an exercise session was not mentioned. When necessary the exercise programme was adjusted during these sessions.</p> <p>The control group received care as usual.</p>
Outcomes	<p>Physical fitness:</p> <p><u>Body composition:</u> BMI, lean body mass, and percentage body fat. The lean body mass and body fat were measured by DXA (lumbar spine and total body)</p> <p><u>Flexibility:</u> passive ankle dorsiflexion; the range of motion past the neutral position received a positive notation and less than neutral a negative notation</p> <p>Motor performance of children less than 3.5 years of age was assessed by the use of the Dutch BSID-II; ≥ 4 years old by the use of the Dutch version of the Movement-ABC</p> <p>Secondary outcomes:</p> <p>None of the secondary outcomes were assessed.</p>

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At diagnosis randomisation into the intervention or the control group was carried out in randomly permuted blocks of randomly chosen size, using sealed envelopes prepared by the statistician"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'. The use of assignment envelopes are described, but it remains unclear whether envelopes were sequentially numbered, or opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and parents were not blinded for randomisation; this was unclear for physiotherapists The investigators and treating physicians were blinded for the study randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors who performed the study outcome tests were blinded for study randomisation
Incomplete outcome data (attrition bias) All outcomes	High risk	The study authors used a simple imputation method: for children who did not complete the study, data prior to elimination were included. No further information was provided on the imputation of some value for missing data
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome measures were listed in the methods section and reported in the results section
Other bias	Low risk	There was no baseline imbalance found, the baseline differences between both groups were not significant. In addition, the number of measurements did not differ for the intervention group or control group

Macedo 2010

Methods	<p>Design: single-centre RCT</p> <p>Setting: Brazil</p> <p>Department: paediatric oncology/haematology</p> <p>Randomisation: random assignment but no further specifications available</p> <p>Stratification: not mentioned</p> <p>Study duration: 10 weeks</p> <p>Timing: inclusion of the study started during maintenance therapy of the childhood ALL treatment</p> <p>End point measurements: in the intervention group at baseline plus an evaluation every alternate week. In the control group at baseline and 10 weeks thereafter</p>
Participants	<p>n = 14</p> <p>Diagnosis: ALL</p> <p>Age at start study: mean age of the whole group was 8.3 ± 2.6 years (range 5 to 14 years). The mean age of the intervention group was 7.0 years and that of the control group 9.0 years</p> <p>Sex: 5 boys and 9 girls</p> <p>Exclusion criteria: children with a chronic lung disease, neuromuscular disease, or those receiving or having received radiotherapy treatment</p>
Interventions	<p>This study investigated an inspiratory muscle training programme. They studied the effects of a domiciliary inspiratory muscle training with a duration of 15 minutes, performed twice a day, for 10 weeks. The training was performed with a threshold device using a load of 30% of the maximal inspiratory pressure</p> <p>The control group received care as usual</p>
Outcomes	<p>Physical fitness:</p> <p><u>Muscle endurance/strength:</u> respiratory muscle strength (maximal inspiratory pressure and maximal expiratory pressure) assessed with a digital manometer</p> <p>Secondary outcomes:</p> <p>None of the secondary outcomes were assessed</p>
Notes	Article was written in Portuguese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were randomly selected and randomly assigned to 2 groups, but the exact randomisation methods were not reported
Allocation concealment (selection bias)	Unclear risk	The exact randomisation methods were not reported. It was not clear whether the researchers used sealed envelopes, central allocation, or another method

Macedo 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	The study did not address the blinding of participants and personnel. However, due to the nature of the interventions blinding was virtually impossible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study did not address blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting: the authors stated that sample losses occurred; however, they did not report the reasons for these sample losses, neither did they provide information on the used imputation methods
Selective reporting (reporting bias)	Low risk	Respiratory muscle strength was the primary outcome. By assessing and reporting on (changes over time of) both the maximal inspiratory pressure and maximal expiratory pressure there was no selective reporting of the study data
Other bias	High risk	Differential diagnostic activity: the intervention group and the control group received an unequal number of measurements However, this study was free of baseline imbalance; the baseline differences between the control group and intervention group on outcome related items were not significant

Marchese 2004

Methods	Type of study: single-centre RCT Setting: USA Department: paediatric rehabilitation, paediatric oncology, paediatric physiotherapy Randomisation: primary investigator offered the children an envelope to select assignment into the intervention or control group Stratification: children were stratified according to their childhood cancer risk group and first versus second part of the maintenance therapy Study duration: 4 months Timing: inclusion of the study started during maintenance therapy End point measurements: at baseline and 4 months later
Participants	n = 28 Diagnosis: ALL Age at start study: median age of the whole group was 7.7 years (range 4.3-15.8 years)

	<p>. The median age of the intervention group was 7.6 years (range 4.3-10.6 years) and of the control group 8.6 years (range 5.1-15.8 years) Sex: 20 boys and 8 girls Exclusion criteria: a history of antecedent neurological, developmental, or genetic disorders and those receiving a physiotherapy intervention at the start of the study</p>	
Interventions	<p>The intervention programme included 5 hospital-based physiotherapy sessions (week 0, 2, 4, 8, and 12) of 20-60 minutes. The first session was performed immediately after the baseline testing Next to the hospital-based programme, the programme also included an individualised home exercise programme. This programme consisted of ankle dorsiflexion stretching exercises (30 seconds, 5 days a week), bilateral lower extremity strengthening exercises (3 sets of 10 repetitions, 3 days a week), and aerobic exercise (daily). The aerobic exercise could be walking, cycling, or swimming; chosen by the participant The control group received care as usual</p>	
Outcomes	<p>Physical fitness: <u>Cardiorespiratory fitness or peak work rate:</u> 9-minute run-walk test and the timed up-and-down stairs test <u>Muscle endurance/strength:</u> knee extension strength and ankle dorsiflexion strength both tested with a hand-held dynamometer. This study also used the time up-and-down stairs test and the 9-minute run-walk test <u>Flexibility:</u> ankle dorsiflexion range of motion Secondary outcomes: <u>Health-related quality of life:</u> PedsQL version 3.0 <u>Adverse events:</u> any negative effect from the exercises or experienced complications attributed to the physical programme</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The children were stratified by risk group and by whether they were in the first or second half of the maintenance therapy. After that the primary investigator offered the children an envelope to select assignment into the intervention or control group
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'. The use of assignment envelopes is described, but it remains unclear whether envelopes were sealed, sequentially numbered, or maybe opaque

Marchese 2004 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and parents were not blinded for randomisation; for personnel this was unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors for hand-held dynamometry , the timed up-and-down stairs test and the 9 minute run-walk test were blinded for study randomisation. Therefore these items had a low risk for detection bias The PedsQL (quality of life) questionnaires were filled in by both parents and children. Parents and children were not blinded for the study randomisation and therefore the quality of life assessment was found to be of high risk for detection bias We judged the overall risk of detection bias for this item to be low because the researchers blinded outcome assessors as much as possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors reported missing data for daily logs of activity and heart monitor. But no information was reported on methods used for data imputation in case of missing data
Selective reporting (reporting bias)	Low risk	All the prespecified primary and secondary outcomes of the study were listed in the methods section and reported in the results section
Other bias	Unclear risk	The non-significant baseline differences were reported for patient characteristics, however, not for study outcome measures. It remains unclear whether the mean differences between the control group and the intervention group at baseline were significant or not Furthermore we checked for differential diagnostic activity. During the study all children were pretested and post-tested. The number of measurements did not differ for the intervention group or control group

Moyer-Mileur 2009

Methods	<p>Type of study: single-centre RCT Setting: USA Department: paediatric oncology Randomisation: not mentioned Stratification: not mentioned Study duration: 12 months Timing: the inclusion of the study started during the ALL maintenance chemotherapy End point measurements: measures of physical size were obtained at baseline and every 3 months, physical activity was measured at baseline and at 6 and 12 months</p>	
Participants	<p>n = 14 Diagnosis: standard-risk ALL Age at start study: mean age (\pm SD) of the intervention group was 7.2 ± 0.7 years and the mean age of the control group was 5.9 ± 0.7 years Sex: 7 boys and 6 girls; 1 unknown (drop-out) Exclusion criteria: not mentioned</p>	
Interventions	<p>The intervention included a 12-month home-based exercise and nutrition programme. Children were prescribed to perform a minimum of 3 'fifteen to twenty-minute' sessions of moderate-to-vigorous activity per week. Activity examples were provided on the pyramid for youth and parents were asked to record the type and amount of physical activity, immediately after the activity was performed. Children received nutrition education materials on the basis of the United States Department of Agriculture Food Guide Pyramid and nutrition-related activities monthly. The control group received care as usual.</p>	
Outcomes	<p>Physical fitness: <u>Cardiorespiratory fitness or peak work rate:</u> progressive aerobic cardiovascular endurance run <u>Muscle endurance/strength:</u> push-ups, the sit-and-reach test <u>Body composition:</u> BMI, muscle mass (measured by the analysis of the tibia using peripheral quantitative computed tomography) <u>Flexibility:</u> sit-and-reach distance test <u>Level of daily activity:</u> pedometer combined with an activity diary (monthly, 2 weekdays and 1 weekend day) and the ACTIVITY GRAM questionnaire Secondary outcomes: None of the secondary outcomes were assessed</p>	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not provided in the article
Allocation concealment (selection bias)	Unclear risk	The method of randomisation was not provided in the article

Moyer-Mileur 2009 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	The study did not address this item. However, due to the nature of the interventions blinding was virtually impossible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study did not address this item
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although authors reported that 1 child withdraw after 3 months (caused by lack of interest and data of this child were not taken into analysis), the information provided was insufficient to decide whether there this withdrawal could have had influence on the study outcomes
Selective reporting (reporting bias)	Low risk	The article presented both the mean (plus confidence interval or SD) of all outcome variables and figures including the individual changes of the participants
Other bias	Low risk	There was no baseline imbalance found, the baseline differences between both groups were not significant Furthermore we checked for differential diagnostic activity. During the study all children were pretested and post-tested. The number of measurements did not differ for the intervention group or control group

Yeh 2011

Methods	Type of study: single-centre CCT feasibility study (quasi-experimental) Setting: Taiwan Department: paediatric oncology Randomisation: not performed Stratification: the intervention group and controls were matched by age and sex Timing: the inclusion of the study started during the ALL maintenance chemotherapy (1 week after completion of the dexamethasone treatment) Study duration: 10 weeks End point measurements: at baseline, once weekly during the 5-week intervention, at the end of the intervention and 1 month after the intervention
Participants	n = 24 Diagnosis: ALL Age at start study: mean age intervention group 11.0 ± 3.56 years, mean age of the control group 12.5 ± 3.86 years Sex: 12 boys and 10 girls; 2 unknown (drop-outs)

	Exclusion criteria: children who were unwilling to perform an aerobic exercise, or those with physical and developmental impairment	
Interventions	<p>The intervention consisted of a home-based aerobic exercise instructed by video. 1 session included a warm-up of 5 minutes, aerobic exercise of 25 minutes and a cooling down period of 5 minutes. The exercises were performed at least 3 times a week, over a total of 6 weeks. In addition, children recorded their physical activity and heart rate data during the exercises in a physical activity log for 3 days with 24 1-hour blocks</p> <p>The aerobic exercise sessions aimed to increase 40-60% of the child's heart rate reserve</p> <p>The control group received care as usual</p>	
Outcomes	<p>Physical fitness: None of the physical fitness outcomes were assessed</p> <p>Secondary outcomes: <u>Fatigue:</u> PedsQL multidimensional fatigue scale</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The researcher-team used a quasi-experimental design that had no random assignment
Allocation concealment (selection bias)	High risk	The researcher-team used a quasi-experimental design that had no random assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study did not address this item. However, due to the nature of the interventions blinding was virtually impossible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study did not address this item
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 types of analyses were conducted: ITT analysis used the data of all children, and the per-protocol analysis, which included only those children who adhered to the exercise prescription
Selective reporting (reporting bias)	High risk	Not all the prespecified primary outcomes have been reported. In addition, adherence was mentioned to be extra or a secondary outcome. However, in the results the authors focused in this item

Other bias	Unclear risk	The non-significant baseline differences were reported for fatigue study outcomes. However, it remains unclear whether the intervention and control group had different baseline scores on the other study outcomes: physical activity log, OMNI walk/run scale, and the stages of change. Furthermore we checked for differential diagnostic activity. The number of measurements did not differ for the intervention group or control group. Therefore this study was free from differential diagnostic activity.
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ALL: acute lymphoblastic leukaemia; BMD: bone mineral density; BMI: body mass index; BSID-II: Bayley Scales of Infant development; CCT: controlled clinical trial; DXA: dual energy x-ray absorptiometry; ITT: intention to treat; Movement-ABC: Movement Assessment Battery for Children; OMNI walk/run scale: Omnibus - walk/run scale; PedsQL: Paediatric Quality of Life Inventory; RCT: randomised controlled trial.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chamorro-Vina 2010	The exercise intervention was offered less than 4 weeks
Hinds 2007	The exercise intervention was offered less than 4 weeks
Speyer 2010	Cross-over randomised trial without data presentation after the first intervention period (before cross-over)
Te Winkel 2008	This study presents pilot data of a study that was reported by Hartman et al (2009). Hartman et al. was already included in the review (Hartman 2009)

Characteristics of studies awaiting assessment [ordered by study ID]

Elkateb 2007

Methods	Type of study: single-centre CCT Setting: Egypt Department: paediatric oncology Randomisation: not performed Stratification: not included Timing: children were during chemotherapy treatment for cancer Study duration: not mentioned End point measurements: at baseline, daily in the first week, after the first week, in the third week and in the sixth week
Participants	n = 50 Diagnosis: childhood cancer Age at start study: preschool- and school-aged children Sex: not mentioned Exclusion criteria: not mentioned
Interventions	Undefined exercise programme for the intervention group Undefined programme for the control group
Outcomes	Physical fitness: <u>Level of daily activity:</u> observational checklist for recording activities Secondary outcomes: <u>Fatigue:</u> observational checklist for sleeping conditions
Notes	This study was published as a conference paper. Based on the currently available information it was not possible to decide if this study was eligible for inclusion in this review

CCT: controlled clinical trial.

Characteristics of ongoing studies [ordered by study ID]

Braam 2011

Trial name or title	Quality of Life in Motion: A Combined Physical Exercise and Psychosocial Training Program to Improve Physical Fitness in Children with Cancer
Methods	Type of study: multicentre RCT Setting: Netherlands Department: paediatric oncology/haematology Randomisation: independent assistant manage a randomisation list. The researcher calls the independent assistant after the baseline measurement than the randomisation is performed Stratification: the participants are stratified by (i) cancer (haematological versus solid cancer), (ii) sex and age (boys under 12 vs. ≥ 12 years and girls under 11 years vs. ≥ 11 years) and (iii) during or after cancer treatment Timing: children are during or within the first year following childhood cancer therapy. Children who are during treatment should be treated on an outpatient basis, without overnight hospital staying Study duration: 12 months

	<p>End point measurements: At baseline, 4 months, 7 months and 12 months Trial register: www.trialregister.nl/trialreg/admin/rctview.asp?TC=1531 (accessed 6 March 2013)</p>
Participants	<p>n = 100 Diagnosis: childhood cancer (treated with chemotherapy, radiotherapy, or both) Age at start study: 8-18 years Exclusion criteria: receiving a bone marrow transplant as a part of the childhood cancer treatment, receiving growth hormones as a part of the childhood cancer treatment, permanent wheelchair use/inability to ride a bike, retardation/inability to make a self reflexion and follow sports instructions</p>
Interventions	<p>The 12-week intervention consists of a combined physical exercise (twice per week) and psychosocial support programme (once every 2 weeks) followed by a 1-day booster session The physical exercise programme includes a protocol with both cardiorespiratory and muscle strength training. The sessions are guided by a paediatric physiotherapist and performed at a local paediatric physiotherapist institute. The psychosocial support programme (6 child and 2 parent sessions) contains psychoeducation and cognitive-behavioural therapy (given by a paediatric psychologist and performed at the treating hospital) The control group will receive care as usual In addition, parents are asked to fill in a cost-diary over the whole period of the study Non-responders characteristics, physical activity level, and quality of life will be assessed in a survey including three important questionnaires of the study, to determine whether the study population represents the entire population</p>
Outcomes	<p>Physical fitness: <u>Cardiorespiratory fitness or peak work rate:</u> cardiopulmonary exercise tests (CPET and SRT) on a cycle ergometer to measure VO_{2peak}, and peak work rate <u>Muscle endurance/strength:</u> hand-held-dynamometer <u>Body composition:</u> DXA and BMI <u>Activity energy expenditure:</u> accelerometry <u>Level of daily activity:</u> activity questionnaire and activity diary (4 x 4 days over 1 year) <u>Time spent exercising (more than daily activity):</u> activity questionnaire Secondary outcomes: <u>HRQoL:</u> PedsQL Generic <u>Fatigue:</u> PedsQL Multidimensional Fatigue scale <u>Anxiety and depression:</u> Children's Depression Inventory <u>Self efficacy:</u> Youth self report and Child Behavior Checklist <u>Adverse events</u></p>
Starting date	1 March 2009
Contact information	Katja Irene Braam, VU University Medical Center, Amsterdam, The Netherlands: katja.braam@vumc.nl
Notes	

Cox 2011

Trial name or title	Physical Activity to Modify Sequelae and Quality of Life in Childhood Acute Lymphoblastic Leukaemia (PAQOL)
Methods	<p>Type of study: single-centre RCT Setting: USA Department: paediatric oncology Randomisation: not described Stratification: not included Timing: children were in the second to eighth day of the ALL treatment protocol Study duration: 135 weeks End point measurements: at baseline (BMD, HRQoL), after 8 weeks (HRQoL), after 15 weeks (HRQoL), and at completion of therapy (BMD and HRQoL) clinicaltrials.gov/ct2/show/NCT00902213</p>
Participants	<p>n = 208 Diagnosis: newly diagnosed with ALL (immunophenotypic diagnosis of non-B cell ALL) Age at start study: 4-18 years Exclusion criteria: age < 4 years or ≥ 19 years at diagnosis, no parents or legal guardian (≥ 18 years) of the study subject who speaks and understands the English language, a diagnosis of cerebral palsy or Down's syndrome, children with a second malignancy, chromosome breakage syndrome, or severe congenital immunodeficiency, inability to obtain written informed consent from parent/young adult and child assent, or females who are pregnant</p>
Interventions	<p>Tailored parent- and child-focused physical activity programme An advanced practice nurse will meet twice weekly with the child and family for the first 4 weeks of the intervention to initiate the motivation-based dialogue and therapeutic interaction; this will be followed by once weekly visits during weeks 5-8 of the intervention; and monthly visits during weeks 9 through to end of therapy The physiotherapist will meet at least once weekly with the child and family during weeks 1-4 to initiate the prescriptive tailored exercise programme; subsequent visits to reinforce and modify the programme will occur at least once every other week during weeks 5-8, and at least once monthly during weeks 9-135 of the intervention. The physiotherapist will visit at least once weekly during weeks 1-4, at least once every other week during weeks 5-8, and at least once monthly during weeks 9-135. During weeks 9-135 of the intervention, the advanced practice nurse will call between the monthly in-person visits to assure fidelity to the intervention and to provide booster support to the intervention where needed</p>
Outcomes	<p>Physical fitness: <u>Muscle endurance/strength:</u> muscle strength, range of motion, endurance, gross motor skills, used method is not specified <u>Body composition:</u> BMD and bone mineral content <u>Flexibility:</u> range of motion Secondary outcomes: <u>Health-related quality of life:</u> method used not mentioned in the protocol <u>Adverse events</u></p>
Starting date	November 2009
Contact information	Cheyl Cox, info@stjude.org

Notes

ALL: acute lymphoblastic leukaemia; BMD: bone mineral density; BMI: body mass index; CPET: cardiopulmonary exercise test; DXA: dual-energy x-ray absorptiometry; HRQoL: health-related quality of life; RCT: randomised controlled trial; SRT: steep ramp test; VO_{2peak} : maximal oxygen consumption.

For Preview Only

DATA AND ANALYSES

Comparison 1. Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 9-minute run-walk test	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.42, 1.07]
2 Timed up-and-down stairs test	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.64, 0.85]

Comparison 2. Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone mineral density	1	51	Std. Mean Difference (IV, Random, 95% CI)	1.07 [0.48, 1.66]
2 Body mass index	2	64	Std. Mean Difference (IV, Random, 95% CI)	0.59 [-0.23, 1.41]

Comparison 3. Flexibility outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Flexibility	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Active ankle dorsiflexion	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.46 [-0.29, 1.22]
1.2 Passive ankle dorsiflexion	1	51	Std. Mean Difference (IV, Random, 95% CI)	0.69 [0.12, 1.25]

Comparison 4. Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Knee strength	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.49, 1.00]
2 Ankle dorsiflexion strength	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.46, 1.04]
3 Inspiratory breathing muscle strength	1	14	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.77, 1.43]

4 Expiratory breathing muscle strength	1	14	Std. Mean Difference (IV, Random, 95% CI)	0.0 [-1.09, 1.09]
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Comparison 5. Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PedsQL - general	1	28	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.98, 0.51]
2 PedsQL - cancer	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.58, 0.91]
3 Parents PedsQL - general	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.37, 1.13]
4 Parents PedsQL - cancer	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.70, 0.79]

Comparison 6. Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

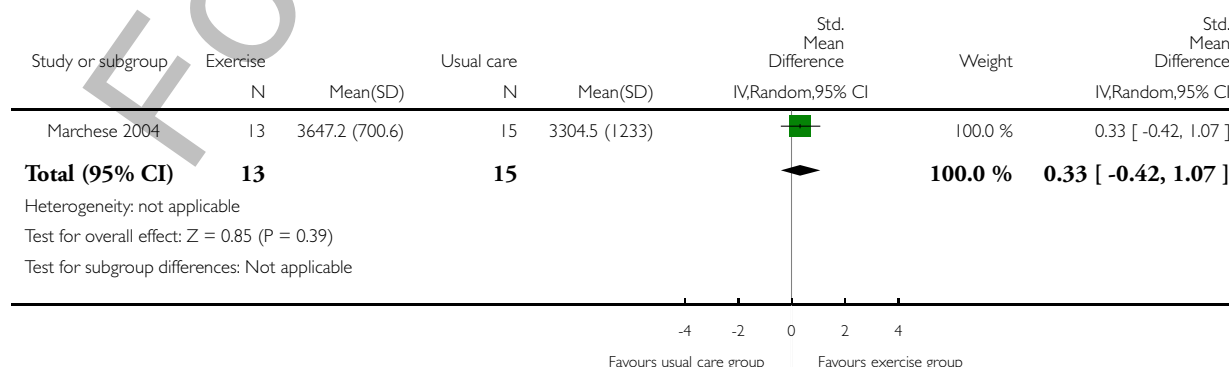
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PedsQL - general fatigue	1	22	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.88, 0.80]
2 PedsQL - sleep/rest fatigue	1	22	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.85, 0.83]
3 PedsQL - cognitive fatigue	1	22	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.77, 0.91]

Analysis 1.1. Comparison 1 Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 1 9-minute run-walk test.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 1 Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 1 9-minute run-walk test

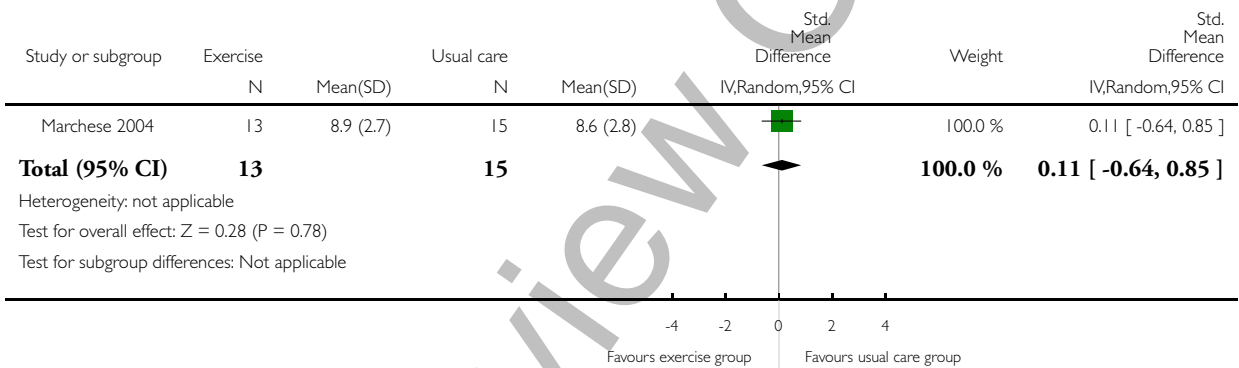


Analysis 1.2. Comparison 1 Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 2 Timed up-and-down stairs test.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 1 Cardiorespiratory fitness outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 2 Timed up-and-down stairs test

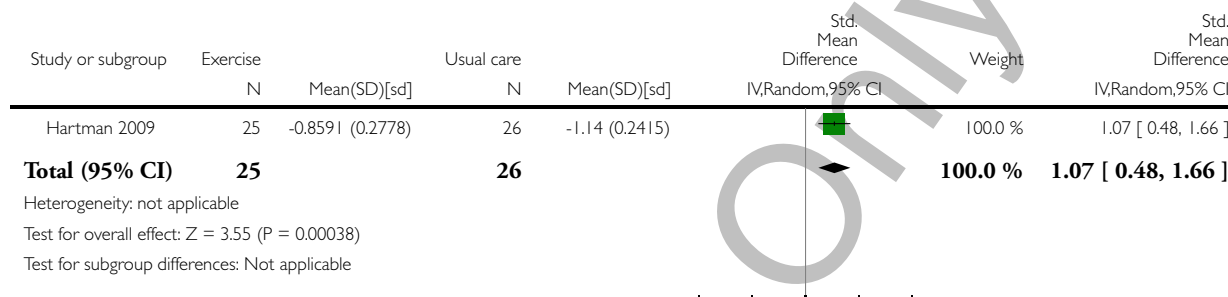


Analysis 2.1. Comparison 2 Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 1 Bone mineral density.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 2 Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 1 Bone mineral density



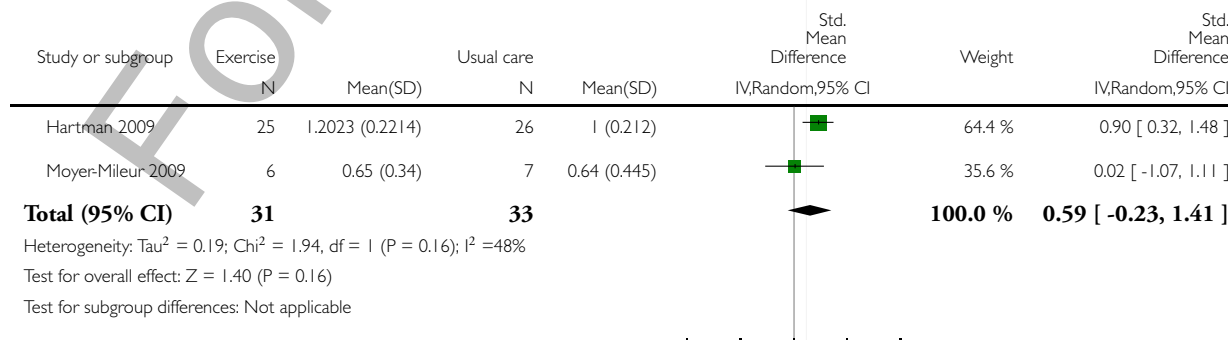
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 Favours usual care group Favours exercise group

Analysis 2.2. Comparison 2 Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 2 Body mass index.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 2 Body composition outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 2 Body mass index



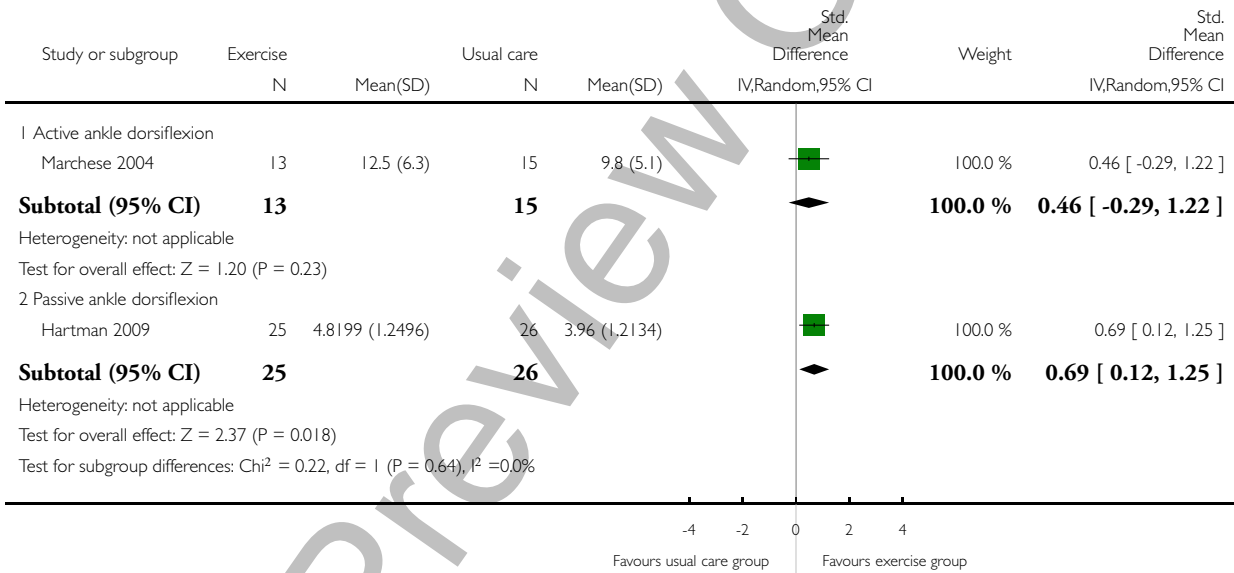
-4 -2 0 2 4
 Favours usual care group Favours exercise group

Analysis 3.1. Comparison 3 Flexibility outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 1 Flexibility.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 3 Flexibility outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 1 Flexibility

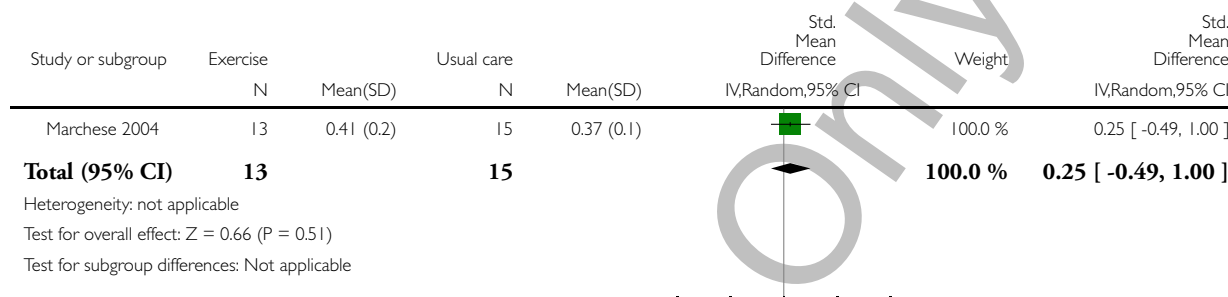


Analysis 4.1. Comparison 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 1 Knee strength.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 1 Knee strength



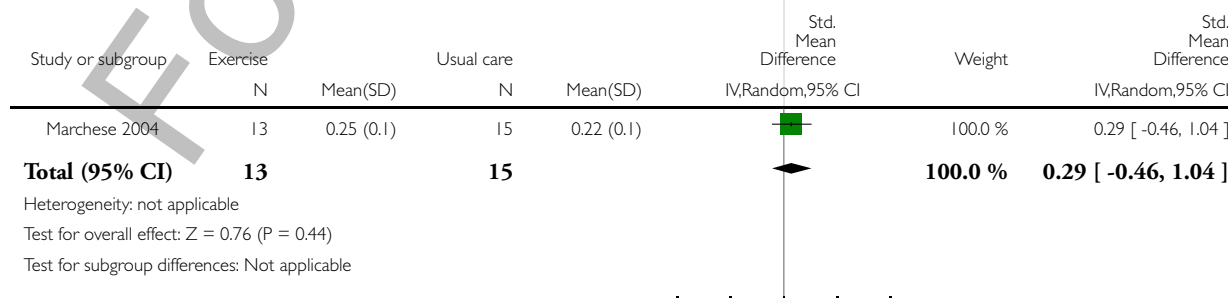
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 Favours usual care group Favours exercise group

Analysis 4.2. Comparison 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 2 Ankle dorsiflexion strength.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 2 Ankle dorsiflexion strength



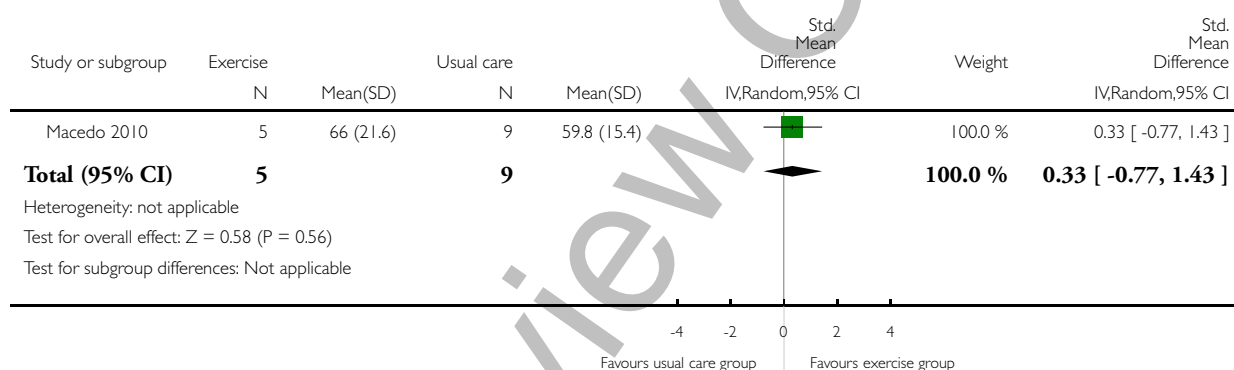
-4 -2 0 2 4
 Favours usual care group Favours exercise group

Analysis 4.3. Comparison 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 3 Inspiratory breathing muscle strength.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 3 Inspiratory breathing muscle strength

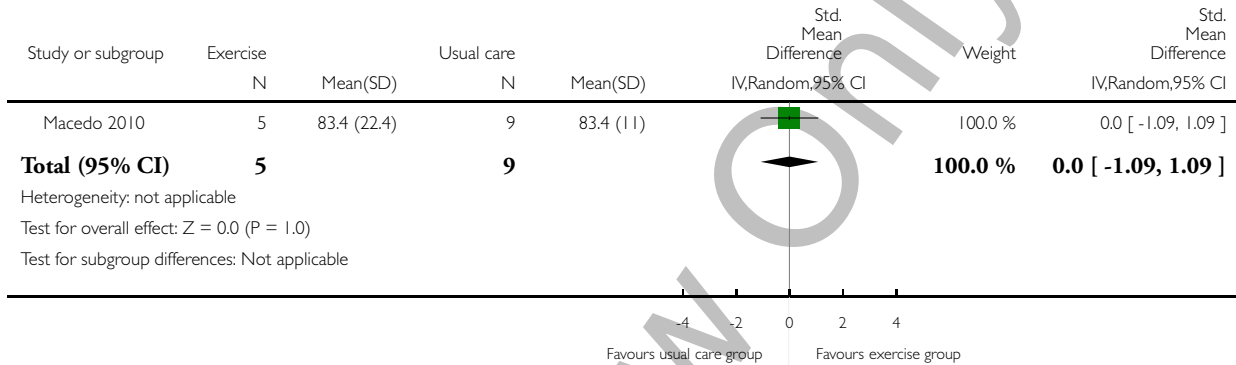


Analysis 4.4. Comparison 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 4 Expiratory breathing muscle strength.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 4 Muscle endurance/strength outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 4 Expiratory breathing muscle strength

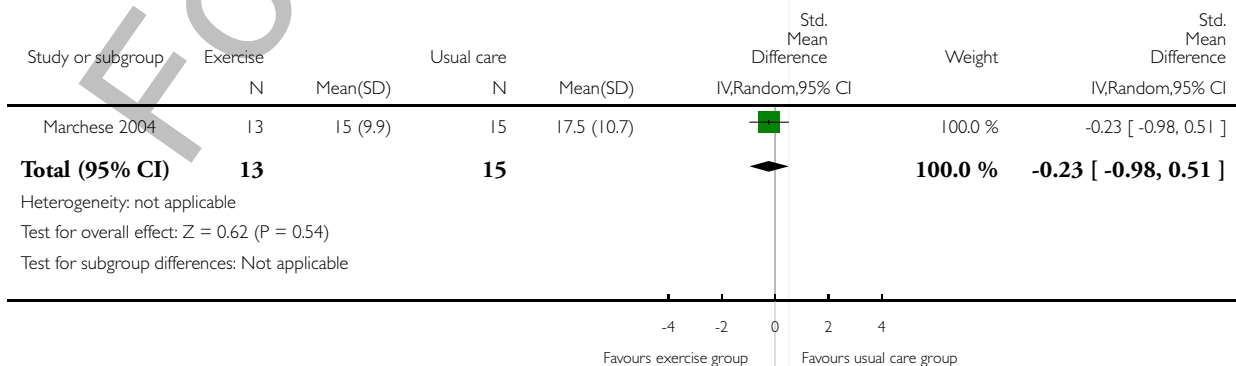


Analysis 5.1. Comparison 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 1 PedsQL - general.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 1 PedsQL - general

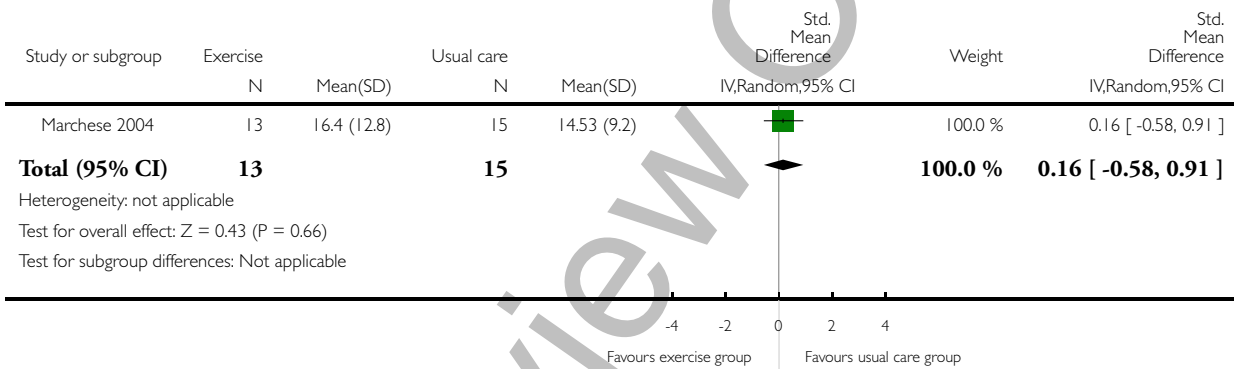


Analysis 5.2. Comparison 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 2 PedsQL - cancer.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 2 PedsQL - cancer

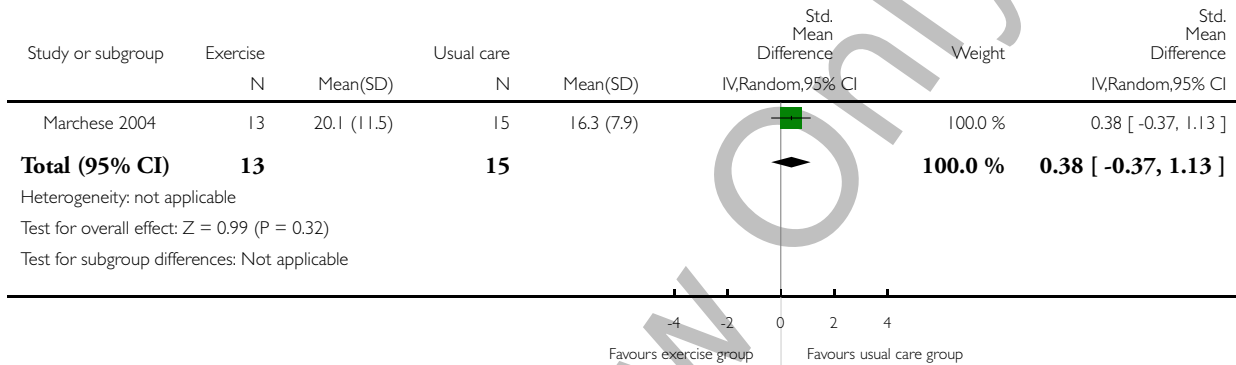


Analysis 5.3. Comparison 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 3 Parents PedsQL - general.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 3 Parents PedsQL - general

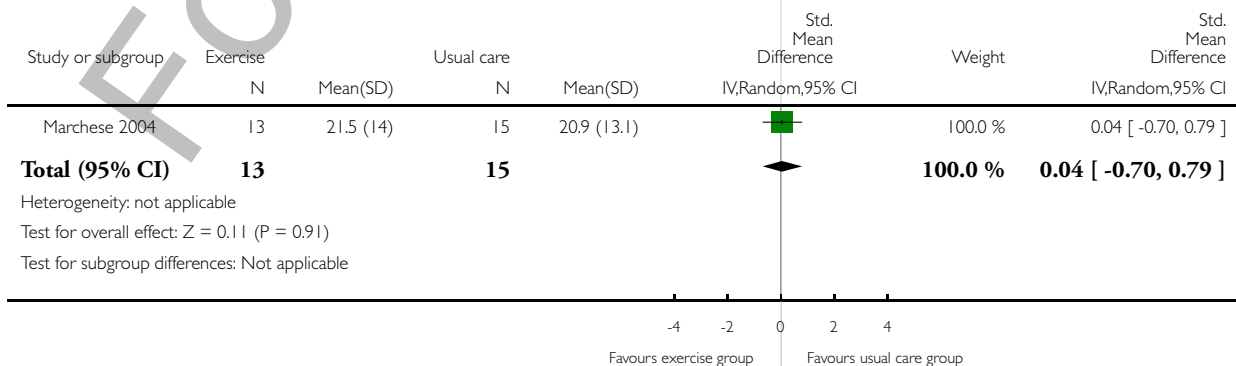


Analysis 5.4. Comparison 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 4 Parents PedsQL - cancer.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 5 Health-related quality of life outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 4 Parents PedsQL - cancer

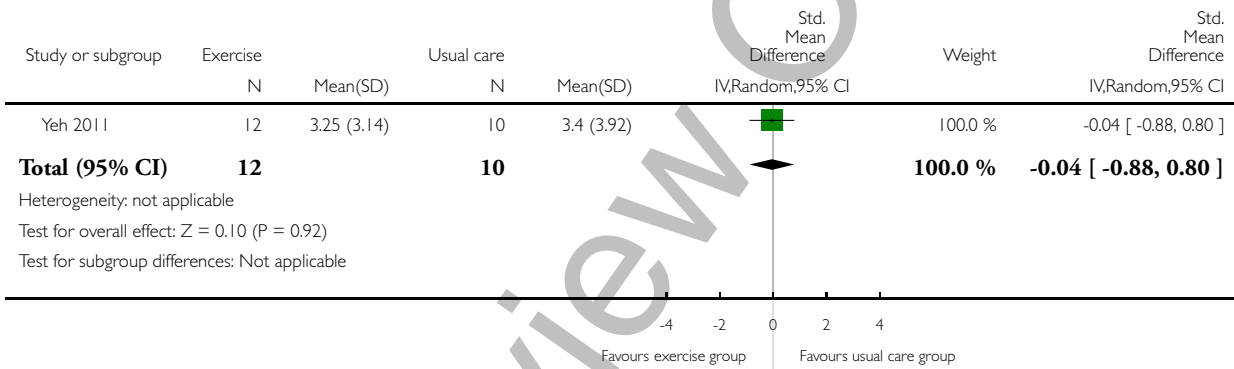


Analysis 6.1. Comparison 6 Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 1 PedsQL - general fatigue.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 6 Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 1 PedsQL - general fatigue

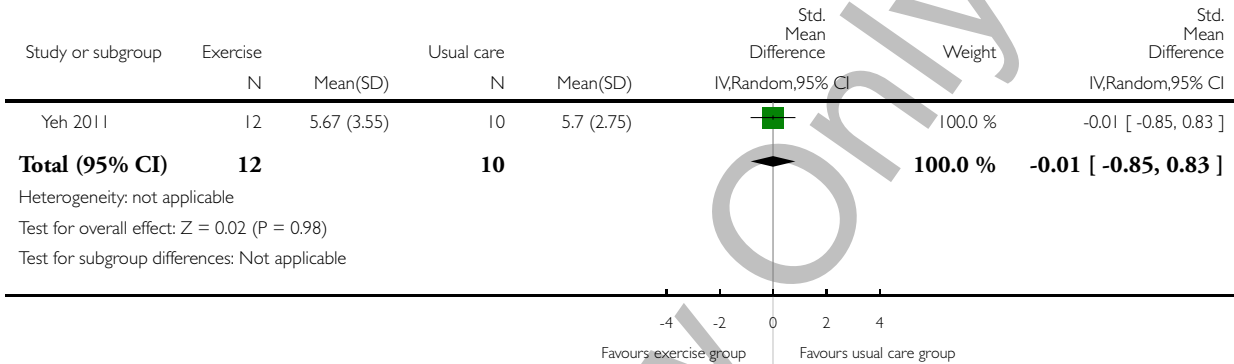


Analysis 6.2. Comparison 6 Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 2 PedsQI - sleep/rest fatigue.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 6 Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 2 PedsQI - sleep/rest fatigue

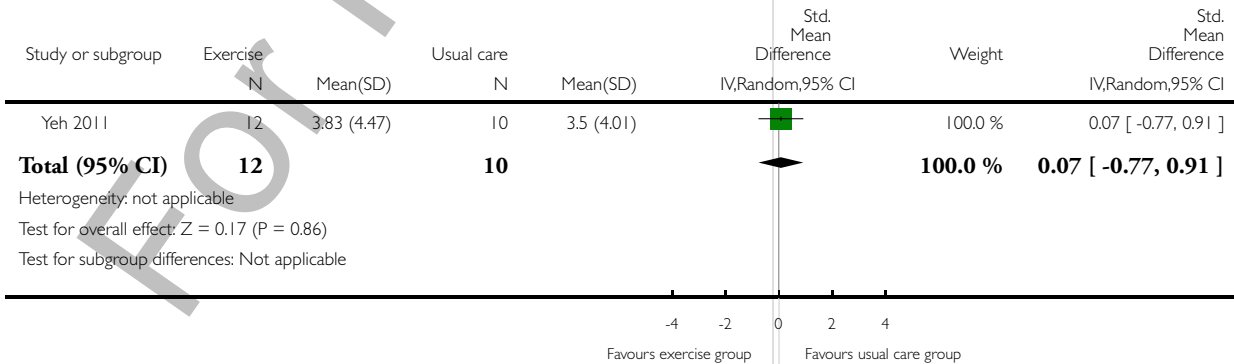


Analysis 6.3. Comparison 6 Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer, Outcome 3 PedsQI - cognitive fatigue.

Review: Physical exercise training interventions for children and young adults during and after treatment for childhood cancer

Comparison: 6 Fatigue outcomes after physical exercise training intervention for children and adolescents during or after childhood cancer

Outcome: 3 PedsQI - cognitive fatigue



APPENDICES

Appendix I. Search strategy for MEDLINE/PubMed

1. For **children** the following MeSH headings and text words were 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 paediatric* 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 were 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 hematocological 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 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 (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 physical **exercise training therapy** the following MeSH headings and text words were 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 **outcome** the following MeSH headings and text words were 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, involuntal 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 were 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 2011](#))

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

Appendix 2. Search strategy for EMBASE/OVID

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

1. (leukemia or leukemia\$ 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 were 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 **exercise training therapy** the following Emtree terms and text words were 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 or 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 were 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 were 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

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

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

(leukemia OR leukemia* 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 were 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 **exercise training therapy** the following text words were 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 were 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 involuntal depression 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

Final search:

1 and (2 or 3) and 4 and 5

[*]=1+ more characters

Appendix 4. Search strategy for CINAHL

1. For **children** the following the following MeSH headings (MH) and text words were used for searching Title, Abstract, or Keywords: "schoolage" OR (MH "Schools+") OR "paediatric" OR "paediatric" OR "pediatric" OR (MH "Puberty+") OR "juvenile" OR "under-age" 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 and childhood cancer** the following the following MeSH headings (MH) and text words were 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 physical **exercise training therapy** the following the following MeSH headings (MH) and text words were 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 were 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 were 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

Appendix 5. Search strategy for PEDro

1. For **children** the textword “paediatrics” was used in <Subdiscipline> field
2. For **cancer and childhood cancer** the textwords “cancer” OR “oncolog” OR “neoplasm” OR “carcinom” or “tumor” OR “malignan” were used in the <Abstract & Title> field
3. For physical **exercise training therapy** the textword “exercise” was used in the <Abstract & Title> field and combined (with OR) with the textwords “fitness training” OR “hydrotherapy, balneotherapy” OR “neurodevelopmental therapy, neurofacilitation” OR “skill training” OR “strength training” in the <Therapy> field
4. For **RCTs and CCTs** the textword “clinical trial” was used in the <Method> field

Final search

1 and 2 and 3 and 4

For **outcome** no search terms were defined

CONTRIBUTIONS OF AUTHORS

KB and PT were the principle authors of this Cochrane review and all other authors contributed to the writing of the review. ED and MV were involved in the overall content and quality of the review while TT also was the third-party arbitrator in case of discrepancies or no consensus and the expert on childhood physiology discussions. GJK is head of the paediatric oncology/haematology department of VU University Medical Center. He was responsible for the medical and oncological background of the review protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Pediatric oncology hematology, VU University Medical Center, Amsterdam, Netherlands.
- Child Development & Exercise Center, Wilhelmina Children's Hospital/University Medical Center Utrecht, Netherlands.
- Dutch Cochrane Center (DCC), Netherlands.

systematic review course

External sources

- Alphe d'HuZes/Dutch Cancer Society, Netherlands.
- Roparun, Netherlands.
- VONK, Netherlands.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review differed from the protocol on a number of aspects.

Instead of using the Cochrane Childhood Cancer Group module for the risk of bias, we used the latest update, which was described in the *Cochrane Handbook for Systematic Reviews of Interventions* of March 2011 to assess the risk of bias of the included studies (Higgins 2011).

The study of [Hartman 2009](#) included children at diagnosis who were aged one to 18 years. In the protocol we reported our intention to include studies with participants older than three years of age. We opted to change this because some of the studies introduced a tailored exercise programme that could be adjusted for the child's age. To see changes in outcomes a child needs to be trainable, co-operative, and testable. For intensive training, which we had in mind when writing the protocol, children aged less than three years will not be able to complete the exercises. However, the study of [Hartman 2009](#) did not assess the effect of a structured intensive training programme, but included physiotherapy sessions with exercises that were appropriate for all ages.

We added possible tests that could have been used to assess the primary outcome.

Finally, we added the clinical trial database as resource for the search of ongoing trials (www.clinicaltrials.gov). We also searched the clinical trial database for missed studies.