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Aerobic physical exercise for adult patients with haematological malignancies (Review)

Knips L, Bergenthal N, Streckmann F, Monsef I, Elter T, Skoetz N

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[Intervention Review]

Aerobic physical exercise for adult patients with haematological malignancies

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ABSTRACT

Background

Although people with haematological malignancies have to endure long phases of therapy and immobility, which is known to diminish their physical performance level, the advice to rest and avoid intensive exercises is still common practice. This recommendation is partly due to the severe anaemia and thrombocytopenia from which many patients suffer. The inability to perform activities of daily living restricts them, diminishes their quality of life and can influence medical therapy.

Objectives

In this update of the original review (published in 2014) our main objective was to re-evaluate the efficacy, safety and feasibility of aerobic physical exercise for adults suffering from haematological malignancies considering the current state of knowledge.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*the* Cochrane Library, 2018, Issue 7) and MEDLINE (1950 to July 2018) trials registries (ISRCTN, EU clinical trials register and clinicaltrials.gov) and conference proceedings. We did not apply any language restrictions. Two review authors independently screened search results, disagreements were solved by discussion.

Selection criteria

We included randomised controlled trials (RCTs) comparing an aerobic physical exercise intervention, intending to improve the oxygen system, in addition to standard care with standard care only for adults suffering from haematological malignancies. We also included studies that evaluated aerobic exercise in addition to strength training. We excluded studies that investigated the effect of training programmes that were composed of yoga, tai chi chuan, qigong or similar types of exercise. We also excluded studies exploring the influence of strength training without additive aerobic exercise as well as studies assessing outcomes without any clinical impact.

Data collection and analysis

Two review authors independently screened search results, extracted data and assessed the quality of trials. We used risk ratios (RRs) for adverse events, mortality and 100-day survival, standardised mean differences (SMD) for quality of life (QoL), fatigue, and physical performance, and mean differences (MD) for anthropometric measurements.

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Main results

In this update, nine trials could be added to the nine trials of the first version of the review, thus we included eighteen RCTs involving 1892 participants. Two of these studies (65 participants) did not provide data for our key outcomes (they analysed laboratory values only) and one study (40 patients) could not be included in the meta-analyses, as results were presented as changes scores only and not as endpoint scores. One trial (17 patients) did not report standard errors and could also not be included in meta-analyses. The overall potential risk of bias in the included trials is unclear, due to poor reporting.

The majority of participants suffered from acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), malignant lymphoma and multiple myeloma, and eight trials randomised people receiving stem cell transplantation. Mostly, the exercise intervention consisted of various walking intervention programmes with different duration and intensity levels.

Our primary endpoint overall survival (OS) was only reported in one of these studies. The study authors found no evidence for a difference between both arms (RR = 0.67; P = 0.112). Six trials (one trial with four arms, analysed as two sub-studies) reported numbers of deceased participants during the course of the study or during the first 100 to 180 days. For the outcome mortality, there is no evidence for a difference between participants exercising and those in the control group (RR 1.10; 95% CI 0.79 to 1.52; P = 0.59; 1172 participants, low-certainty evidence).

For the following outcomes, higher numbers indicate better outcomes, with 1 being the best result for the standardised mean differences. Eight studies analysed the influence of exercise intervention on QoL. It remains unclear, whether physical exercise improves QoL (SMD 0.11; 95% CI -0.03 to 0.24; 1259 participants, low-certainty evidence). There is also no evidence for a difference for the subscales physical functioning (SMD 0.15; 95% CI -0.01 to 0.32; 8 trials, 1329 participants, low-certainty evidence) and anxiety (SMD 0.03; 95% CI -0.30 to 0.36; 6 trials, 445 participants, very low-certainty evidence). Depression might slightly be improved by exercising (SMD 0.19; 95% CI 0.0 to 0.38; 6 trials, 445 participants, low-certainty evidence). There is moderate-certainty evidence that exercise probably improves fatigue (SMD 0.31; 95% CI 0.13 to 0.48; 9 trials, 826 patients).

Six trials (435 participants) investigated serious adverse events. We are very uncertain, whether additional exercise leads to more serious adverse events (RR 1.39; 95% CI 0.94 to 2.06), based on very low-certainty evidence.

In addition, we are aware of four ongoing trials. However, none of these trials stated, how many patients they will recruit and when the studies will be completed, thus, potential influence of these trials for the current analyses remains unclear.

Authors' conclusions

Eighteen, mostly small RCTs did not identify evidence for a difference in terms of mortality. Physical exercise added to standard care might improve fatigue and depression. Currently, there is inconclusive evidence regarding QoL, physical functioning, anxiety and SAEs .

We need further trials with more participants and longer follow-up periods to evaluate the effects of exercise intervention for people suffering from haematological malignancies. To enhance comparability of study data, development and implementation of core sets of measuring devices would be helpful.

PLAIN LANGUAGE SUMMARY

The role of aerobic physical exercise for adults with haematological malignancies

What is the aim of this review?

The aim of this Cochrane Review was to find out whether aerobic physical exercise can improve health, or play a supporting role for adult patients suffering from haematological malignancies. We collected and analysed all relevant studies to answer this question and found 18 relevant studies, of whom 14 reported our pre-defined patient-relevant outcomes.

Key messages

Aerobic physical exercise probably has a positive effect on fatigue and depression of patients with haematological malignancies. Evidence related to mortality, quality of life, and serious adverse events is still unclear.

What was studied in the review?

Haematological malignancies are tumours of the blood-forming system, such as lymphomas, leukaemias, myelomas, myelodysplastic syndromes and myeloproliferative diseases. These diseases represent approximately seven per cent of new cancer diagnoses worldwide. Treatment strategies include wait-and-watch approaches, chemotherapy, radiotherapy, immunotherapy and stem cell transplantation, as well as supportive care to prevent, control or treat complications and side effects.

Although these patients have to endure long phases of therapy and immobility, which has a negative effect on their physical performance level, it is still common practice to recommend rest and to avoid intensive exercise.

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There are several studies and approaches that try to establish another strategy and to include physical exercise, especially aerobic physical exercise, into the treatment strategy of haematological malignancies. In detail, these exercise programmes consist of aerobic, resistance and flexibility components, partly home-based. Some prefer it to be integrated in daily living. A common method is also the use of tools such as bicycle ergometers or stretch bands as well as walking exercises. Aerobic physical exercise might improve oxygen supply to muscles and tissues of the body.

What are the main results of the review?

The review authors of this review update identified nine new trials which could be added to the nine trials of the first version of this review. Of these 18 trials, 14 trials provided sufficient data to be meta-analysed. Although six trials reported how many participants died during the study period or during the first 100 days, there is no evidence for differences in this outcome between the exercise group and the control group.

Eight trials measured quality of life, physical functioning and anxiety and did not show any evidence for a difference between additional exercise and usual care. There might be a benefit for the exercise group in terms of fatigue and depression.

The evidence for serious adverse events is based on very low certainty, therefore results are still uncertain.

In addition, we are aware of four ongoing trials. However, none of these trials stated, how many patients they will recruit and when the studies will be terminated, thus, potential influence of these trials for the current analyses remains unclear.

How up-to-date is the review?

The review authors searched for studies that had been published up to July 2018.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Physical exercise versus no physical exercise for adults with haematological malignancies

Physical exercise versus no physical exercise for adults with haematological malignancies

Patient or population: Adults with haematological malignancies
Settings: Inpatient or outpatient
Intervention: Physical exercise versus no physical exercise

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 group without exercise	Physical exercise				
Mortality	149 per 1.000	**164 per 1.000** (117 to 226)	**RR 1.10** (0.79 to 1.52)	1172 (6 RCTs)	⊕⊕⊝⊝ **low** [1,2]	
Quality of Life Scale from: -1 to 1 with 1 indicating best outcome		The mean QoL score in the intervention group was **0.11 higher (better)** (-0.03 to 0.24 higher)	SMD **0.11 higher** (-0.03 to 0.24 higher)	1259 (8 RCTs)	⊕⊕⊝⊝ **low** [2,3]	
Physical functioning/QoL Scale from: -1 to 1 with 1 indicating best outcome		The mean physical functioning/QoL score in the intervention group was **0.15 higher (better)** (-0.01 to 0.32 higher)	SMD **0.15 higher** (-0.01 to 0.32 higher)	1329 (8 RCTs)	⊕⊕⊝⊝ **low** [2,3]	
Depression/QoL Scale from: -1 to 1 with 1 indicating best outcome		The mean depression/QoL score in the intervention group was **0.19 higher (better)** (0 to 0.38 higher)	SMD **0.19 higher** (0.00 to 0.38 higher)	445 (6 RCTs)	⊕⊕⊝⊝ **low** [1,3]	
Anxiety/QoL Scale from: -1 to 1 with 1 indicating best outcome		The mean anxiety/QoL score in the intervention group was **0.03 higher (better)** (-0.30 to 0.36 higher)	SMD **0.03 higher** (-0.30 to 0.36 higher)	445 (6 RCTs)	⊕⊝⊝⊝ **very low** [2,3,4]	

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Fatigue Scale from: -1 to 1 with 1 indicating best outcome		The mean fatigue score in the intervention group was **0.31 higher (better)** (0.13 higher to 0.48 higher)	SMD **0.31 higher** (0.13 higher to 0.48 higher)	826 (9 RCTs)	⊕⊕⊕⊖ **moderate** [3]
Serious adverse events	174 per 1.000	**242 per 1.000** (164 to 359)	**RR 1.39** (0.94 to 2.06)	435 (6 RCTs)	⊕⊖⊖⊖ **very low**[5,6]

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Small number of participants/events leads to downgrading (1 point) for imprecision.
[2]Confidence interval including clinically relevant benefits or harms leads to downgrading (1 point) for imprecision.
[3]Outcome assessor (participant) not blinded in participant-reported outcome (QoL questionnaires) leads to downgrading by one point for risk of bias.
[4] High heterogeneity leads to downgrading by one point due to inconsistency.
[5] Baseline imbalances, especially usage of erythropoietin and thalidomide unknown in both intervention arms leads to downgrading by one point due to inconsistency.
[6]Very small number of participants and events, very wide confidence interval to downgrading (2 points) for imprecision.

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BACKGROUND

Description of the condition

A haematological malignancy is a tumour of the myeloid or lymphatic cell lines affecting blood, bone marrow or the lymph nodes with possible involvement of other organs. Lymphomas, leukaemias, myelomas, myelodysplastic syndromes and myeloproliferative diseases are all haematological malignancies and account for nearly 10% of new cancer diagnoses in the USA (Howlader 2012). The global age-adjusted incidence rate of haematological malignancies is 40.3 new cases per 100,000 men and women per year. Individual scores are leukaemia (12.6), lymphoma (22.4) and myeloma (5.6) with all their various subcategories (Altekruse 2009).

Depending on the type and stage of the neoplastic disease, the clinical course can be indolent or aggressive with different patterns of treatment behaviour and treatment response. Various treatment options are available for people with haematological malignancies, extending from watch-and-wait approaches to single- or multi-agent chemotherapy, radiotherapy, immunotherapy and autologous or allogeneic stem cell transplantation. Best supportive care is provided to make people more comfortable and to prevent, control or treat complications and side effects (Cullen 2001).

The prevailing advice for patients is to rest and avoid intensive exercise, without taking note of the unfavourable consequences of omitting physical exertion. This advice is mainly based on the properties of cytopenia (reduction in the numbers of any of the blood cell elements) from which most patients suffer. A low performance status due to severe anaemia and thrombocytopenia can potentially lead to haemorrhages, while the reduced immune status due to leukopenia increases the risk for infections (Tosetto 2009).

Description of the intervention

One important challenge in treating people with haematological cancer is physical deconditioning. It is highly prevalent in this population and is the result of various circumstances such as the oncologist's advice to rest, cardiotoxic, neurotoxic or pulmo-toxic anti-cancer therapy, anaemia, thrombocytopenia or cachexia. Exercise has been introduced to improve physical functioning and to increase the ability to cope with activities of daily living. Some evidence suggests that physical exercise, especially aerobic exercise that aims to improve the oxygen system, increases cardiorespiratory fitness, muscle strength and physical well-being in people with haematological cancer (Coleman 2012; Courneya 2009; Moyer-Mileur 2009; Thorsen 2005).

People undergoing intensive chemotherapy suffer from unintended effects of the therapy such as inflammation due to long-lasting immunosuppression and leukopenia. Apart from this, the inability to perform normal physical activity is a decisive limiting factor in the treatment of people with haematological malignancies. For them, this implies detrimental effects on their quality of life, as several studies have shown (Broers 2000; Fife 2000). Nevertheless, physical exercise programmes still occupy a minor role in the treatment concepts of haematological malignancies. Furthermore, we lack reliable data from randomised controlled trials (RCTs) about risk factors, feasibility and outcomes of exercise in people with haematological malignancies, particularly with regard to overall survival (OS).

The first study of therapeutic exercise in the follow-up treatment of people suffering from breast cancer explicitly showed a positive physical and psychological effect (Schule 1983). Owing to the positive impact of this and further studies, exercise therapy has become a part of oncological treatment concepts (Dimeo 1996; Mock 1994; Peters 1994). The former opinion that exercise as part of health-orientated therapy, concomitant with or immediately after medical therapy, could be harmful and should not be started before complete remission is achieved, has proved to be incorrect (Andrykowski 1989; Dimeo 1996). The most intensively investigated types of cancer are breast, colorectal and prostate cancers, where large prospective phase III trials are active and clear recommendations for activity were given (Courneya 2013; Dieli-Conwright 2014; Doyle 2006). Important factors such as quality of life, physical functioning, depression and many other factors could be improved in those patients performing exercise (McCullough 2014).

Another essential burden for people with cancer is cancer-related fatigue. It is defined as debilitating symptoms of physical, emotional and cognitive tiredness or exhaustion related to cancer or cancer treatment (NCCN 2014). Cancer-related fatigue is very common during or after treatment and is reported by 60% to 90% of people with cancer (Wagner 2004). In recent meta-analyses physical exercise has resulted in some reduction of cancer-related fatigue in people with solid tumours (Velthuis 2010).

Aside from this recent development, the extent of physical exercise for people suffering from blood cancers remains unclear. Previous studies suggest that aerobic exercise can be safely carried out immediately after high-dose chemotherapy and can partially prevent loss of physical performance (Dimeo 1996; Dimeo 1997). Data from Dimeo 1997 suggest that exercise mediates better maximal physical performance at discharge and shorter durations of neutropenia, thrombopenia and hospitalisation.

How the intervention might work

There is some evidence for a protective role of physical activity for cancer, in particular colon, breast (postmenopausal) and endometrial cancers (Parent 2011). A 20% to 40% reduced risk of several cancer types is reported in the current literature (Parent 2011). The precise/further underlying mechanisms for physical activity in reducing cancer risk remain to be elucidated. Several biological mechanisms have been suggested, which could equally apply to many cancer entities (Friedenreich 2001). These include a decrease in obesity and central adiposity, hormone level and growth factor modulation, modification of carcinogen activation and improvement in immune function (Li 2010a). Li 2010b reported immunomodulation due to physical activity as an increase of human natural killer activity and enhanced expression of intracellular anti-cancer proteins in lymphocytes.

Why it is important to do this review

This is the updated version of the first systematic review taking into consideration the evidence from randomised comparisons on the impact of physical exercise in adults with haematological malignancies. The main question stated is whether physical exercise in addition to standard care is beneficial regarding OS,

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fatigue and quality of life compared to standard care alone. Further questions elucidate the role of physical exercise in terms of physical strength, well-being and adverse effects.

In order to obtain conclusive evidence on the impact of physical exercise, we have performed a systematic review and meta-analysis. A summary of all results will help us to choose the best available physical exercise approach and to reach conclusions about safety and effectiveness.

OBJECTIVES

To evaluate the efficacy, safety and feasibility of aerobic physical exercise for adults suffering from haematological malignancies.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs) for inclusion. We included both full-text and abstract publications.

Types of participants

We included trials on adults (18 years and over) with confirmed diagnoses of haematological malignancies. We did not apply gender or ethnicity restrictions. We considered all subtypes and stages of haematological malignancies, including newly-diagnosed patients and those with relapsed or drug-resistant disease. If trials had consisted of mixed populations with different conditions or types of cancer, we would have used data only from the haematological malignancy subgroups. If subgroup data for these participants had not been provided (after contacting the authors of the trial), we would have excluded the trial if fewer than 80% of participants had haematological malignancies.

Types of interventions

The main intervention was aerobic physical exercise in addition to standard care, compared to standard care alone. We only included studies that evaluated the response of the participant to aerobic exercise, intending to improve the oxygen system. Accordingly, we included studies that chose exercise interventions such as moderate cycling, walking, Nordic walking, running, swimming and other related forms of sport. These kinds of sports are easy to regulate with regards to load control. We also included studies that analysed further physical exercise programmes, such as moderate strength training in addition to the aerobic exercise programme. We did not include training programmes that were composed of yoga, tai chi chuan, qigong and similar types of exercise. We also excluded studies solely exploring the influence of strength training. Additionally, we excluded studies assessing outcomes without any clinical impact.

Types of outcome measures

We included all trials fitting the above mentioned inclusion criteria, irrespective of outcomes reported

Primary outcomes

We predefined overall survival (OS) as the primary efficacy outcome. As this outcome was reported in one trial only, but mortality was reported in six trials, we also evaluated mortality.

Secondary outcomes

We analysed the following outcomes as secondary outcomes:

- quality of life;
- fatigue;
- physical performance (e.g. aerobic capacity, cardiovascular fitness);
- anthropometric measurements (e.g. weight, body mass index);
- adverse events.

Search methods for identification of studies

Electronic searches

We adapted the search strategies as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We applied no language restriction, to reduce the language bias. There were no restrictions by date or by publication status (e.g. abstract, conference proceedings, unpublished data, dissertations, etc).

We searched the following databases and sources.

- Databases of medical literature:
  - Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2018, Issue 7) (for search strategy, see Appendix 1);
  - MEDLINE (1950 to 30 July, 2018) (for search strategy, see Appendix 2).
- Conference proceedings of annual meetings (1990 to 2018) of the following societies for abstracts if not included in CENTRAL:
  - American Society of Hematology (ASH) (2011 to 2017);
  - American Society of Clinical Oncology (ASCO) (2011 to 2018);
  - European Hematology Association (2011 to 2018).
- Databases of ongoing trials:
  - for the original version of the review:
    - meta-register of controlled trials: www.controlled-trials.com/mrct/.
  - for the update: we electronically searched in the database of ongoing trials up to 01 July 2018
    - ISRCTN: http://www.isrctn.com;
    - EU clinical trials register: https://www.clinicaltrialsregister.eu/ctr-search/search;
    - Clinicaltrials.gov: https://clinicaltrials.gov/.

Searching other resources

- Handsearching of references:
  - we checked references of all identified trials and relevant review articles for further literature.

Data collection and analysis

Selection of studies

Three review authors (LK, NS; NB and NS for the first version of the review) independently screened the results of the search strategies for eligibility for this review by reading relevant abstracts. In case of disagreement, we obtained the full-text publication (Higgins 2011b).

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We documented the study selection process in a flow chart as recommended in the PRISMA statement (Moher 2009) showing the total numbers of retrieved references and the numbers of included and excluded studies.

Data extraction and management

Two review authors (LK, NS; NB and NS for the first version of the review) independently extracted the data according to the guidelines proposed by Cochrane (Higgins 2011b). We used a standardised data extraction form containing the following items.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Quality assessment: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other potential sources of bias.
- Study characteristics: trial design, aims, setting and dates, source of participants, inclusion and exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation.
- Participant characteristics: underlying disease, stage of disease, histological subtype, additional diagnoses; age, gender, ethnicity; number of participants recruited, allocated, evaluated; participants lost to follow-up; type of treatment (multi-agent chemotherapy, intensity of regimen, number of cycles), additional radiotherapy, type and dosage of monoclonal antibodies, bone marrow transplantation.
- Interventions: type, duration and intensity of physical exercise; standard care; duration of follow-up.
- Outcomes: OS, aerobic capacity, cardiovascular fitness, anthropometric measurements, quality of life, fatigue, adverse events.

We used both full-text versions and abstracts including additional information (for example slides) of eligible studies to retrieve the data. We extracted trials reported in more than one publication on one form only. Where these sources did not provide sufficient information, we had planned to contact the authors for additional details.

Assessment of risk of bias in included studies

To assess quality and risk of bias, two review authors (NS, LK) independently assessed the risk of bias for each study using the following criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a):

- Sequence generation
- Allocation concealment
- Blinding (participants, personnel, outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other potential sources of bias.

For every criterion, we made a judgement using one of three categories.

- 'Low risk': if the criterion was adequately fulfilled in the study, i.e. the study was at a low risk of bias for the given criterion;
- 'High risk': if the criterion was not fulfilled in the study, i.e. the study was at high risk of bias for the given criterion;
- 'Unclear': if the study report did not provide sufficient information to allow for a judgement of 'Yes' or 'No' or if the risk of bias was unknown for one of the criteria listed above.

Measures of treatment effect

We estimated treatment effect measures of individual studies as relative effect measures (RR) with 95% confidence intervals (CI) for dichotomous data. For survival data, we estimated treatment effects by extracting hazard ratios (HR) of individual studies and analysing these using the methods described by Parmar (Parmar 1998) and Tierney (Tierney 2007).We calculated continuous outcomes as mean differences (MD) or in case of different scales in various studies as standardised mean differences (SMDs) with 95% CIs for each trial.

Dealing with missing data

As suggested in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), there were many potential sources of missing data which we had to take into account, at a study level, outcome level, and summary data level. Firstly, it was important to distinguish between 'missing at random' and 'not missing at random'. We did not identify any missing data.

Assessment of heterogeneity

In meta-analyses with at least three trials, we assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. In that case, we used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Deeks 2011). We explored potential causes of heterogeneity by sensitivity and subgroup analyses where possible.

Assessment of reporting biases

In a meta-analysis with at least 10 trials, we would have explored potential reporting bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2011). A P value less than 0.1 would have been considered significant for this test. However, we only included maximum nine trials in one meta-analysis, so this test was not performed.

Data synthesis

We performed analyses according to the recommendations of chapter nine of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into the Cochrane statistical package Review Manager (RevMan) 5.3. One review author entered data into RevMan software and an another review author checked it for accuracy. Due to variation of types of haematological malignancies of participants and the different duration and intensity of the physical intervention, we performed meta-analyses using a random-effects model.

If appropriate, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH).

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We used the software GRADEpro 3.2 to create 'Summary of Finding' tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann 2011).

We ranked the following outcomes as the most patient-relevant outcomes and presented them in the 'Summary of findings' table: overall survival (OS)/mortality, quality of life, physical functioning/quality of life (QoL), depression/QoL, anxiety/QoL, fatigue, serious adverse events.

Subgroup analysis and investigation of heterogeneity

We considered the following characteristics for subgroup analyses, but data were too sparse to perform subgroup analyses.

- Age of included patients
- Type of therapy of underlying disease (chemotherapy versus radiotherapy versus no treatment)
- Type, duration, intensity of physical exercise

We analysed subgroups for patients receiving stem cell transplantation versus non stem cell transplantation as treatment of their underlying disease.

Sensitivity analysis

We analysed quality components (high risk of bias versus low risk of bias). We considered analysing full-text publications versus abstract publications, but all the included trials were reported as full texts.

RESULTS

Description of studies

Results of the search

Our literature search led to 4314 new publications to screen for this update. We excluded 4231 publications because they did not correspond with our inclusion criteria or were duplicates. We retrieved the remaining 51 publications as full-text or abstract publications for further evaluation. Of these 72 publications, we finally excluded 34. At the end of our screening procedure, nine new studies (17 publications) could be added to the nine studies (21 references) from the first version of the review, leading to 18 studies with 38 publications in total.

We did not meta-analyse data from four of these 18 included trials, which evaluated outcomes that are not patient-relevant (laboratory values only) (Cunningham 1986; Kim 2006), or reported data in a way that could not be included in the meta-analysis (Alibhai 2014; Bryant 2018). Cunningham 1986 investigated the influence of training on muscle strength or muscle protein status. Kim 2006 investigated the effect of physical exercises on lymphocyte and T-cell subsets. One trial (40 patients) reported change-scores only (Alibhai 2014); another trial evaluating 17 patients did not report standard difference or standard error (Bryant 2018), therefore both trials could not be included in meta-analyses.

For the first version of the review, nine studies with 20 publications were included in the analysis of the review.

Additionally, currently four RCTs are ongoing (Abildgaard 2018; Courneya 2017; Oberste 2016; Walsh 2005). As the authors of these trials do not report, how many participants they will recruit and when the trial will be terminated, the potential influence of these trials for the current analyses is unclear. The study by Walsh 2005 and colleagues started in 2005 and according to the study registry, clinicaltrials.gov it still seems to be active and recruiting patients. One study has been published as an abstract only and is awaiting classification as it remains unclear, due to missing information, whether this trial fits our pre-defined inclusion criteria (Wehrle 2018).

The overall number of references screened, identified, selected, excluded and included is documented according to the PRISMA flow diagram (Figure 1).

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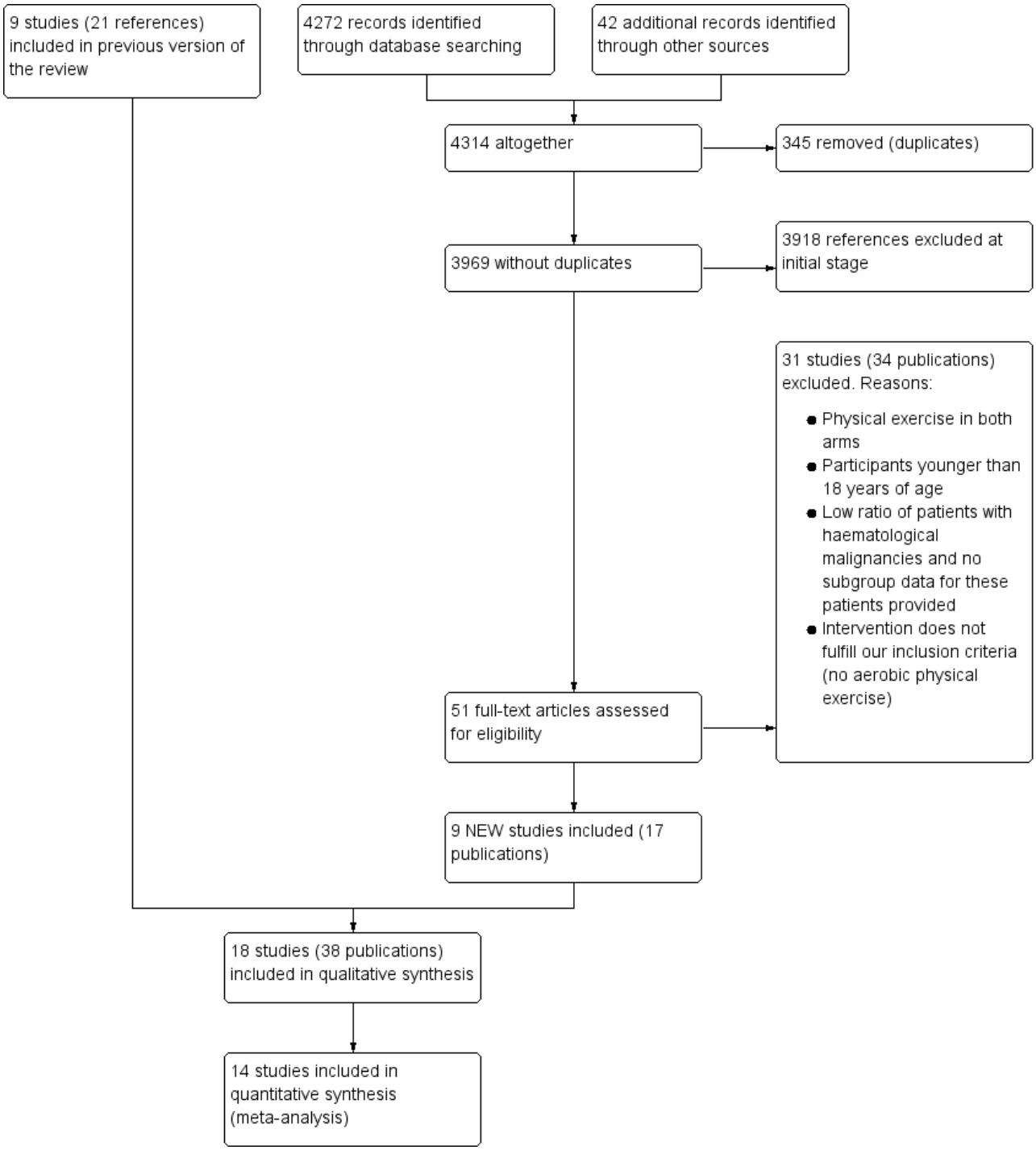
Figure 1. Flow diagram.



Included studies

Eighteen trials in 38 publications, including a total of 1892 participants (range 18 to 711), fulfilled the inclusion criteria (Alibhai 2014; Baumann 2010; Bryant 2018; Chang 2008; Coleman 2003; Coleman 2012; Courneya 2009; Cunningham 1986; DeFor 2007; Furzer 2016; Jacobsen 2014; Jarden 2016; Kim 2006; Knols 2011; Mello 2003; Persoon 2017; Streckmann 2014; Wiskemann 2015).

We did not meta-analyse two (65 participants) of these 18 RCTs because they evaluated laboratory values only and did not report the pre-specified outcomes of this review (Cunningham 1986; Kim 2006). One further trial (17 participants) did not provide data in a sufficient way to be meta-analysed (without confidence intervals or standard deviations) (Bryant 2018). Another trial (40 participants) reported change scores instead of endpoint scores, prohibiting data to be meta-analysed (Alibhai 2014).

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We summarise the features of the included trials in the Characteristics of included studies table.

Nine trials reported no periods for trial recruitment. The earliest trial started recruitment in 2002 (Baumann 2010) until 2004, and the latest trials stopped in 2015 (Bryant 2018). All trials were published as full-text publications.

Design

Sixteen of the included trials were two-armed randomised controlled trials (RCTs), one was a three-armed RCT (Cunningham 1986) and one was a four-armed RCT (Jacobsen 2014). In order to include this last trial into our review, we divided it into two subgroups and analysed it correspondingly. One subgroup (Jacobsen 2014a) included participants with the goal to exercise three to five times a week for 20 to 30 minutes at 50% to 75% of estimated heart rate reserve compared with participants offered usual care, without any structured or supervised training and without encouragement to do physical exercise. The other subgroup (Jacobsen 2014b) evaluated participants with the advice to exercise three to five times a week for 20 to 30 minutes at 50% to 75% of estimated heart rate reserve and to perform stress management training consisting of paced abdominal breathing, progressive muscle relaxation with guided imagery, and coping self-statements. Participants in the control group received usual care and performed only the stress management training.

Sample sizes

The smallest trial (Mello 2003) randomised 18 participants and the largest trial 711 participants (Jacobsen 2014). Seven trials provided sample size calculation (Alibhai 2014; Coleman 2012; Jacobsen 2014; Jarden 2016; Kim 2006; Knols 2011; Streckmann 2014). However, Coleman 2012 provided different calculations in various publications and Streckmann 2014 was stopped early due to slow recruitment.

Location

Six trials were conducted in the USA (Bryant 2018; Coleman 2003; Coleman 2012; Cunningham 1986; DeFor 2007; Jacobsen 2014); two trials were conducted in Canada (Alibhai 2014; Courneya 2009), one in Taiwan (Chang 2008), one in Switzerland (Knols 2011), one in Australia (Furzer 2016), one in Denmark (Jarden 2016), one in the Netherlands (Persoon 2017), one in Brazil (Mello 2003), one in South Korea (Kim 2006) and three in Germany (Baumann 2010; Streckmann 2014; Wiskemann 2015).

Participants

A total of 1892 men and women with haematological malignancies were randomly allocated either to a physical exercise group plus standard care or to a standard care alone group. The type of underlying haematological malignancy differed between studies. Two studies only included people with acute myeloid leukaemia (Alibhai 2014; Chang 2008). Three studies involved people with acute leukaemia (Bryant 2018; Cunningham 1986; Jarden 2016). In two studies all evaluated participants suffered from multiple myeloma (Coleman 2003; Coleman 2012). Two studies randomised participants with lymphomas (Courneya 2009; Streckmann 2014), one study included explored people with multiple myeloma or lymphomas (Persoon 2017). In the trials by Baumann 2010, DeFor 2007, Furzer 2016, Jacobsen 2014, Kim 2006, Knols 2011, Mello 2003 and Wiskemann 2015, participants suffered from various haematological diseases (mainly acute myeloid leukaemia or acute lymphatic leukaemia).

In nine trials, participants received stem cell transplantation (Alibhai 2014; Baumann 2010; Coleman 2003; Coleman 2012; Cunningham 1986; DeFor 2007; Knols 2011; Mello 2003; Wiskemann 2015). In three trials, participants received autologous blood stem cell transplantation (Coleman 2003; Coleman 2012; Persoon 2017), and in another four trials participants received allogeneic stem cell transplantation (Cunningham 1986; DeFor 2007; Mello 2003; Wiskemann 2015). In two trials, participants received either autologous or allogeneic transplantation, depending on the underlying disease and donor availability (Baumann 2010; Knols 2011). In one trial, only some of the participants received stem cell transplantation (Jarden 2016).

Interventions

In all included trials, physical exercise was performed in addition to standard care and compared with standard care alone. The intensity and the extent of the physical exercise intervention differed between the studies.

Alibhai 2014: participants in the exercise group were offered home-based exercise three to five days per week. Training was supposed to be performed at a moderate intensity for 30 minutes per session. It consisted of aerobic, resistance and flexibility components and required no or minimal equipment, such as a stability ball and resistance bands, which were provided. Additionally, participants were invited to attend weekly group-based booster sessions.

Baumann 2010: participants in the exercise arm were offered endurance training on a bicycle ergometer, for 10 to 20 minutes twice a day. Moreover, they participated twice a day in training activities for daily living to maintain mobility. Mostly, this training consisted of walking, stepping and stretching. The exercise programme started six days before transplantation, for five days a week, and lasted until one day before hospital discharge. People in the control group attended a low-intensity programme of active and passive mobilisation, starting one day after transplantation until hospital discharge.

Bryant 2018: participants in the exercise arm took part in an individualised prescriptive exercise intervention two to four times per week for a period of the induction chemotherapy/in-hospital recovery. Each session was divided into two parts, of which one took part in the morning, the other one in the afternoon. There was a break of at least 36 hours between sessions.

Chang 2008: the exercise intervention consisted of a three-week walking programme of 12 minutes walking for five days a week. The control group did not perform any physical exercise programme. All participants in both arms received chemotherapy with cytarabine and idarubicin.

Coleman 2003: exercise consisted of an aerobic component (usually walking, but depending on the fitness and preferences of the participant, perhaps running or cycling) and strength resistance training (using exercise stretch bands). This programme was home-based. The exercise programme started three months before and ended three months after stem cell transplantation. The control group received best-practice usual care in terms of activity and rest provided by their physician.

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Coleman 2012: participants in the exercise group received individualised exercise and a set of exercise stretch bands with varying resistance. Strength resistance training was included to strengthen muscles so participants could improve the aerobic component of the exercise programme. People in the control group were advised to remain as active as possible and to try to walk 20 minutes a day. Duration of this short-term study was 15 weeks. The first 70 participants who were eligible for long-term participation (i.e. response to erythropoietin) continued in the study for an additional 15 weeks. Participants in both groups (exercise and control) received chemotherapy with an intensive treatment protocol (called Total Therapy II) and stem cell transplantation. Fifty per cent of all participants were randomised to receive additionally thalidomide (400 mg daily) during induction, after transplantation consolidation, and maintenance therapy. Furthermore, 76% (N = 102 participants) received erythropoietin.

Courneya 2009: the exercise programme consisted of bicycle ergometer training three times a week for 12 weeks. Intensity began at 60% of the peak power output and was increased by 5% each week to 75% by the fourth week. Duration began at 15 to 20 minutes for the first four weeks and increased by five minutes a week to 40 to 45 minutes in the ninth week. Additionally, participants in the physical exercise group performed one session a week of interval training. Participants in the control group were asked not to increase exercise above baseline. In both groups, some participants received chemotherapy. These participants may have started treatment before enrolment, but needed to have at least eight weeks of planned treatment remaining. Some participants had already received chemotherapy and some were off treatment.

Cunningham 1986: the exercise programme consisted of the following exercise: 15 repetitions of bicep-tricep curls, bench press, shoulder retractors, straight leg raises, hip extension, hip abduction and sit ups. This was performed three or five times a week, depending on the assignment to one of the exercise groups, for a period of 35 days.

DeFor 2007: participants in the exercise group were asked to walk for at least 15 minutes twice a day on a treadmill that was placed in their hospital room. After discharge, participants in the exercise group were asked to walk once a day for at least 30 minutes. Participants were told to walk at a comfortable speed and to discontinue the workout if they felt any discomfort or dizziness or if the medical staff advised them to do so. This regimen continued until 100 days post transplant. Participants in the control group were not asked to perform any formal exercise, and were not provided with a treadmill unless the participant or staff requested it. In both arms, there was a subset of participants receiving non-myeloablative conditioning and a subset receiving myeloablative conditioning before allogeneic stem cell transplantation. The authors reported that the activity level prior to transplantation did not differ between the two arms (P = 0.45), but that more participants in the intervention arm (93%) exercised during hospital stay compared to the control arm (58%; P = 0.01).

Furzer 2016: participants in the exercise group were asked to attend a mixed training consisting of cardiovascular training and endurance training. Each session included warm-up and cool-down prior to cardiovascular training at 50% of heart rate max, with a maximum duration of 30 minutes per session. Participants used monitors to maintain prescribed heart rate. Exercise progression was achieved by 1) increasing heart rate intensity (up to 70% heart rate max) and 2) decreasing duration (10-15 minutes) while additionally increasing heart rate intensity (up to 85% hear ratio max). The endurance component consisted of eight exercises targeting the major muscle groups (three sets of 10-15 repetitions), a progression in weight was possible.

Jacobsen 2014: see Jacobsen 2014a; Jacobsen 2014b

Jacobsen 2014a: Participants randomised to the exercise arm were given a packet of materials, including a videotape, a brochure, a workbook and an electronic step counter in order to be able to perform and track a home-based exercise program with an emphasis on walking. The intervention was carried out before a planned haematopoietic cell transplantation (HCT). The goal was to exercise 3 to 5 times a week for 20 to 30 minutes per session at 50% to 75% of estimated heart rate reserve. Trained site personnel served as interventionists and introduced the program as well as giving advice concerning proper technique and overcoming potential barriers.

Jacobsen 2014b: participants randomised to the interventional arm were given an packet of materials, including a videotape, a brochure, a workbook and an electronic step counter in order to be able to perform and track a home-based exercise program with an emphasis on walking. Additionally, they were given a relaxation CD. The intervention was carried out before a planned HCT. Concerning the exercise program, the goal was to exercise three to five times a week for 20 to 30 minutes per session at 50% to 75% of estimated heart rate reserve. Trained site personnel served as interventionists and introduced the program as well as giving advice concerning proper technique and overcoming potential barriers. The stress-management goal targeted paced abdominal breathing, progressive muscle relaxation with guided imagery, and coping self-statements to decrease and manage stress.

Jarden 2016: participants allocated to the exercise arm received a 12-week exercise program, three times week, for 60 to 70 minutes per session. Sessions consisted of stationary cycling for 20-25 minutes, six dynamic resistance exercises using hand weights in two sets of 12 repetitions and nutrition support. Additionally, counselling sessions were conducted at week zero, six and 12.

Kim 2006: participants randomised to the exercise group performed an exercise program every day for thirty minutes over a period of six weeks. Sessions consisted of preliminary exercise for 10 minutes, relaxation breathing for 10 minutes and finish exercise for 10 minutes. The preliminary exercises were performed in this sequence: concentrate the attention on lower abdomen for three minutes; put left ankle on right knee for three minutes; put right ankle on left knee for two minutes; and bend both knees for two minutes. The finishing exercises were performed in this sequence: resting and relaxing of body and mind for two minutes; stroking down hair and face for two minutes; right and left rotating of both ankles for two minutes; stretching of legs and arms for two minutes; and stretching out on a bed for two minutes.

Knols 2011: participants were randomised to a 12-week outpatient programme of physical exercise, consisting of supervised aerobic and strength exercises, or to a usual care group without any advice for physical exercise. The physical exercise was performed twice weekly in a physiotherapy practice or fitness centre. Participants

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started with 10 minutes ergometer cycling or walking treadmill, followed by progressive resistance training.

Mello 2003: participants allocated to the exercise arm received a six-week exercise program, carried out five times a week for 40 minutes. It involved exercises for shoulder, elbow, hip, knee and ankle, as well as stretching exercises and a treadmill walking program. Participants allocated to the control group received usual care.

Persoon 2017: participants were randomised to a 18-week exercise programme consisting of high-intensity resistance and interval training. Participants did training on specialised resistance training equipment and bicycle ergometers. In weeks one to 12, participants performed resistance and interval training twice a week for 60 minutes per training session. In weeks 13 to 18, the intensity of exercise was decreased to one session a week with a duration of 60 minutes. Participants in the control group received usual care.

Streckmann 2014: participants in the exercise arm attended an aerobic endurance training programme, consisting of cardiovascular activation on a bicycle dynamometer and 10 to 30 minutes walk on a treadmill or bicycle ergometer at the end of the training. Participants were also offered sensorimotor training, progressively increasing in task difficulty, and a strength training of four resistance exercises carried out for one minute. Participants in the control group received physiotherapy.

Wiskemann 2015: participants started the exercise intervention on an outpatient basis before allogeneic haematopoietic stem cell transplantation (in general one to four weeks before admission to the hospital), proceeded during the inpatient period and continued the intervention until six to eight weeks after discharge from the hospital. The outpatient intervention was continued as a self-directed activity at home, whereas the inpatient period was partly supervised twice a week and adapted to the conditions of an isolation unit. The intervention consisted of three endurance training sessions (up to five during hospitalisation) and two resistance training sessions a week. Endurance training in the outpatient setting was recommended as rapid walking for 20 to 40 minutes. In the inpatient setting the participants performed bicycling and treadmill walking instead of the walking intervention. Additionally, participants performed strength training with and without stretch bands. Participants in the control group were told that moderate physical activity is favourable during the treatment process, without further advice. During the inpatient period, physiotherapy was offered up to three sessions a week (average duration of one session: 30 minutes). For this period, the control group had the same access to stationary bicycles and treadmills as the intervention group (not reported, how many participants exercised). All participants received allogeneic stem cell transplantation.

Outcomes

Primary outcome measure

Our primary outcome OS was only reported in one of the included trials (Wiskemann 2015). Mortality was reported by six trials. One of them assessed 180-day mortality (Jacobsen 2014). One study assessed 100-day mortality (DeFor 2007). Baumann 2010 and Wiskemann 2015 reported the number of participants who died during hospital stay; all deaths occurred as a transplant-related complication. Mello 2003 reported that ten patients died but did not provide any data in which arm the patients died.

Secondary outcome measures

Nine studies reported quality of life (QoL) (Alibhai 2014; Baumann 2010; Courneya 2009; Furzer 2016; Jacobsen 2014; Jarden 2016; Persoon 2017; Streckmann 2014; Wiskemann 2015). Eleven studies mentioned fatigue (Alibhai 2014; Baumann 2010; Chang 2008; Coleman 2012; Courneya 2009; Furzer 2016; Jarden 2016; Knols 2011; Persoon 2017; Streckmann 2014; Wiskemann 2015), however only eight reported data in a similar way to be combined for QoL and nine to be analysed for fatigue. Thirteen trials assessed physical performance data (Alibhai 2014; Baumann 2010; Chang 2008; Coleman 2003; Coleman 2012; Courneya 2009; Furzer 2016; Jarden 2016; Knols 2011; Mello 2003; Persoon 2017; Streckmann 2014; Wiskemann 2015). Anthropometric measurements were captured by three studies (Courneya 2009; Furzer 2016; Knols 2011). Six trials reported serious adverse events or adverse events (Chang 2008; Coleman 2012; Courneya 2009; Jarden 2016; Persoon 2017; Streckmann 2014). Some studies explored further outcomes that are irrelevant for this systematic review, but could be partly relevant for clinical practice. Baumann 2010 reported lung function, Chang 2008 explored the time to recovery after transplantation, DeFor 2007 investigated physical and emotional well-being at discharge and 100 days posttransplant, and Streckmann 2014 reported movement co-ordination and balance control (see Characteristics of included studies).

Conflict of interest

One study was supported by the Lance Armstrong Foundation (Courneya 2009), one study by the National Heart, Lung, and Blood Institute and the National Cancer Institute (Jacobsen 2014), one study by the SolarisCare foundation (Furzer 2016), one study by The Center for Integrated Rehabilitation of Cancer Patients, The Novo Nordic Foundation, The University Hospitals' Centre for Health Research (UCSF), The Lundbeck Foundation, The Novo Nordic Foundation for Clinical Nursing Research and The Danish Cancer Society (Jarden 2016), one by the Zurich cancer league and the Federal Authorities of the Swiss Confederation, Federal Department of Defence, Civil Protection and Sport (Knols 2011), and one study by AMGEN (Streckmann 2014).

Excluded studies

In total, we excluded 31 studies (36 references). Four studies included participants younger than 18 years (Hartman 2009; Marchese 2004; Moyer-Mileur 2009; Tanir 2013). We excluded four studies because exercise was offered in both arms (PETRA study; Schumacher 2015a; Shelton 2009; Vallerand 2018). In one trial, a multimodal intervention was offered, including a structured exercise programme, progressive relaxation, and psycho-education (Jarden 2009). We excluded 15 studies because of the involvement of participants suffering from non-haematological cancers, such as breast cancer, testicular cancer or gynaecological cancer did not report subgroup data (Broderick 2013; Forbes 2017; Grabenbauer 2016; Kampshoff 2015; Kanera 2017; Midtgaard 2013; Oechsle 2014; Peoples 2017; Stacey 2016; Thorsen 2005; Toohey 2016; Tran 2016; Valle 2013; van Waart 2015; Zimmer 2014). We excluded one study because it remained unclear which types of malignancies involved participants had been diagnosed with (Mayo 2014).

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We excluded five studies because the applied exercise interventions did not correspond to our inclusion criteria (Cohen 2004; Hacker 2011; Hacker 2016; Prinsen 2013; Yeh 2016). Cohen 2004 explored the influence of a Tibetan yoga intervention on psychological adjustment and sleep quality. Hacker 2011 and Hacker 2016 explored the effect of strength training on physical activity, muscle strength, health status perception, and quality of life. Prinsen 2013 explored the influence of cognitive behavioural therapy on physical activity, physical fitness and fatigue. Yeh 2016 and colleagues evaluated qigong for patients with non-Hodgkin lymphoma.

Risk of bias in included studies

Overall, the risks of bias were unclear. For detailed information see the 'Risk of bias' tables of included trials and Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

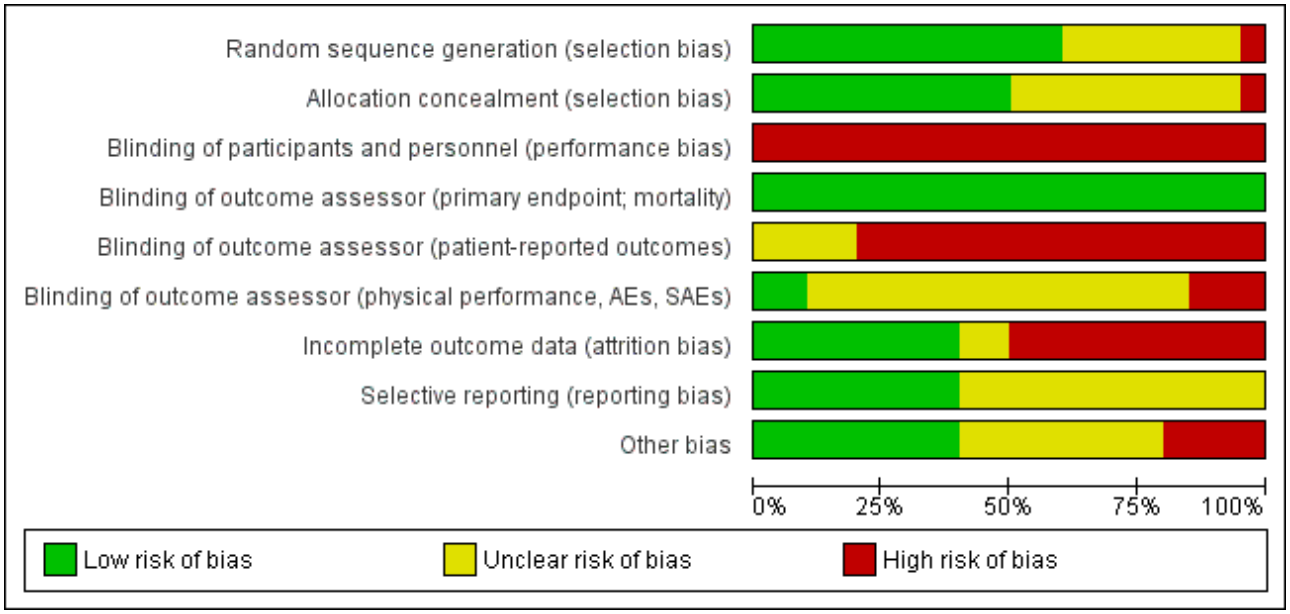

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Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

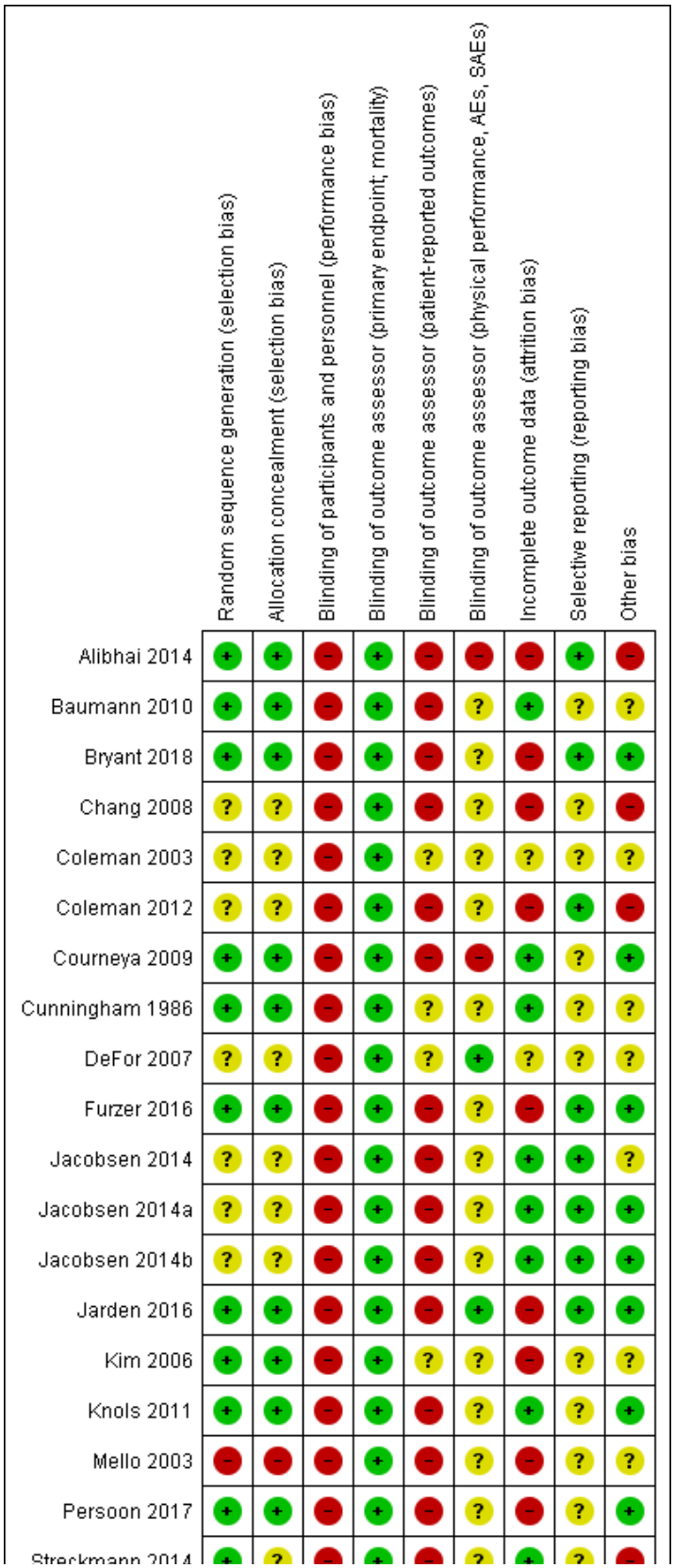

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Figure 3. (Continued)

Allocation

For one study, Mello 2003, we judged both, sequence generation and allocation concealment as high, as it remains unclear when and how patients have been randomised.

For 12 studies, we rated the random sequence generation as adequate (Alibhai 2014; Baumann 2010; Bryant 2018; Courneya 2009; Cunningham 1986; Furzer 2016; Jarden 2016; Kim 2006; Knols 2011; Persoon 2017; Streckmann 2014; Wiskemann 2015), thus we judged the potential risk of bias as 'low'. Five studies reported randomisation procedure, but did not give details, therefore we judged risk of bias as unclear for five studies (Chang 2008; Coleman 2003; Coleman 2012; DeFor 2007; Jacobsen 2014).

Allocation concealment was adequate for 10 trials (Alibhai 2014; Baumann 2010; Bryant 2018; Courneya 2009; Cunningham 1986; Furzer 2016; Jarden 2016; Kim 2006; Knols 2011; Persoon 2017), and unclear for seven studies (Chang 2008; Coleman 2003; Coleman 2012; DeFor 2007; Jacobsen 2014; Streckmann 2014; Wiskemann 2015).

Blinding

Performance bias

When exploring the influence of physical exercise intervention on people suffering from haemological malignancies, it is not feasible to blind participants or physicians. Consequently, in all 18 studies we judged the potential risk of bias for blinding of participants and physicians as 'high'.

Detection bias

As the outcome of mortality is not influenced by the outcome assessor, we judged risk of bias for outcome assessor blinding for as low.

Thirteen studies measured participant-reported outcomes for quality of life or fatigue. As it is not feasible to blind the intervention exercise, the participants were aware of the assigned intervention when they filled out the questionnaires. We therefore judged the risk of bias for outcome assessor blinding for those trials that assessed participant-reported outcomes as high (Alibhai 2014; Baumann 2010; Bryant 2018; Chang 2008; Coleman 2012; Courneya 2009; Furzer 2016; Jacobsen 2014; Jarden 2016; Knols 2011; Mello 2003: Persoon 2017; Streckmann 2014; Wiskemann 2015).

Eleven studies did not report whether the outcome assessors for physical performance or adverse events were blinded, so we judged their risk of bias as 'unclear' (Baumann 2010; Bryant 2018; Chang 2008; Coleman 2003; Coleman 2012; Furzer 2016; Jacobsen 2014; Knols 2011; Mello 2003; Persoon 2017; Streckmann 2014). Two studies did not report outcomes or interest but laboratory values only; risk of bias for these trials is unclear (Cunningham 1986; Kim 2006).

In three studies we judged the assessor bias at 'high' risk (Alibhai 2014; Courneya 2009; Wiskemann 2015), as these trials explicitly stated that outcome assessors were not blinded. In Courneya 2009, the outcome assessors were not always blinded to group assignment, but they were trained in standardising testing procedures. In Wiskemann 2015, the assessors were not blinded to randomisation.

In two studies, the assessor was unaware of the randomised assignment (DeFor 2007; Jarden 2016), and we therefore judged the risk of bias as 'low'.

Incomplete outcome data

For two studies, we judged the risk of attrition bias as 'unclear' as they did not report whether all randomised participants were analysed (Coleman 2003; DeFor 2007). In 10 studies not all the randomised participants were considered in the outcome analysis. Consequently, we judged the risk of attrition bias as 'high' (Alibhai 2014; Bryant 2018; Chang 2008; Coleman 2012; Furzer 2016; Jarden 2016; Kim 2006; Mello 2003; Persoon 2017; Wiskemann 2015). In six studies we could not detect any risk of attrition bias, with all randomised participants analysed in the arm to which they were assigned, so we judged the risk of attrition bias as 'low' for these studies (Baumann 2010; Courneya 2009; Cunningham 1986; Jacobsen 2014; Knols 2011; Streckmann 2014).

Selective reporting

For 12 of the 18 included studies, there is no protocol available at www.controlled-trials.com/mrct/, so we were not able to judge the potential risk of reporting bias (Baumann 2010; Chang 2008; Coleman 2003; Courneya 2009; Cunningham 1986; DeFor 2007; Kim 2006; Knols 2011; Mello 2003; Persoon 2017; Streckmann 2014; Wiskemann 2015), and we therefore rated the potential risk of reporting bias as 'unclear'. For six studies, a protocol was registered (Alibhai 2014; Bryant 2018; Coleman 2012; Furzer 2016; Jacobsen 2014; Jarden 2016). All planned outcomes are reported. According to this, we judged the potential for reporting bias as 'low'.

Other potential sources of bias

In one study the distribution of participants between exercise and control group is unbalanced due to five out of 17 allocated to the control immediately crossing over to the exercise group (Alibhai 2014), we judge risk of other bias as high.

In Chang 2008, the distribution of gender is unbalanced in the exercise and in the control group. In consequence of this distribution, we judged the potential risk of bias as 'high'; however, the unequal distribution could be due to the small number of participants randomised.

In Coleman 2012, 50% of participants received thalidomide. It is was neither reported whether the thalidomide administration was equally distributed between both arms, nor were subgroup

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analyses provided for participants receiving or not receiving thalidomide. We therefore judged the potential risk of bias as 'high'. Moreover, in an abstract publication of the trial, Coleman 2012 reported that all participants (in both the exercise and control group) received erythropoietin. In the study description published as full text, the authors reported that erythropoietin was administered to only 102 of 135 study participants, meaning that some participants did not receive erythropoietin therapy. We therefore judged the potential risk of bias as 'high'.

Streckmann 2014: due to a slow recruitment rate, the trial was stopped early. The authors planned to randomise 240 people, but randomised only 61 participants. They argued that physiological parameters are more important than the primary outcome (QoL). We therefore judged the potential risk of bias as 'high'. Moreover, there is a serious baseline imbalance for the outcome of QoL, favouring the control group. We therefore excluded this trial for the outcome QoL in a sensitivity analysis.

Six studies received financial support by various organisations. After evaluating and reviewing we do not expect any bias due to this (Courneya 2009; Furzer 2016; Jacobsen 2014; Jarden 2016; Knols 2011; Persoon 2017).

One study was finalised before the last six participants were enrolled (Coleman 2003). This premature termination was due to time and funding constraints. There is no indication that the premature stopping could have been due to other reasons. On the basis of this abandonment, we judged the potential risk of bias as 'unclear'.

For the remaining studies we do not have any hint for or against other bias and judged potential risk of bias as unclear (Baumann 2010; Cunningham 1986; DeFor 2007; Kim 2006; Mello 2003; Wiskemann 2015).

Effects of interventions

See: **Summary of findings for the main comparison** Physical exercise versus no physical exercise for adults with haematological malignancies

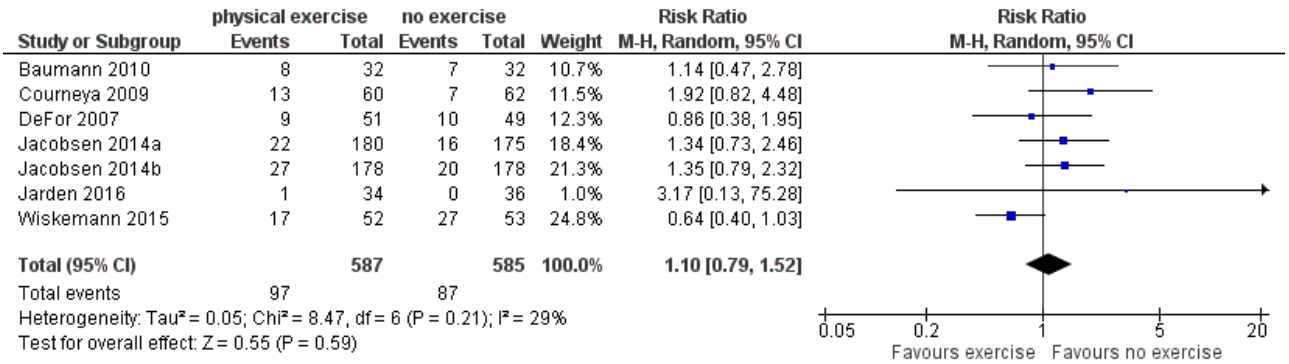
We did not include two trials in the meta-analyses which evaluated outcomes which are not patient-relevant and did not report the pre-specified outcomes of this review (Cunningham 1986; Kim 2006). These trials reported laboratory values only. One trial involving 40 patients reported change-scores instead of endpoint scores (Alibhai 2014), another trial with 17 patients did not report standard difference or standard error (Bryant 2018), therefore both trials could not be included in meta-analyses.

Overall survival (OS)/mortality

The only study investigating our primary outcome OS was Wiskemann 2015. The study authors did not find evidence for participants exercising compared to participants receiving usual care only (risk ratio (RR) = 0.67, P = 0.112). As this was the only trial investigating survival there were no data to pool, therefore a meta-analysis was not conducted.

Instead, six trials (N = 1172) which reported the number of deceased participants (Baumann 2010; Courneya 2009; DeFor 2007; Jacobsen 2014; Jarden 2016; Wiskemann 2015) were meta-analysed. We found no statistically significant difference between exercise and control arms (RR 1.10; 95% confidence interval (CI) 0.79 to 1.52; P = 0.59; Analysis 1.2). Heterogeneity is small (I^2 = 29%) (see Figure 4). The certainty of the evidence is low, because of the small number of patients with an event and a confidence interval that includes both: clinically relevant benefits and harms. We downgraded two points for imprecision.

Figure 4. Forest plot of comparison: 1 Physical exercise versus no physical exercise, outcome: 1.2 Mortality.



The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.1) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.3) did not provide any evidence for differences between those groups (test for subgroup differences not significant).

Quality of life (QoL)

Eight studies measured the outcome quality of life in a comparable way. One of them (Jacobsen 2014) evaluated QoL using the SF-36 survey, its Mental Component Summary score (MCS) was incorporated in our review as an indicator for general QoL.
We found no evidence for a difference (standardised mean difference (SMD) 0.11, 95% CI -0.03 to 0.24; 1259 participants; Analysis 1.4) with small heterogeneity (I^2 = 26%) (see Figure 5). We found no indications of subgroup differences between participants receiving stem cell transplantation (SCT) or chemotherapy only (Analysis 1.5). Moreover, the sensitivity analysis for high versus low risk of overall bias (Analysis 1.6) did not provide any evidence for differences between these groups. The certainty of the evidence is low, due to a confidence interval that includes both, improvement

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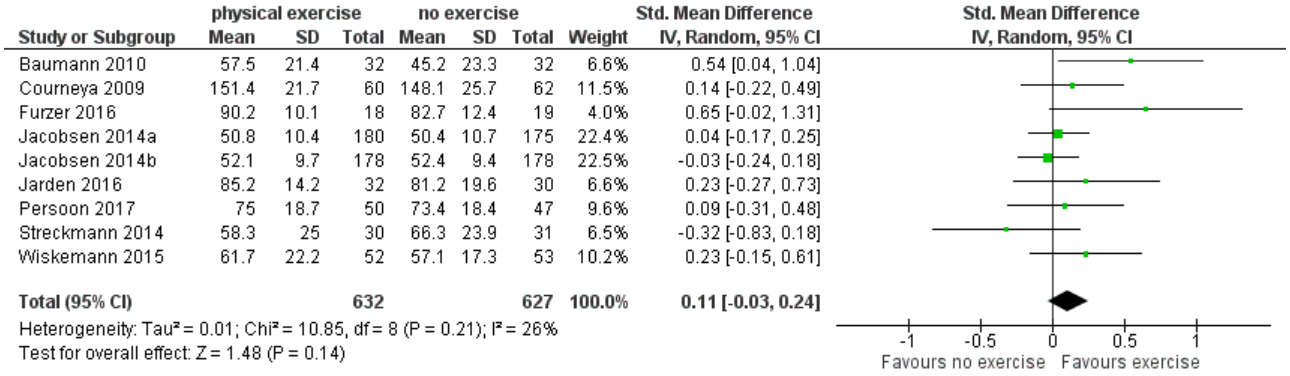
and worsening of QoL (one point downgraded for imprecision) and unblinded outcome assessors (participants) for the participant-reported outcome (QoL questionnaires) (one point downgraded for risk of bias).

Figure 5. Forest plot of comparison: 1 Physical exercise versus no physical exercise, outcome: 1.4 Quality of life (QoL).



Subscale physical functioning

Eight trials with 1329 participants evaluated physical functioning. There is no significant advantage for participants in the exercise arm (SMD 0.15, 95% CI -0.01 to 0.32; Analysis 1.7). Heterogenity is moderate (I^2 = 48%). The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.8) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.9) did not provide any evidence for differences between those groups. Again, the certainty of the evidence is judged to be low, because of the confidence interval that includes both, improvement and worsening of physical functioning (one point downgraded for imprecision) and unblinded outcome assessors (participants) for the participant-reported outcome (one point downgraded for risk of bias).

Subscale depression

The pooled result of six trials (N = 445) for depression show a small effect for patients exercising (SMD 0.19, 95% CI 0.0 to 0.38; I^2 = 0%; Analysis 1.10), without any hints for heterogeneity. The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.11) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.12) did not provide any evidence for differences between those groups. As for QoL and the subscale physical functioning, the certainty of the evidence for the outcome depression is low: we downgraded one point for imprecision because of the small number of participants (445) and potential risk of bias (one point downgraded) because of the unblinded outcome assessor (participants for the participant-reported outcomes).

Subscale anxiety

Anxiety was evaluated by six trials with 445 participants. There is substantial heterogeneity for this analysis (I^2 = 63%), but no evidence for differences between the exercise arm and the standard treatment arm (SMD 0.03, 95% CI -0.30 to 0.36; Analysis 1.13). The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.14) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.16) did not provide any evidence for differences between those groups. As for the aforementioned outcomes, we downgraded certainty of the evidence for a confidence interval including both, potential benefit and harm (one point downgraded for imprecision) and potential risk of bias (one point downgraded for risk of bias) because of the unblinded outcome assessor (participants for the participant-reported outcomes) and in addition, one point downgraded for inconsistency (high statistical heterogeneity). This results in a very low certainty of the evidence.

One trial (Alibhai 2014) delivered data for QoL, physical functioning and depression, but had to be excluded from the meta-analysis due to the fact that only chance values were reported instead of endpoint values. There were no relevant differences between the results of this and the aforementioned meta-analysed outcomes.

Fatigue

Nine studies (N = 826) assessed fatigue and found a statistically significant advantage for those participants exercising (SMD 0.31, 95% CI 0.13 to 0.48; P = 0.0005; Analysis 1.15), with moderate heterogeneity (I^2 = 31%) (see Figure 6). The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.17) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.18) did not provide any evidence for differences between those groups. The certainty of the evidence is moderate, as we downgraded one point for risk of bias due to the unblinded outcome assessment.

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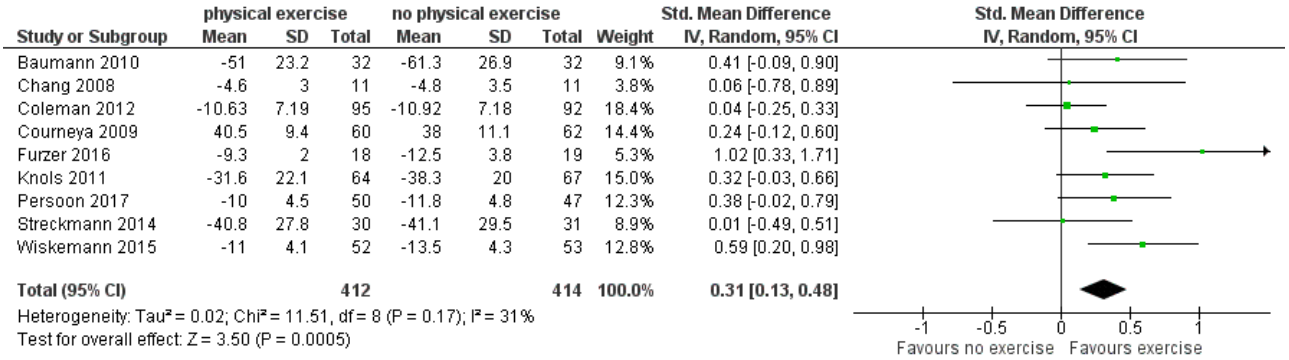
Figure 6. Forest plot of comparison: 1 Physical exercise versus no physical exercise, outcome: 1.15 Fatigue.



Alibhai 2014 had to be excluded from the meta-analysis because of reporting of chance scores instead of endpoint values. There was no hint for different results of this trial compared to the pooled analysis.

Physical performance (e.g. aerobic capacity, cardiovascular fitness)

Thirteen studies evaluated physical performance (Alibhai 2014; Baumann 2010; Chang 2008; Coleman 2003; Coleman 2012; Courneya 2009; Furzer 2016; Jarden 2016; Knols 2011; Mello 2003; Persoon 2017; Streckmann 2014; Wiskemann 2015). However, all studies used different concepts, measuring instruments and outcome definitions, and we therefore have not pooled the data.

Alibhai 2014 assessed functional endurance using the six-minute walk test. Endurance improved in both exercise and control group over the course of the intervention. There were no significant differences reported between the groups for the six-minute walk test (mean difference (MD) 34.6; P = 0.99), as well as for grip strength (MD 0.16 kg; P = 0.56) and sit and reach test (MD 1.3 cm; P = 0.29).

Baumann 2010 reported statistically significant differences in the inter-group comparison for repeated measurements for endurance (P = 0.004), endurance time (P = 0.004) and relative endurance (P = 0.031) between the exercise and the control group, favouring the exercise arm. There were no statistically significant intra-group changes in the exercise arm between admission and discharge, but there were significant changes between these data in the control group. Endurance between these two time points decreased from 86.5 Watt (W) to 60 W (P = 0.001) and endurance time reduced from 5.4 minutes to 3.3 minutes (P < 0.001) in the control group.

Chang 2008 assessed physical performance by a 12-minute walking test. In this test, participants were encouraged to walk at a speed to reach their specific heart rate, predefined by the study protocol. At baseline there were no statistically significant differences between the two study arms.The authors reported a statistically significant decrease in 12-minute walking distance for the control group (estimate -119.1 metre (m); 95% CI -207.1 to -31.0 m; P = 0.008). On the other hand, the 12-minute walking distance for participants in the exercise programme increased over time.

Coleman 2003 investigated the outcomes strength changes and treadmill minutes. Strength changes were tested by four strength tests using Keiser pneumatic equipment. Treadmill minutes, in detail the measurement of aerobic exercise capacity, were measured by a modified Balke protocol. Comparison between exercise and control groups did not achieve statistical significance, either for strength change or for treadmill minutes. The authors provided no further data.

In Coleman 2012 all participants performed a six-minutes walking test before and after intervention. The mean values for the walking test showed a tendency for improved performance in the short-term exercise group, but not in the short-term control group. Aerobic capacity, measured by the six-minute walking test, decreased over time in both arms, but less so in the exercise group. No further precise data were published for this outcome.

Courneya 2009 measured VO_2 peak power output, VO_2 peak (mL/kg/min) and ventilatory threshold (L/min). In all three measures, the exercise group was statistically significantly superior to the control group.

Furzer 2016 measured cardiovascular fitness and muscle strength. Significant improvements for both measures were found from baseline to 12 weeks (P ≤ 0.001) comparing exercise group to usual care. Additionally, after usual care participants had started exercising from week 12 to week 24, the usual care group showed significantly improved cardiovascular fitness (P = 0.018) and MS (P ≤ 0.001), too.

Jarden 2016 assessed physical capacity and functional performance by measuring six-minute walking distance, VO_2 max, sit-to-stand test and biceps curls. Improvements in all measures found in the intervention group differed significantly from the usual care group in favour of the intervention group (P ≤ 0.001)

Knols 2011 reported statistically significantly improved six-minute walking test results (P = 0.011), increased walking speed (P = 0.000) and improved knee extension for the exercise arm compared to the standard care arm from baseline to follow-up examination three months after programme completion. The authors found no difference for grip strength between the two arms (P = 0.624).

Mello 2003 reported a significant benefit for the exercise arm measuring maximal isometric voluntary strength from four muscle groups of the upper limbs and five muscle groups of the lower limbs.

Persoon 2017 reported improvements in fitness and reduced levels of fatigue for both the exercise and control group without significant differences between the groups.

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Streckmann 2014 reported that the aerobic performance level increased statistically significantly in the exercise group over time compared to the control group with deteriorating activity levels (P = 0.03). This is true for balance control, with improving balance control in the exercise arm and reducing control in the standard arm (dynamic control P = 0.007; static control P = 0.02).

In the trial by Wiskemann 2015, participants in the exercise group achieved statistically significantly more metres in the six-minute walking test six to eight weeks after discharge; no more detailed data was published.

Anthropometric measurements

Three studies (N = 964) provided data for body weight (Courneya 2009; Jacobsen 2014; Knols 2011). There was no significant difference between exercise and control groups (MD 0.44 kg; 95% CI -1,94 to 2,82; P = 0.72; Analysis 1.19), without evidence for heterogeneity (I^2 = 0%). The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.20) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.21) did not provide any evidence for differences between those groups.

Alibhai 2014 had to be excluded from the meta-analysis due to reporting change values instead of endpoint values for the outcome body weight. No significant differences between the groups were reported.

Three studies (Courneya 2009; Furzer 2016; Knols 2011, N = 290) measured lean body mass. There was no statistically significant difference between the groups for this outcome (MD 1.26 kg; 95% CI -1,22 to 3,74; P = 0.69; I^2 = 0%; Analysis 1.22). The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.23) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.24) did not provide any evidence for differences between those groups.

Adverse events

Six studies (435 participants) reported serious adverse events (SAEs) (Alibhai 2014; Chang 2008; Coleman 2012; Courneya 2009; Furzer 2016; Persoon 2017) and were pooled in one analysis. There is uncertain evidence whether exercise is related to more serious adverse events (RR 1.39; 95% CI 0.94 to 2.06; P = 0.10; I^2 = 0%); Analysis 1.25), without heterogeneity. The certainty of the evidence is very low as we downgraded one point for inconsistency because of baseline imbalances, especially usage of erythropoietin and thalidomide remains unknown in both study arms of one included study. In addition, we downgraded two points for imprecision, as only a very small number of SAEs were observed, leading to very wide confidence intervals.

The subgroup analysis for stem cell transplantation versus chemotherapy only (Analysis 1.26) and the sensitivity analysis for high versus low risk of overall bias (Analysis 1.27) did not provide any evidence for differences between those groups.

Chang 2008 reported that one participant in each arm (8%) dropped out of the study due to a SAE. The participant in the exercise group experienced severe bleeding, and the participant in the control group a severe infection.

In the trial by Coleman 2012, the most common SAEs were fever, hyponatraemia, pneumonia, hyperglycaemia, deep vein thrombosis, infection and neutropenia. In the short-term groups, 15 out of 23 participants (65%) experienced one or more SAEs, while the corresponding rate in the control group was eight out of 28 participants (28%).

Regarding the long-term study group, 15 out of 35 participants (43%) in the exercise group experienced at least one SAE and 14 out of 34 (41%) in the control group. As the authors reported variations in cancer treatment between both study arms (whether erythropoietin or thalidomide, or both were administered or not), the reasons for the differences between study arms remain unclear.

Courneya 2009 reported that no SAE occurred in either arm, but three (5%) adverse events (back, hip and knee pain) related to the exercise programme. One participant with knee pain withdrew from the exercise programme, and the other two participants proceeded with a modified exercise programme. In the control group (N = 62) no adverse events were reported (RR 7.23; 95% CI 0.38 to 137.05; P = 0.19).

Alibhai 2014 and Furzer 2016 each reported that no SAE occurred in either arm.

Persoon 2017 reported four SAEs in each arm.

Streckmann 2014 (61 participants) reported that the number of cancer-related side effects was statistically significantly reduced in the exercise group by 2.1 compared to baseline (P = 0.043). In the control group, the side effects were reduced by only 0.4 (P = 0.514).

DISCUSSION

Summary of main results

For this review we evaluated the safety, feasibility and efficacy of aerobic physical exercise for adults with haematological malignancies. We included 18 randomised controlled trials (RCTs) of which 14 could be included in the analyses with the following results.

- Only one small trial (105 participants) reported overall survival (OS), without any evidence for a difference between both arms. Additionally, instead of measuring the OS, six trials evaluated mortality (1172 patients). For this outcome there is no evidence for a difference between the exercise and control arms.
- The quality of life (QoL) was measured in eight studies, but it remains uncertain, whether physical exercise improves QoL (1259 participants). There is no evidence for a difference between participants exercising and those participants receiving standard care only for the subscales physical functioning (1329 participants) and anxiety (445 participants).
- Nine trials evaluated fatigue (826 participants). There is moderate-quality evidence that exercise has a positive effect on fatigue. Additionally, there is low-certainty evidence, that exercise might improve depression (subscale from QoL instruments).
- Thirteen trials evaluated physical performance. Since they used different concepts, measuring instruments and outcomes, the data could not be pooled. Eight trials reported significant benefits for the exercise arm.

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- Four studies reported anthropometric measurements, without delivering evidence for differences in body weight (964 participants) and lean body mass (290 participants).
- Serious adverse events (SAEs) were evaluated in six trials (435 participants). Due to very low-certainty evidence, it remains unclear, whether there is a disadvantage for participants in the exercise arm.
- Two trials could not be analysed as they did not report any of our pre-specified patient-relevant outcomes but laboratory values only. One trial (40 participants) had to be excluded from the meta-analysis for the endpoints QoL with subscales, fatigue and body weight due to reporting change scores instead of endpoint scores, another trial (17 patients) did not report standard differences or errors.

Overall completeness and applicability of evidence

Interpreting the results of this meta-analysis, the following aspects should be considered.

- The 18 included studies, consisting of 1892 participants, may not be adequately powered to detect small differences, especially concerning outcomes with few events.
- Two of these trials reported laboratory values only, two further trials of this set of included trials could not be meta-analysed due to missing standard differences or errors or reporting of change scores only.
- Data appear deficient, in particular for the outcome OS. We noticed a lack of data, which requires further research.
- The differences in exercise programme (type, duration and follow-up), supportive care and medical treatment between studies could have influenced the outcomes.
- Four RCTs are currently ongoing, but as the authors of these trials do not report how many participants they will recruit and when the trial will be terminated, the potential influence of these trials for the current analyses remains uncertain. One of these studies started in 2003 and according to the study registry, clinicaltrials.gov it still seems to be active and recruiting patients.
- Although there are statistical differences in the fatigue and depression scores, especially the clinical significance for the outcome depression remains uncertain, as the confidence interval of the standardised mean difference (SMD) is very close to the zero effect. As the outcome fatigue was measured with different instruments in various RCTs, we had to meta-analyse the SMD instead of the mean difference. (MD) The clinical meaning of an advantage in the SMD is always difficult to interpret, because no clinically relevant minimal important difference is known for the standardised value. However, as the effect is quite large, we assume the effect is clinically meaningful.

Quality of the evidence

Overall, we judged the potential risk of bias of the 18 included trials as unclear. All the included trials were reported as randomised and as open-label studies. In seven of the 18 included studies, the scientific quality of allocation concealment remained unclear. The open-label design and unclear allocation concealment could lead to selection, performance or detection biases. In the included studies, blinding of participants as well as blinding of physicians in the context of physical exercise was impossible. Consequently, we judged the risk of performance bias as high for all studies. As the outcome mortality is not influenced by the outcome assessor, we judged risk of detection bias for this outcome as low. As it is not feasible to blind the intervention exercise, we judged the risk of detection bias for participant-reported outcomes as high. For the other reported outcomes, most studies did not report whether outcome assessors were blinded, and we therefore judged risk of detection bias for these outcomes as unclear. For seven trials we judged the potential risk of attrition bias as high, because not all participants randomised were analysed.

We judged the certainty of the evidence body as low to moderate for most outcomes, because of an open-label design, unblinded outcome assessment and a small number of events, leading to wide confidence intervals and imprecision of the results. For the outcome anxiety, we judged the certainty of the evidence body as very low, due to the aforementioned reasons and additionally high statistical heterogeneity, leading to relevant inconsistency. For SAEs, we also judged the certainty as very low, because of baseline imbalances. Especially the usage of erythropoietin and thalidomide was unknown for both arms of one trial and both agents are known to have a high potential for SAEs. This led to downgrading by one point for inconsistency. In addition, very wide confidence intervals led to downgrading (two points) for imprecision.

Potential biases in the review process

We tried to avoid bias by doing all relevant processes in duplicate. We are not aware of any obvious deficiencies in our process of conducting the review. With sensitive search strategies and handsearching of conference proceedings, we tried to avoid retrieval bias.

As the number of included studies is too low to perform tests for publication bias, we cannot be sure that we obtained all relevant studies. Moreover, as this type of intervention, aerobic physical exercise, is usually evaluated in investigator-initiated trials, there is no manufacturer or company available to ask for missing data. Additionally, for an intervention like physical exercise there might be less need to be registered in advance in clinical trials registries, as this applies more cogently to RCTs of pharmaceutical interventions. We included four trials in the review, but without sufficient data to be used in the meta-analyses. Two of these trials reported laboratory values only, the other two trials reported data without confidence intervals or standard deviations. Addtionally, the four RCTs which are currently ongoing did not report when they will be terminated and how many participants they plan to recruit. Thus, the potential influence of these trials for the current meta-analyses remains unclear. One of these four studies if of special concern, as it started in 2003 and according to the study registry, clinicaltrials.gov, it still seems to be active and recruiting patients (last access 9 September 2018). All these points could have induced publication bias.

Agreements and disagreements with other studies or reviews

This is the update of a review published first in 2014, based on RCTs assessing the efficacy, safety and feasibility of aerobic exercise for adult patients suffering from haematological malignancies.

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We identified two recent systematic reviews and meta-analyses which are comparable to our analyses, as they also included patients with haematological malignancies and evaluated exercise interventions.

Zhou 2016 and colleagues investigated the effects of exercise in paediatric or adult patients with acute leukaemia. The authors included nine trials with 314 participants (eight RCTs and one quasi-experimental design).Two of these trials have been conducted in adults and were also included in this review update (Alibhai 2014; Chang 2008), the remaining trials evaluated children. The review authors came to the conclusion that exercise compared to no exercise has positive effects on cardiorespiratory fitness, muscle strength and functional mobility. However, as they did not assess the certainty of the evidence, they did not take the very small number of participants, the mixed participant population (children and adults) and the clinical and statistical heterogeneity into account while interpreting their data. As the review authors came to their conclusions because of significant P values only, they might have overrated their results. The review did not find significant results for participants exercising for the outcomes fatigue, anxiety, depression or quality of life and concluded that these outcomes are not improved. Again, the interpretation of results based on P values only could be misleading, as a non-significant P value in such a small population could be explained by the small sample size which is not large enough to detect significant differences.

Liang 2018 and colleagues assessed the effect of exercise for participants with haematological malignancies who were also haematopoietic stem cell transplantation recipients. The authors included RCTs only and included 10 trials with 607 participants. Eight of these trials are also included in the current version of this review update, two trials they included have been excluded in our review, as patients did not practice aerobic exercise, but strength training only (Hacker 2011; Hacker 2016). As discussed before, these review authors also interpreted their findings based on significant or non-significant P values only, which might overestimate an imprecise, indirect or inconsistent effect. Liang 2018's results for the outcome fatigue are in line with our review, showing an advantage for those patients exercising compared to them not exercising. They also concluded that muscle strength and quality of life is improved for participants exercising. We did not find evidence for improved quality of life, due to the small sample size. However, as the effect estimate in our analysis is in favour for participants exercising, further studies and a larger number of included participants might change the currently non-significant result to a significant result favouring the exercise arm. As mentioned before, Liang 2018's conclusion that exercise has no effect on participants' cardiorespiratory fitness, upper muscle strength, psychosocial fitness and adverse events could be misleading, as no effect is not the same as no evidence for a difference and could be explained by a small sample population only.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is moderate- to very low-quality evidence available for the benefits and harms of aerobic physical exercise in adults with haematological malignancies. Aerobic physical exercise in addition to standard care probably improves fatigue and depression. There is currently no evidence for differences in terms of mortality, quality of life, physical functioning and anxiety between people exercising and the control group. Certainty of the evidence related to serious adverse events (SAEs) is very low, exercise might increase number of SAEs.

Implications for research

To establish the most effective type and intensity of physical exercise, further trials with more participants and longer follow-up periods are needed. To enhance comparability of study data, we require the development and implementation of core sets of measuring devices. As neither the number of planned patients nor potential completion date is published for the four ongoing trials, the potential impact of these trials for a future update remains unclear.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alibhai 2014

Methods	Randomisation • 2 arms: home-based exercise versus standard care Recruitment period • November 2008 to November 2010 Median follow-up time • Additional 24 weeks Sample size calculation • Based on the ability to estimate recruitment rates and effect sizes with reasonable precision
Participants	Eligibility criteria • Adults (≥ 40 years of age) • Completion of intensive chemotherapy or at least 100 days post-haematopoietic stem cell transplant

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Alibhai 2014 *(Continued)*

	• Good English language skills • Written informed consent Participants (N = 40) • Intervention group (N = 22) • Control group (N = 18) Mean age • Intervention group: 53.9 years • Control group: 58.8 years Stage/type of disease • Intervention group: 22 AML • Control group: 18 AML Country • Canada
Interventions	Exercise group • Home-based exercise at 3 to 5 days per week at a moderate intensity (30 minutes) • Consisting of aerobic, resistance and flexibility components • No or minimal equipment needed (stability ball, resistance bands were provided) • Participants were invited to attend once-weekly group- based booster sessions Control group • Maintenance of the usual level of physical activity • Assessments every 3 weeks • Optional crossing over to the exercise group after 12 weeks
Outcomes	Reported and relevant for this review • Quality of life • Fatigue • Physical performance • Anthropometric measures • Adverse events Reported and not relevant for this review • None
Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomized using opaque numbered sealed envelopes"
Allocation concealment (selection bias)	Low risk	Quote:"Subjects were randomized using opaque numbered sealed envelopes"

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Alibhai 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	High risk	Quote:"Outcomes assessors were not blinded to treatment arm"
Incomplete outcome data (attrition bias) All outcomes	High risk	Two participants of the exercise group and one of the control group dropped out which makes a ratio of 8%. Reported reasons were quote: "early discontinuation due to relapse" respectively "lost to follow-up"
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	High risk	Out of 17 participants allocated to the control group 5 immediately crossed over to the exercise group

Baumann 2010

Methods	Randomisation • 2 arms: endurance and activity of daily living-training twice a day versus standard care Recruitment period • March 2002 to July 2004 Median follow-up time • No follow-up analysis Sample size calculation • Based on a pragmatic approach
Participants	Eligibility criteria • Adults (≥ 18 years of age) • Malignant disease scheduled to receive transplantation • Good German language skills • Written informed consent Participants (N = 64) • Intervention group (N = 32) • Control group (N = 32) Mean age

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Baumann 2010 *(Continued)*

	• Intervention group: 49.4 years • Control group: 44.1 years Stage/type of disease • Intervention group: 10 AML, 6 ALL, 2 CML, 4 multiple myeloma, 5 NHL/CLL, 4 MDS, 1 solid tumour • Control group: 15 AML, 3 ALL, 1 CML, 5 multiple myeloma, 3 NHL/CLL, 2 MDS, 2 solid tumour, 1 immunodeficiency Country • Germany
Interventions	Exercise group • Endurance training on bicycle ergometer (10 to 20 minutes) • Activities of daily living training: included elements of daily living to maintain participant's mobility; daily 20 minutes including walking, stepping and stretching • Twice a day • Started 6 days before transplantation Control group • Passive and active mobilisation (gymnastics, massage, extensions, co-ordination training) with low intensity on 5 days per week • Started 1 day after transplantation until 1 day before discharge
Outcomes	Reported and relevant for this review • Quality of life • Fatigue • Participant's endurance • Strength Reported and not relevant for this review • Lung function • Blood count
Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"randomization was achieved....using computer-generated numbers"
Allocation concealment (selection bias)	Low risk	Quote:"randomization was achieved....using computer-generated numbers"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding

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Baumann 2010 *(Continued)*

Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote:"All 64 randomized patients represented the intent-to-treat population"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Not reported

Bryant 2018

Methods	Randomisation • Randomised controlled trial • 2 arms: individualised prescriptive exercise intervention 2 to 4 times per week for a period of the induction chemotherapy/in-hospital recovery vs usual care Recruitment period • May 2014 to November 2015 Median follow-up time • 6 weeks Sample size calculation • Not reported
Participants	Eligibility criteria • Newly diagnosed with acute leukaemia by pathology report • Admitted for induction chemotherapy within in the previous 96 hours or +/- 3 days from initiation of induction chemotherapy • An expected hospital stay of 3 to 4 weeks or longer • Participation in the study must be approved by the physician directly responsible for the patient's care • Age ≥ 21 years • Ability to speak and understand English • Ability to use a computer • No severe comorbidity that would not allow physical training • Give written informed consent Participants (N = 17) • Intervention group (N = 8) • Control group (N = 9) Mean age • Interventions group: 52 years

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Bryant 2018 *(Continued)*

- Control group: 49 years

Stage of disease

- Intervention group: not reported
- Control group: not reported

Country

- USA

Interventions	Exercise group • Individualised prescriptive exercise intervention 2 to 4 times per week for a period of the induction chemotherapy/in-hospital recovery • The exercise intervention began on week 1 of the study, the day after the first batteries of initial assessments were concluded • Each exercise session was divided into two parts. One part was administered in the morning and the second one late in the afternoon. There was a period of rest of at least 36 hours between each exercise session Control group • Standard care
Outcomes	Reported • Anthropometric measurements • Physical performance • Fatigue • Quality of sleep • Anxiety • Depression • Quality of life Not reported but relevant • Overall survival Reported but not relevant • none Primary outcome • Fatigue
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"The randomization sequence was generated by the study's statistician. The statistician and research outcome assessors were blinded to the randomization allocation"
Allocation concealment (selection bias)	Low risk	Quote:"The randomization sequence was generated by the study's statistician. The statistician and research outcome assessors were blinded to the randomization allocation"

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Bryant 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Quote:"The randomization sequence was generated by the study's statistician. The statistician and research outcome assessors were blinded to the randomization allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote:"1 dropped before the intervention started" (intervention group)
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	Low risk	None

Chang 2008

Methods	Randomisation • 2 arms: 3-week walking intervention programme versus standard care Recruitment period • Not reported Median follow-up time • No follow-up analysis was executed Sample size calculation • Not reported
Participants	Eligibility criteria • Adults (> 18 years of age) diagnosed with AML and aware of their diagnosis • Prescribed chemotherapy • Eastern Cooperative Oncology Group Performance Status 0 to 3 • Willing to sign a consent form to participate Participants (N = 24) • Intervention group (N = 12) • Control group (N = 12) Mean age • Intervention group: 49.4 years

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Chang 2008 *(Continued)*

	• Control group: 53.3 years Stage of disease • Not reported Country • Taiwan
Interventions	Exercise group • 3-week walking exercise programme consisted of 12 minutes walking in the hospital hallway 5 days per week. Participants were encouraged to walk at a speed to reach their target heart rate (resting heart rate plus 30) Control group • No walking intervention All participants received cytarabine plus idarubicin
Outcomes	Reported and analysed in this review • Worst fatigue intensity • Average fatigue intensity • 12-minute walking distance • Anxiety • Depressive status • Adverse events
Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported

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Chang 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Two patients out of 24 (9%) dropped out because of severe complications. It is unclear whether these complications are related to the intervention Quote: "One patient dropped out of each group due to severe complications"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Gender distribution unbalanced between arms

Coleman 2003

Methods	Randomisation • 2 arms: daily execution of aerobic and strength exercise versus standard care Recruitment period • Not reported Median follow-up time • Data were collected 3 months before the first transplantation, when the first transplantation was received, and approximately 3 months after the first transplantation Sample size calculation • Not reported
Participants	Eligibility criteria • Adults ≥ 40 years • New diagnosis of multiple myeloma • Not at high risk for pathologic fracture as determined by magnetic resonance imaging, radiology reports, and physician assessment Participants (N = 24) • Intervention group (N = 14) • Control group (N = 10) Mean age • Across both groups: 55 years Stage of disease • Not reported Country • USA
Interventions	Exercise group • The home-based exercise consists of aerobic component (usually walking or running or cycling) and strength resistance training with exercise stretch bands. The extend and intensity varied from day to day and from person to person. The exercise programme during hospital stay consisted of walking, stretching, endurance and strength exercise • Exercise started 10 weeks before first transplant and lasted until 2nd transplantation.

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Coleman 2003 *(Continued)*

	Control group • Encouragement to remain active and walk 20 minutes at least 3 times a week All participants received high-dose chemotherapy including tandem transplantation. Half of them were randomised to receive thalidomide during induction, posttransplantation consolidation, and maintenance therapy
Outcomes	Reported and analysed in this review • Strength change • Treadmill minutes • Lean body weight Reported but not relevant for this review • Effects of thalidomide • Sleeptime
Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding.
Blinding of outcome assessor (patient-reported outcomes)	Unclear risk	Outcome not reported
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Study was finalised before the last 6 participants were enrolled due to funding constraints

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Coleman 2012

Methods	Randomisation • 2 arms: stretching, aerobics and strength resistance training versus standard care Recruitment period • Not reported Median follow-up time • No follow-up analysis Sample size calculation • unclear, various assumptions in the published papers
Participants	Eligibility criteria • New diagnosis of multiple myeloma • Eligible for tandem autologous peripheral-blood stem cell transplantation • No risk for pathologic fractures or spinal cord compression Participants (N = 187) • Intervention group (N = 95) • Control group (N = 92) Mean age • Intervention group: 56.0 years • Control group: 56.4 years Stage of disease • Not reported Therapy • Intervention group: 69% Total Therapy II, 31% Total Therapy III; 36% no thalidomide, 64% thalidomide • Control group: 75% Total Therapy II, 25% Total Therapy III; 43% no thalidomide, 57% thalidomide Country • USA
Interventions	Exercise group • Aerobic exercise: walking to tolerance (until tired) • Stretching: performed daily for various muscles • Strength resistance training on alternate days with stretch bands. Control group • Participants advised to follow written exercise recommendations provided by their physician. Advised to remain as active as possible and to try to walk 20 minutes per day • All participants received high-dose therapy and tandem transplantation (Total Therapy II or Total Therapy III). 50% of those receiving Total Therapy II were randomised to receive thalidomide during induction, after transplantation consolidation, and maintenance therapy. All Total Therapy III participants (62) received thalidomide. EPO administered to first 102 study participants (investigational algorithm) that allowed haemoglobin levels to reach 15 g/dL before dose reduction or delay, and started before chemotherapy unless baseline haemoglobin was < 15 g/dL, differing from recommend-

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Coleman 2012 *(Continued)*

	ed haemoglobin parameters for EPO administration to participants who are receiving chemotherapy outside of a clinical trial setting. • Duration of short-term study was 15 weeks. The first 70 participants who met eligibility for long-term participation (i.e. response to EPO) continued in the study for an additional 15 weeks, which included administration of DCEP, melphalan and the first peripheral-blood stem cell transplantation • EPO was administered to the first 102 study participants according to an investigational algorithm that allowed haemoglobin levels to reach 15 g/dL before dose reduction or delay, and started before chemotherapy unless baseline haemoglobin was less than 15 g/dL.
Outcomes	Reported and analysed in this review • Fatigue • 6-minute walk test • Adverse events Reported but not relevant for this review • Response to intensive treatment protocol for multiple myeloma • Time to recovery after transplantation • Haemoglobin levels • Number of red blood cell- and platelet transfusions • Number of attempts at and total days of stem cell collection
Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	15 participants who dropped out were not analysed
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported

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Coleman 2012 *(Continued)*

Other bias	High risk	50% of participants received thalidomide. In the study analysis this drug administration was not considered and no subgroup data were provided for participants receiving or not receiving thalidomide

Courneya 2009

Methods	Randomisation • 2 arms: cycle ergometer exercise 3 times per week for 12 weeks versus standard care Recruitment period • May 2005 to May 2008 Median follow-up time • 6-month follow-up Sample size calculation • Not reported
Participants	Eligibility criteria • English speaking • > 17 years old • Histologically confirmed Hodgkin lymphoma or non-Hodgkin lymphoma (NHL) • Participants receiving chemotherapy may have started treatment before enrolment but needed to have at least 8 weeks of planned treatment remaining • Participants not receiving treatments had to have no planned treatments during the intervention period Participants (N = 122) • Intervention group (N = 60) • Control group (N = 62) Mean age • Intervention group: 52.8 years • Control group: 53.5 years Stage of disease • Intervention group: Stage I 18%, stage II 13.3%, stage III 15%, stage IV 25%, no evidence of disease 26.7%, unclear 1.7% • Control group: Stage I 11.3%, stage II 24.2%, stage III 12.9%, stage IV 21%, no evidence of disease 29%, unclear 1.6% Country • Canada
Interventions	Exercise group • Exercise completed on an upright or recumbent cycle ergometer 3 times per week for 12 weeks. Intensity began at 60% of the peak power output, which corresponded with baseline peak oxygen consumption (VO_2peak), and was increased by 5% each week to 75% by the 4th week. Duration began at 15 to 20 minutes for the first 4 weeks and increased by 5 minutes per week to 40 to 45 minutes in the 9th week.

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Courneya 2009 *(Continued)*

	• 1 session per week of interval training above the ventilatory threshold in week 7 and 1 session of VO_2peak interval training in week 9. Control group • No exercise intervention
Outcomes	Reported and analysed in this review • Quality of life • Fatigue • Physical performance • Anthropometric measurements • Adverse events Reported but not relevant for this review • Chemotherapy completion rate and treatment response • Participant-rated physical functioning
Notes	Financially supported by Lance Armstrong Foundation. No conflicts of interest reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After completing baseline tests, participants were stratified by major disease type and current treatment status and were randomly assigned to aerobic exercise training or usual care by using a computer-generated program. The allocation sequence was generated independently and concealed in opaque envelopes from the study coordinator who assigned participants to groups."
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was generated independently and concealed in opaque envelopes from the study coordinator who assigned participants to groups."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	High risk	Quote: "Outcomes assessors were not always blinded to group assignment but were trained in standardising testing procedures"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were considered in study analysis in conformity with their randomised group assignment

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Courneya 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	Study supported by Lance Armstrong Foundation. Any bias due to this support is not expected. No other sources of potential bias were reported

Cunningham 1986

Methods	Randomisation • 3 arms: physical therapy thrice weekly vs. physical therapy five times a week vs. control group Recruitment period • not reported Median follow-up time • 35 days Sample size calculation • Not reported
Participants	Eligibility criteria • Suffering from acute leukaemia • Undergoing bone marrow transplantation from a histocompatible donor • Within 80 to 110% of ideal body weight • Normal renal function Participants (N = 30) • Intervention group 1 (N = 10) • Intervention group 2 (N = 10) • Control group (N = 10) Mean age • Intervention group 1 (physical therapy thrice a week): 20.8 years • Intervention group 2 (physical therapy five times a week): 26.0 years • Control group: 22.5 years Stage of disease • Intervention group 1: status remission 7, relapse 3 • Intervention group 2: status remission 6, relapse 4 • Control group: status remission 8, relapse 2 Country • USA
Interventions	Exercise groups • Patients randomised to one of the exercise groups were advised to do the following programme 3 or 5 times a week: 15 repetitions of bicep-tricep curls, bench press, shoulder retractors, straight leg raises, hip extension, hip abduction, sit ups

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Cunningham 1986 *(Continued)*

	Control group • No exercise intervention
Outcomes	Reported and analysed in this review • None Reported but not relevant for this review • Arm muscle measures • Biochemical parameters
Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized (by computer-generated random permutations of a number unknown to investigators)"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized (by computer-generated random permutations of a number unknown to investigators)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported
Blinding of outcome assessor (patient-reported outcomes)	Unclear risk	Not reported
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Not reported

DeFor 2007

Methods	Randomisation • 2 arms: structured walking regimen for 30 minutes a day until 100 days post transplant versus standard care

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DeFor 2007 *(Continued)*

	Recruitment period • July 2003 to August 2005 Median follow-up time • 100 day posttransplant. Follow-up measured only for functional impairment (Karnofsky Score) Sample size calculation • Not reported
Participants	Eligibility criteria • All adults who were able to walk and consented to receive an allogeneic transplant at the University of Minnesota One Participants (N = 100) • Intervention group (N = 51) • Control group (N = 49) Mean age • Intervention group: 46 years • Control group: 49 years Stage/type of disease • Intervention group: various haematological diseases with diverse stages of disease. Major part: ALL/AML N = 30 (59%) • Control group: various haematological diseases with diverse stages of disease. Major part: ALL/AML N = 22 (45%) Country • USA
Interventions	Exercise group • Twice a day for 15 minutes on a treadmill • After discharge, participants were asked to walk once a day for at least 30 minutes. Participants were told to walk at a comfortable speed and to discontinue the workout if they felt any discomfort or dizziness or if the medical staff recommended it.This exercise regimen continued until 100 days posttransplant. Control group • Control group were not asked to perform any formal exercise, and were not provided with a treadmill unless requested by the participant or staff
Outcomes	Reported and analysed in this review • Overall survival • Quality of life • Physical performance Reported but not relevant for this review • Physical and emotional well-being at discharge and 100 days posttransplant • Perceived benefit (open-ended question) • Length of hospitalisation

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DeFor 2007 *(Continued)*

Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	Unclear risk	Outcome not reported
Blinding of outcome assessor (physical performance, AEs, SAEs)	Low risk	100-day assessment was performed in a clinic that was separate from the hospital so the physician was unaware of the randomised assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Not reported

Furzer 2016

Methods	Randomisation • 2 arms: 12-week exercise rehabilitation programme versus usual care Recruitment period • Period of 18 months Median follow-up time • 24 weeks Sample size calculation • Not reported
Participants	Eligibility criteria

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Furzer 2016 *(Continued)*

	• Adults (≥ 18 and ≤ 70 years of age) • Histologically confirmed HEM and having completed chemotherapy treatment within the previous 4 weeks • Informed consent Participants (N = 44) • Intervention group (N = 22) • Control group (N = 22) Mean age • Intervention group: 48.2 (22 to 64) years • Control group: 49.6 (25 to 68) years Stage/type of disease • Intervention group: 4 Hodgkin lymphoma, 11 NHL, 3 multiple myeloma; 18 chemotherapy, 5 radiation therapy 3 stem cell transplant • Control group: 2 Hodgkin lymphoma, 16 NHL, 1 multiple myeloma; 19 chemotherapy, 5 radiation therapy, 2 stem cell transplant Country • Australia
Interventions	Exercise group • Each session included warm-up and cool-down prior to cardiovascular training at 50% of heart rate max, with a maximum duration of 30 minutes per session • Participants used heart rate monitors to maintain prescribed heart rate • Exercise progression was achieved by 1) increasing heart rate intensity (up to 70% heart rate max) and 2) decreasing duration (10 to 15 minutes) while additionally increasing heart rate intensity (up to 85% heart rate max) • Endurance training consisted of 8 exercises targeting the major muscle groups (3 sets of 10-15 repetitions). Progression in weight was possible. Control group • Usual care, provided with a diary and received general healthy lifestyle advice but did not complete any structured exercise
Outcomes	Reported and analysed in this review • Cancer-related fatigue • QoL • Physical performance • Adverse events Reported but not relevant for this review • Bone mineral density
Notes	Financially supported by the SolarisCare foundation. The authors report no competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement

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Furzer 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were block randomised"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were block randomised"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Not reported
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven participants out of 44 (16%) dropped out due to different reasons (withdrew, illness, disease relapse), four having been part of the exercise group and three of the usual care group.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	Low risk	Financially supported by the SolarisCare foundation. Any bias due to this support is not expected

Jacobsen 2014

Methods	Randomisation • 4 arms: exercise training, stress management training, combination of both, and usual care Recruitment period • January 2011 to June 2012 Median follow-up time • 60 days Sample size calculation • Reported, quote: quote: "sample size was inflated... resulting in a target accrual of 700 patients"
Participants	Eligibility criteria • Adults (≥ 18 years of age) • Ability to exercise at a low to moderate intensity • Ability to speak and read English • No requirement for supplemental oxygen

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Jacobsen 2014 *(Continued)*

- HCT planned within 6 weeks
- Written informed consent

Participants (N = 711)

- Intervention group 1 (Exercise) (N = 180)
- Intervention group 2 (Stress Management) (N = 178)
- Intervention group 3 (Both) (N = 178)
- Control group (N = 175)

Mean age

- Intervention group 1: 58 (20 to 76) years
- Intervention group 2: 58 (20 to 75) years
- Intervention group 3: 57 (18 - 75) years
- Control group: 55 (19 - 76) years

Stage/type of disease

- Intervention group 1: 42 AML/ALL, 5 CML, 19 MDS/MPS, 50 multiple myeloma, 54 lymphoma, 5 CLL, 4 other, 1 missing; 14 previous transplantation
- Intervention group 2: 47 AML/ALL, 5 CML, 16 MDS/MPS, 43 multiple myeloma, 60 lymphoma, 4 CLL, 3 other; 16 previous transplantation
- Intervention group 3: 40 AML/ALL, 2 CML, 15 MDS/MPS, 44 multiple myeloma, 66 lymphoma, 6 CLL, 2 other 3 missing; 17 previous transplantation
- Control group: 42 AML/ALL, 2 CML, 13 MDS/MPS, 57 multiple myeloma, 50 lymphoma, 7 CLL, 3 other, 1 missing; 19 previous transplantation

Country

- USA

Interventions	Exercise group • All participants received a packet of materials including a videotape, brochure, workbook and an electronic step counter to perform home-based exercises with an emphasis on walking • The goal was to exercise 3 to 5 times a week for 20 to 30 minutes at 50% to 75% of estimated heart rate reserve Control group • Usual care, without any structured or supervised training and without encouragement to do physical exercise
Outcomes	Reported and analysed in this review • Overall survival • QoL • Cancer and treatment distress
Notes	Financially supported by the National Heart, Lung, and Blood Institute and the National Cancer Institute. The authors report no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized using a factorial design"

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Jacobsen 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote:"patients were randomized using a factorial design"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Survival and missing data rates were similar across the study arms"
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	Unclear risk	Financially supported by the National Heart, Lung, and Blood Institute and the National Cancer Institute. No competing interests were reported

Jacobsen 2014a

Methods	Randomisation • 2 arms: exercise training vs usual care Recruitment period • January 2011 to June 2012 Median follow-up time • 60 days Sample size calculation • Reported, "sample size was inflated... resulting in a target accrual of 700 patients"
Participants	Eligibility criteria • Adults (≥ 18 years of age) • Ability to exercise at a low to moderate intensity • Ability to speak and read English • No requirement for supplemental oxygen • HCT planned within 6 weeks • Written informed consent Participants (N = 355)

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Jacobsen 2014a *(Continued)*

- Intervention group (N = 180)
- Control group (N = 175)

Mean age

- Intervention group: 58 (20 to 76) years
- Control group: 55 (19 to 76) years

Stage/type of disease

- Intervention group: 42 AML/ALL, 5 CML, 19 MDS/MPS, 50 multiple myeloma, 54 lymphoma, 5 CLL, 4 other, 1 missing; 14 previous transplantation
- Control group: 42 AML/ALL, 2 CML, 13 MDS/MPS, 57 multiple myeloma, 50 lymphoma, 7 CLL, 3 other, 1 missing; 19 previous transplantation

Country

- USA

Interventions	Exercise group • All participants received a packet of materials including a videotape, brochure, workbook and an electronic step counter to perform home-based exercises with an emphasis on walking • The goal was to exercise 3 to 5 times a week for 20 to 30 minutes at 50% to 75% of estimated heart rate reserve Control group • Usual care, without any structured or supervised training and without encouragement to do physical exercise
Outcomes	Reported and analysed in this review • QoL • Cancer and treatment distress • Pain • Nausea
Notes	Financially supported by the National Heart, Lung, and Blood Institute and the National Cancer Institute. Any bias due to this support is not expected

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized using a factorial design"
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomized using a factorial design"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding

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Jacobsen 2014a *(Continued)*

Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Survival and missing data rates were similar across the study arms"
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	Low risk	Financially supported by the National Heart, Lung, and Blood Institute and the National Cancer Institute. Any bias due to this support is not expected

Jacobsen 2014b

Methods	Randomisation • 2 arms: exercise training combined with stress management training vs stress management only Recruitment period • January 2011 to June 2012 Median follow-up time • 60 days Sample size calculation • Reported, quote: "sample size was inflated... resulting in a target accrual of 700 patients"
Participants	Eligibility criteria • Adults (≥ 18 years of age) • Ability to exercise at a low to moderate intensity • Ability to speak and read English • No requirement for supplemental oxygen • HCT planned within 6 weeks • Written informed consent Participants (N = 356) • Intervention group (N = 178) • Control group (N = 178) Mean age • Intervention group: 57 (18 to 75) years • Control group: 58 (20 to 75) years Stage/type of disease • Intervention group: 40 AML/ALL, 2 CML, 15 MDS/MPS, 44 multiple myeloma, 66 lymphoma, 6 CLL, 2 other 3 missing; 17 previous transplantation

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Jacobsen 2014b *(Continued)*

	• Control group: 47 AML/ALL, 5 CML, 16 MDS/MPS, 43 multiple myeloma, 60 lymphoma, 4 CLL, 3 other; 16 previous transplantation Country • USA
Interventions	Exercise group • All participants received a packet of materials including a videotape, brochure, workbook and an electronic step counter to perform home-based exercises with an emphasis on walking and a relaxation CD • The goal was to exercise 3 to 5 times a week for 20 to 30 minutes at 50% to 75% of estimated heart rate reserve and to perform stress management training consisting of paced abdominal breathing, progressive muscle relaxation with guided imagery, and coping self-statements Control group • Participants of the CG performed only the stress management training
Outcomes	see Jacobsen 2014
Notes	see Jacobsen 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized using a factorial design"
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomized using a factorial design"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Survival and missing data rates were similar across the study arms"
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	Low risk	Financially supported by the National Heart, Lung, and Blood Institute and the National Cancer Institute. Any bias due to this support is not expected

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Jarden 2016

Methods	Randomisation • 2 arms: 12-weeks exercises and counselling versus usual care Recruitment period • July 2011 to January 2014 Median follow-up time • 12 weeks Sample size calculation • Reported, sample size 35 participants per arm: quote: "Sample size calculation is based on the primary endpoint; the 6-minute walk distance (6MWD) and the results from our pilot study"
Participants	Eligibility criteria • Adults (≥ 18 years of age) • Diagnosed with acute leukaemia • In complete remission after completing induction treatment • Written informed consent Participants (N = 70) • Intervention group (N = 34) • Control group (N = 36) Mean age • Intervention group: 54 years (not reported individually) • Control group: 54 years (not reported individually) Stage/type of disease • Intervention group: 34 acute leukaemia • Control group: 36 acute leukaemia Country • Denmark
Interventions	Exercise group • All participants received a 12-week exercise program, 3 times week, 60 to 70 minutes per session • Sessions consisted of stationary cycling for 20-25 minutes, six dynamic resistance exercises using hand weights in 2 sets of 12 repetitions and nutrition support • Counseling sessions were conducted at week 0, 6 and 12 Control group • Usual care, without any structured or supervised training and without encouragement to do physical exercise • Patients were not asked to refrain from physical activity
Outcomes	Reported and analysed in this review • Physical capacity • Functional performance

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Jarden 2016 *(Continued)*

- Leisure-time activity
- QoL
- Fatigue
- Adverse events

Notes	Financially supported by The Center for Integrated Rehabilitation of Cancer Patients, The Novo Nordic Foundation, The University Hospitals' Centre for Health Research (UCSF), The Lundbeck Foundation, The Novo Nordic Foundation for Clinical Nursing Research and The Danish Cancer Society. The authors report no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized... using the computerized Clinical Trial Management System"
Allocation concealment (selection bias)	Low risk	Quote: "A block design with allocation weight of 1:1 will be used to generate treatment allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Low risk	Quote: "however the outcome assessors...be blinded to the participants study allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 70 participants 62 completed study requirements (89%). 8 participants dropped out, 2 from the IG and 6 from the CG
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol are reported
Other bias	Low risk	Financially supported by The Center for Integrated Rehabilitation of Cancer Patients, The Novo Nordic Foundation, The University Hospitals' Centre for Health Research (UCSF), The Lundbeck Foundation, The Novo Nordic Foundation for Clinical Nursing Research and The Danish Cancer Society. Any bias due to this support is not expected

Kim 2006

Methods	Randomisation • 2 arms: bed exercise for 30 minutes every day for 6 weeks vs usual care Recruitment period

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Kim 2006 *(Continued)*

- Not reported

Median follow-up time

- 6 weeks

Sample size calculation

- Reported, sample size 21 participants per arm: quote: "Sample size was estimated using power analysis in which a minimum sample of 42 (21 for the bed exercise (BE) group, 21 for control group) was needed to achieve an effect size of 0.90, an alpha significance level of 0.05 and beta of 0.20"

Participants	Eligibility criteria • Ability to communicate with the research team and understand the goals, methods and procedures of the study. • Diagnosed with leukaemia or severe aplastic anaemia • Having received allogeneic BMT in a haemopoietic stem cell transplantation unit for 6 weeks Participants (N = 35) • Intervention group (N = 18) • Control group (N = 17) Mean age • Intervention group: 32.9 (±7.0) years • Control group: 34.3 (±7.8) years Stage/type of disease • Intervention group: 10 ALL, 4 AML, 4 SAA • Control group: 8 ALL, 4 AML, 5 SAA Country • South Korea
Interventions	Exercise group • The participants performed an exercise program every day for thirty minutes over a period of six weeks • Sessions consisted of preliminary exercise for 10 minutes, relaxation breathing for 10 minutes and finish exercise for 10 minutes • The preliminary exercises were performed in this sequence: concentrate the attention on lower abdomen for 3 minutes; put left ankle on right knee for 3 minutes; put right ankle on left knee for 2 minutes; and bend both knees for 2 minutes. • The finish exercises were performed in this sequence: resting and relaxing of body and mind for 2 minutes; stroking down hair and face for 2 minutes; right and left rotating of both ankles for 2 minutes; stretching of legs and arms for 2 minutes; and stretching out on a bed for 2 minutes. Control group • Usual care, without any structured or supervised training and without encouragement to do physical exercise
Outcomes	Reported but not relevant • Lymphocyte count and the percentage of CD3+, CD4+ and CD8+, and CD4+/CD8+ ratio
Notes	

Risk of bias

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Kim 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomized by random-permuted block design using a random number table"
Allocation concealment (selection bias)	Low risk	Quote: "Randomized by random-permuted block design using a random number table"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported
Blinding of outcome assessor (patient-reported outcomes)	Unclear risk	Not reported
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Seven subjects were lost before completing the post-test. One died of cerebral haemorrhage, two died of acute renal failure, four refused before completing the post-test"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Not reported

Knols 2011

Methods	Randomisation • 2 arms: 12-weeks outpatient aerobic and strength exercises versus usual care Recruitment period • January 2005 to May 2008 Median follow-up time • 12 weeks Sample size calculation • Reported, sample size 64 participants per arm
Participants	Eligibility criteria • Adults (≥ 18 years of age) • 3 weeks up to 6 months after autologous or allogeneic stem cell transplantation • Without graft versus host disease > grade I or requiring treatment • Written informed consent

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Knols 2011 *(Continued)*

	Participants (N = 131) • Intervention group (N = 64) • Control group (N = 67) Mean age • Intervention group: 46.7 (18 to 75) years • Control group: 46.6 (20 to 67) years Stage/type of disease • Intervention group: 5 Hodgkin lymphoma, 11 NHL, 17 multiple myeloma, 19 AML, 5 CLL, 7 other; 27 allogeneic stem cell transplantation, 37 autologous stem cell transplantation • Control group: 9 Hodgkin lymphoma, 14 NHL, 20 multiple myeloma, 12 AML, 9 CLL, 2 ALL, 1 other; 24 allogeneic stem cell transplantation, 43 autologous stem cell transplantation Country • Switzerland
Interventions	Exercise group • All participants started with a 10-minutes warming up on an ergometer cycle or walking treadmill • Aerobic performance for at least 20 minutes (from 50% to 60% of maximum heart rate (220 - participant's age) to 70% to 80%) • Progressive resistance training including squats, step-ups and -downs, barbell rotation, upright rowing. Could be extended to chest press, triceps extension, biceps curl and calf raises. Control group • Usual care, without any structured or supervised training and without encouragement to do physical exercise
Outcomes	Reported and analysed in this review • Physical function • Fatigue • Physical performance • Anthopometric measures
Notes	Financially supported by Zürcher Krebsliga ("Zurich cancer league") and Eidgenössische Sportkommission (Federal Authorities of the Swiss Confederation, Federal Department of Defence, Civil Protection and Sport)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "minimization procedure was used to achieve an optimal balance between groups for the factors age, sex and type of transplantation"
Allocation concealment (selection bias)	Low risk	Quote: "opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible

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Knols 2011 *(Continued)*

Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"was carried out on intention to treat analysis"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	Financially supported by Zürcher Krebsliga ("Zurich cancer league") and Eidgenössische Sportkommission (Federal Authorities of the Swiss Confederation, Federal Department of Defence, Civil Protection and Sport). Any bias due to this support is not expected

Mello 2003

Methods	Randomisation • 2 arms: 6-week exercise program with active exercise, muscle stretching and treadmill walking vs usual care Recruitment period • not reported Median follow-up time • 6 weeks Sample size calculation • Not reported
Participants	Eligibility criteria • Adults (≥ 18 years of age) • Controlled clinical status • Absence of pain, musculoskeletal or neurological disturbances • No evidence of cardiovascular or pulmonary impairment Participants (N = 18) • Intervention group (N = 9) • Control group (N = 9) Mean age • Intervention group: 27.9 (18 to 39) years • Control group: 30.2 (18 to 44) years

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Mello 2003 *(Continued)*

	Stage/type of disease • Intervention group: 4 CML, 2 AML, 1 severe aplastic anaemia, 2 NHL/MDS • Control group: 6 CML, 2 AML, 1 severe aplastic anaemia Country • Brazil
Interventions	Exercise group • Exercises for shoulder, elbow, hip, knee and ankle • Stretching exercises for hamstring, triceps surae and quadriceps muscles • A treadmill walking program • Each session lasted 40 minutes, was carried out each day on weekdays for six weeks Control group • Usual care
Outcomes	Reported and analysed in this review • Physical performance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Unclear which patients and when patients have been randomised
Allocation concealment (selection bias)	High risk	Methods of randomisation not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 18 out of 32 patients have been evaluated. Ten patients have died but it is unclear in which treatment arm
Selective reporting (reporting bias)	Unclear risk	No study protocol available

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Mello 2003 *(Continued)*

Other bias	Unclear risk	Not reported

Persoon 2017

Methods	Randomisation • Single-blind randomised controlled trial • 2 arms: high intensity resistance und interval training for 18 weeks versus standard care Recruitment period • March 2011 to February 2014 Median follow-up time • 12 month follow-up
Participants	Eligibility criteria • Diagnosed with multiple myeloma in first line or with HL/NHL in first relapse and treated with HDC and ASCT 6 - 12 weeks ago • Sufficiently recovered from the ASCT: Hb > 6.5 mmol/L, WBC > 3.0 × 109/L, platelets > 100 × 109/L • Aged 18 to 65 years • Able to cycle on a bicycle ergometer with a load of at least 25 Watt • Able to walk at least 100 metres independently without crutches/cane(s) or walking frame • Give written informed consent Participants (N = 109) • Intervention group (N = 54) • Control group (N = 55) Mean age • Interventions group: 53.5 • Control group: 56 Stage of disease • Intervention group: not reported • Control group: not reported Country • the Netherlands
Interventions	Exercise group • 18-week exercise programme consisting of high-intensity resistance and interval training. Participants will train on specialised resistance training equipment and bicycle ergometers. In weeks 1 - 12, participants will perform resistance and interval training twice a week for 60 minutes per training session. In weeks 13 - 18 the intensity of exercise will be decreased to 1 session a week with a duration of 60 minutes. Control group • No exercise intervention
Outcomes	Reported

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Persoon 2017 *(Continued)*

- Physical performance
- Fatigue
- Anthropometric measurements
- Quality of life
- Adverse events

Not reported but relevant

- Overall survival

Reported but not relevant

- Neuropathy objective and self-reported physical activity level Mood disturbance
- Functioning in daily life
- Return to work
- Cost from a social perspective
- Bone mineral density

Primary outcome

- Cardiorespiratory fitness, muscle strength and fatigue

Notes	This study was supported by the Alpe d'HuZes/KWF Fund. The authors declare that no competing interests exist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was concealed, took place after completion of baseline assessments (T0) and was performed by an independent data manager using a validated software program."
Allocation concealment (selection bias)	Low risk	Quote: "...proceeded using block randomization with block sizes varying randomly between 2, 4 and 6."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported. The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Body composition was assessed by the sports physician and it remains unclear if he was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "However, we had a relatively high number of missing values"

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Persoon 2017 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	This study was supported by the Alpe d'HuZes/KWF Fund. The authors declare that no competing interests exist

Streckmann 2014

Methods	Randomisation • 2 arms: 36-week sensorimotor-, endurance- and strength training versus standard care Recruitment period • May 2008 to July 2011 Median follow-up time • 36 weeks Sample size calculation • Reported, but stopped early due to low recruitment rate
Participants	Eligibility criteria • Adults (≥ 18 years of age) diagnosed with malignant lymphoma • Indication for chemotherapy • Karnofsky performance score > 60 • Written informed consent Participants (N = 61) • Intervention group (N = 30) • Control group (N = 31) Mean age • Intervention group: 44 (20 to 67) years • Control group: 48 (19 to 73) years Stage of disease • Intervention group: 7 Hodgkin lymphoma, 13 B-NHL, 3 T-NHL, 5 multiple myeloma; 21 newly diagnosed, 5 relapses, 2 progressive disease • Control group: 5 Hodgkin lymphoma, 13 B-NHL, 3 T-NHL, 8 multiple myeloma; 23 newly diagnosed, 4 relapses, 1 progressive disease Country • Germany
Interventions	Exercise group • Aerobic endurance training: cardiovascular activation on a bicycle dynamometer (60% - 70% max heart rate), 10- to 30-minute walk on a treadmill or bicycle dynamometer at the end of the session • Sensorimotor training: 4 postural stabilisation tasks, progressively increasing task difficulty • Strength training: 4 resistance exercises carried out for 1 minute Control group

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Streckmann 2014 *(Continued)*

	• Standard care including physiotherapy
Outcomes	Reported and analysed in this review • QoL • Cancer therapy-induced side effects • Strength Reported but not relevant for this review • Movement co-ordination
Notes	Financially supported by a grant by AMGEN, the authors report no competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "carried out by an independent randomization office"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	Outcome not reported
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Intention to treat strategies for substituting missing values"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Study stopped early, due to low recruitment. Quote: "At this point, we considered physiological parameters much more relevant to evaluate the intervention than QoL, hence the study was stopped early" Statistically significant baseline imbalances for QoL, favouring the control arm

Wiskemann 2015

Methods	Randomisation

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Wiskemann 2015 *(Continued)*

- 2 arms: self-administered exercise intervention versus standard care

Recruitment period

- May 2007 (German Clinic for Diagnostics) or October 2007 (University Clinic of Heidelberg) until September 2008

Median follow-up time

- No follow-up analysis was executed

Sample size calculation

- Not reported

Participants	Eligibility criteria • Not reported Participants (N = 105) • Intervention group (N = 52) • Control group (N = 53) Mean age • Intervention group: 47.6 years • Control group: 50 years Disease • Intervention group: 12 AML, 6 ALL, 2 CML, 2 CLL, 7 MDS, 6 secondary AML, 7MPS, 2 multiple myeloma, 7 lymphoma, 1 aplastic anaemia • Control group: 10 AML, 8 ALL, 2 CML, 2 CLL, 5 MDS, 5 secondary AML, 6 MPS, 1 multiple myeloma, 13 lymphoma, 1 aplastic anaemia Country • Germany
Interventions	Exercise group • 1 - 4 weeks before admission to hospital participants started exercise programme, continued during inpatient period and until 6 - 8 weeks after discharge from hospital • Outpatient intervention self-directed at home • Inpatient intervention partly supervised, twice per week and adjusted to the isolation unit conditions • 3 - 5 endurance and 2 resistance training sessions per week • Endurance training: rapid walking for 20 - 40 minutes; bicycling or treadmill walking • Strength training: with and without colour-coded stretch bands with different levels of resistance (8 - 20 repetitions, 2 or 3 sets) Control group • Explanation that moderate physical activity is favourable during treatment process without further advice. During inpatient period, physiotherapy was offered up to 3 times per week (30 minutes). Participants had the same access to stationary cycles and treadmills as exercise group All participants received allogeneic stem cell transplantation
Outcomes	Reported and relevant for this review • Fatigue • Physical performance

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Wiskemann 2015 *(Continued)*

- Quality of life
- Physical/psychologic distress

Notes	Conflict of interest not reported, funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by the minimisation procedure stratified by age, disease, and sex for each centre to an exercise or a control group“
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (primary endpoint; mortality)	Low risk	The review authors judge that the outcome mortality in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding of outcome assessor (patient-reported outcomes)	High risk	Blinding in this context is not feasible
Blinding of outcome assessor (physical performance, AEs, SAEs)	High risk	Quote: "The testers were not blinded to randomisation but not involved in the therapeutic supervision of the patients.“
Incomplete outcome data (attrition bias) All outcomes	High risk	112 participants were randomly assigned to both study arms. In study analysis only 105 participants were included. Moreover, it is not reported, how many patients in the control arm performed exercise
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Not reported

ALL: acute lymphoblastic leukaemia; **AML:** acute myeloid leukaemia;**ASCT: autologous stem cell transplant; BMT:** bone marrow transplant; **B-NHL:** B-cell non-Hodgkin's lymphoma; **CLL:** chronic lymphoblastic leukaemia; **CML:** chronic myeloid leukaemia; **DCEP:** dexamethasone, cyclophosphamide, etoposide, and cisplatin;**EPO:** erythropoietin;**Hb:** haemoglobin; **HCT:** haematopoietic cell transplantation; **HL:** Hodgkin's lymphoma; **MDS:** myelodysplastic syndrome; **NHL:** non-Hodgkin's lymphoma; **OS:** overall survival; **T-NHL:** T-cell non-Hodgkin's lymphoma;**QoL:** quality of life

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Broderick 2013	Only 7% of the included participants suffer from haematological malignancies
Cohen 2004	Study investigated influence of Tibetan yoga intervention on psychological adjustment and sleep quality. This intervention does not correspond to our prescribed exercise intervention

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Study	Reason for exclusion
Forbes 2017	In this study, participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
Grabenbauer 2016	In this study, participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
Hacker 2011	Exercise intervention only consisted of strength training. This intervention does not correspond to our predefined types of exercise intervention
Hacker 2016	Exercise intervention only consisted of strength training. This intervention does not correspond to our predefined types of exercise intervention
Hartman 2009	Study included participants up to the age of 18 years
Jarden 2009	Control group received standard treatment care and physiotherapy. Intervention consisted of physical exercise together with psycho-education and progressive relaxation
Jones 2014	In this study, participants suffering from cancer in general were included, no subgroup analyses for those with haematological malignancies were provided
Kampshoff 2015	Only 10 % of the included participants suffer from haematological malignancies
Kanera 2017	In this study, participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
Marchese 2004	Study included participants up to the age of 18 years
Mayo 2014	In this study, it is not made clear which kind of malignancies have been diagnosed
Midtgaard 2013	In this study, only 13% of the participants suffer from haematological malignancies
Moyer-Mileur 2009	Study included participants up to the age of 18 years
Oechsle 2014	In this study only 75% of the participants suffer from haematological malignancies
Peoples 2017	In this study, participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
PETRA study	Study did not compare an exercise group with a standard care group. In this study the control group receives a relaxation program
Prinsen 2013	Intervention is cognitive behavioural therapy. This intervention does not correspond to our prescribed exercise intervention
Schumacher 2015a	Both study arms were asked to exercise, either with a physiotherapist or with Nintendo Wii
Shelton 2009	Study did not compare an exercise group with a standard care group. In this study both groups conducted physical exercise intervention
Stacey 2016	In this study, participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
Tanir 2013	Study included participants up to the age of 18 years

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Study	Reason for exclusion
Thorsen 2005	In this study, participants suffering from different cancer types (lymphomas, breast, gynaecologic or testicular cancer) were included, no subgroup analyses for those with haematological malignancies were provided
Toohey 2016	In this study, participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
Tran 2016	In this study participants suffering from different cancer types were included, no subgroup analyses for those with haematological malignancies were provided
Valle 2013	In this study, only 30% percent of the participants suffer from haematological exercises
Vallerand 2018	Study did not compare an exercise group with a standard care group. In this study both, intervention and control group, were asked to exercise
van Waart 2015	In this study, only participants suffering from breast cancer were included
Yeh 2016	Intervention is qigong. This intervention does not correspond to our prescribed exercise intervention
Zimmer 2014	In this study, only 75% of the participants were suffering from haematological malignancies

Characteristics of studies awaiting assessment *[ordered by study ID]*

Wehrle 2018

Methods	Randomisation • Randomised controlled trial • 3 arms: endurance training, resistance training, control group Recruitment period • not reported Median follow-up time • not reported
Participants	Eligibility criteria • Adult patients with acute leukaemia undergoing induction chemotherapy Participants (N = 29) • Endurance group (N = not reported) • Resitance group (N = not reported) • Control group (N = not reported) Mean age • Not reported Stage of disease • Not reported Country

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Wehrle 2018 *(Continued)*

	• Not reported
Interventions	The intervention took place during induction chemotherapy with three exercise sessions per week for 30 to 45 minutes each Endurance group • Endurance capacity at individual anaerobic threshold Resitance group • Not reported Control group • Not reported.
Outcomes	Reported • Knee extension strength • Endurance capacity • Maximum strength • Stndardised phase angle Not reported but relevant • Quality of life
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

Abildgaard 2018

Trial name or title	Early initiated individualized physical training in newly diagnosed multiple myeloma patients; effects on physical function, physical activity, quality of life, pain, and bone disease.
Methods	Randomisation • Randomised controlled trial • 2 arms: supervised exercise combined with home based exercise and physical activity vs usual care consisting of advice regarding exercise, physical activity, person lifting and moving Recruitment period • Recruitment period not yet completed Median follow-up time • 12 month follow-up
Participants	Eligibility criteria • Newly diagnosed with multiple myeloma requiring treatment • The patient must be able to speak and understand Danish • Age ≥ 18 years • No severe comorbidity that would not allow physical training • Give written informed consent Participants (N = not reported)

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Abildgaard 2018 *(Continued)*

	• Intervention group (N = not reported) • Control group (N = not reported) Mean age • Interventions group: not reported • Control group: not reported Stage of disease • Intervention group: not reported • Control group: not reported Country • Denmark
Interventions	Exercise group • 8 supervised in-hospital training sessions in a period of 10 weeks. The intervention will consist of strength exercise, aerobic exercise and physical activity. Control group • No exercise intervention
Outcomes	Reported • Isometric knee extension strength • Physical performance • Fatigue • Quality of sleep • Quality of life Not reported but relevant • Overall survival Reported but not relevant • Bone mineral density Primary outcome • Isometric knee extension strength
Starting date	May 2015
Contact information	Niels Abildgaard, Zealand University Hospital, Roskilde, Denmark
Notes	

Courneya 2017

Trial name or title	Improving quality of life in hematologic cancer survivors by closing the exercise intention—behavior gap: a phase II randomized controlled trial of a theory-based, telephone-delivered exercise counselling intervention
Methods	Randomisation

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Courneya 2017 *(Continued)*

	• Randomised controlled trial • 2 arms: telephone counselling exercise vs usual care Recruitment period • Recruitment period not yet completed Median follow-up time • 12 weeks
Participants	Eligibility criteria • Histologically-confirmed haematological cancer • Willing to participate in a 12-week exercise telephone counselling intervention • Give written informed consent • Age between 18 and 80 years • Ability to speak and understand English • Living in Alberta • No severe comorbidity that would not allow physical training Participants (N = 66) • Intervention group (N = 33) • Control group (N = 33) Mean age • Interventions group: not reported • Control group: not Reported Stage of disease • Intervention group: not reported • Control group: not reported Country • Canada
Interventions	Exercise group • Participants will be asked to increase their exercise by at least 60 minutes per week and will receive a copy of Canada's Physical Activity Guideline plus 12 weekly telephone counselling sessions aimed at helping survivors follow-through on their exercise intention. Control group • Participants will be asked to increase their exercise by at least 60 minutes per week and will receive a copy of Canada's Physical Activity Guideline
Outcomes	<u>Reported</u> • Exercise levels • Quality of life • Fatigue <u>Not reported but relevant</u> • Overall survival <u>Reported but not relevant</u>

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Courneya 2017 *(Continued)*

	• Exercise motivation Primary outcome • Exercise levels
Starting date	February 2017
Contact information	Kerry Courneya, University of Alberta, Canada
Notes	

Oberste 2016

Trial name or title	The effect of a chemotherapy accompanying 4-week aerobic endurance exercise intervention on incidence and severity of cancer related cognitive impairments in leukemia patients. A randomized controlled trial
Methods	Randomisation • Randomised controlled trial • 3 arms: cycling on an ergometer vs myofascial release training vs usual care during 4 weeks of induction chemotherapy Recruitment period • Recruitment period not yet completed Median follow-up time • 8-month follow-up
Participants	Eligibility criteria • Diagnosed with AML (apart from M3 subtype) or MDS • Impended medical treatment according to S-HAM or TAD-HAM chemotherapy protocol • Age ≥ 18 years • Able to participate in the exercise or myofascial release training • Give written informed consent Participants (N = 83) • Intervention group (N = not reported) • Placebo group (N = not reported) • Control group (N = not reported) Mean age • Interventions group: not reported • Placebo group: not reported • Control group: not reported Stage of disease • Intervention group: not reported • Placebo group: not reported • Control group: not reported Country

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Oberste 2016 *(Continued)*

	• Germany
Interventions	Exercise group • 4-week supervised aerobic exercise program which is supposed to take place at three times a week for 30 minutes at moderate to vigorous intensity (5-minute warm-up at low intensity, 20 minutes at 65% to 70% of individual maximum heart rate, 5-minute cool-down at low intensity) on a stationary bicycle ergometer Placebo group • 4-week supervised myofascial release and stretching training at a low cardiovascular level. This training also will be carried out three times a week for 30 minutes per session. Control group • No exercise intervention
Outcomes	Reported • Physical performance • Fatigue • Quality of sleep • Quality of life Not reported but relevant • Overall survival Reported but not relevant • Cognitive performance • Serum levels of inflammatory and anti-inflammatory cytokines (TNF- α, IL-1, IL-10) as well as serum levels of neurotrophic factors (BDNF, VEGF, IGF-1) • Side effect of chemotherapy Primary outcome • Cognitive performance
Starting date	Not reported
Contact information	Department of Molecular and Cellular Sport Medicine, Institute of Cardiovascular Research and Sports Medicine, German Sport University Cologne, Cologne, Germany
Notes	Will be financially supported by the Marga und Walter Boll Stiftung. The authors report no conflict of interest

Walsh 2005

Trial name or title	Randomised controlled trial to investigate the effects of an exercise programme on physical performance and quality of life after a bone marrow transplant
Methods	Randomisation • Randomised controlled trial • 3 arms: aerobic plus active exercise vs aerobic plus resistance exercise vs usual care

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Walsh 2005 *(Continued)*

	Recruitment period • Not available Median follow-up time • 6 weeks follow-up
Participants	Eligibility criteria • Recipient of bone marrow transplant at Alfred Hospital • Platelets >= 20 x 10E9 • Absolute neutrophil count of 1x10E9 30 days after bone marrow transplant • At least 18 years old • Give written informed consent • Stable medical condition • No febrile neutropenia • No active GvHD • No cardiomyopathy Participants (N = not reported) • Intervention group 1 (N = not reported) • Intervention group 2 (N = not reported) • Control group (N = not reported) Mean age • Interventions group 1: not reported • Interventions group 2: not reported • Control group: not reported Stage of disease • Intervention group 1: not reported • Intervention group 2: not reported • Control group: not reported Country • Australia
Interventions	Exercise group 1 • Aerobic exercise plus resistance exercise for 6 weeks Exercise group 2 • Aerobic exercise plus active exercise for 6 weeks Control group • No exercise plus weekly phone calls
Outcomes	Reported • Physical performance • QoL • Anthropometry and grip strength • Heart rate • Adverse events

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Walsh 2005 *(Continued)*

	Not reported but relevant • Overall survival Reported but not relevant • None Primary outcome • Physical performance • QoL • Anthropometry and grip strength
Starting date	November 2003, no further information when the trial will be terminated in study registry clinicaltrials.gov. The status still ongoing (last access 09.12.2018)
Contact information	Alfred Hospital Physiotherapy Dept, Melbourne, Australia
Notes	Financially supported by Bayside Health

AML: acute myeloid leukaemia; **BDNF**: brain-derived neurotrophic factor; **GvHD:** graft-versus-host-diease;**MDS:** myelodysplastic syndrome; **QoL:** quality of life; **VEGF:** Vascular endothelial growth factor Vascular endothelial growth factor

DATA AND ANALYSES

Comparison 1. Physical exercise versus no physical exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality: SCT versus no SCT	7	1172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.52]
1.1 SCT	5	980	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.41]
1.2 no SCT	2	192	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.88, 4.50]
2 Mortality	7	1172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.52]
3 Mortality sensitivity analysis: high risk of bias versus low risk of bias	7	1172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.52]
3.1 High Risk	1	70	Risk Ratio (M-H, Random, 95% CI)	3.17 [0.13, 75.28]
3.2 Low Risk	6	1102	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.77, 1.53]
4 Quality of life (QoL)	9	1259	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.03, 0.24]
5 QoL: SCT versus no SCT	9	1259	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.03, 0.24]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 SCT	5	977	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.06, 0.24]
5.2 no SCT	4	282	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.20, 0.47]
6 QoL sensitivity analysis: high risk of bias versus low risk of bias	9	1259	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.03, 0.24]
6.1 High Risk	4	257	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.22, 0.47]
6.2 Low Risk	5	1002	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.05, 0.25]
7 Physical functioning/QoL	9	1329	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.01, 0.32]
8 Physical functioning/QoL: SCT versus no SCT	9	1329	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.00, 0.32]
8.1 SCT	6	1108	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.07, 0.33]
8.2 no SCT	3	221	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.00, 0.53]
9 Physical functioning/QoL sensitivity analysis: high risk of bias versus low risk of bias	9	1329	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.00, 0.32]
9.1 High Risk	3	196	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.14, 0.46]
9.2 Low Risk	6	1133	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.04, 0.36]
10 Depression/QoL	6	445	Std. Mean Difference (IV, Random, 95% CI)	0.19 [0.00, 0.38]
11 Depression/QoL: SCT versus no SCT	6	445	Std. Mean Difference (IV, Random, 95% CI)	0.19 [0.00, 0.38]
11.1 SCT	2	202	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.32, 0.63]
11.2 no SCT	4	243	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.04, 0.47]
12 Depression/QoL sensitivity analysis: high risk of bias versus low risk of bias	6	445	Std. Mean Difference (IV, Random, 95% CI)	0.19 [0.00, 0.38]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 High Risk	4	218	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.15, 0.38]
12.2 Low Risk	2	227	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.00, 0.52]
13 Anxiety/QoL	6	445	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.30, 0.36]
14 Anxiety/QoL: SCT versus no SCT	6	445	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.30, 0.36]
14.1 SCT	2	202	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.82, 0.19]
14.2 no SCT	4	243	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.09, 0.51]
15 Fatigue	9	826	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.13, 0.48]
16 Anxiety/QoL sensitivity analysis: high risk of bias versus low risk of bias	6	445	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.30, 0.36]
16.1 High Risk	4	218	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.08, 0.51]
16.2 Low Risk	2	227	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.81, 0.20]
17 Fatigue: SCT versus no SCT	9	826	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.13, 0.48]
17.1 SCT	5	584	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.12, 0.51]
17.2 no SCT	4	242	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.09, 0.69]
18 Fatigue sensitivity analysis: high risk of bias versus low risk of bias	9	826	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.13, 0.48]
18.1 High Risk	5	404	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.06, 0.57]
18.2 Low Risk	4	422	Std. Mean Difference (IV, Random, 95% CI)	0.37 [0.18, 0.57]
19 Weight	4	964	Mean Difference (IV, Random, 95% CI)	0.44 [-1.94, 2.82]
20 Weight SCT: versus no SCT	4	964	Mean Difference (IV, Random, 95% CI)	0.44 [-1.94, 2.82]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 SCT	3	842	Mean Difference (IV, Random, 95% CI)	-0.07 [-2.68, 2.55]
20.2 no SCT	1	122	Mean Difference (IV, Random, 95% CI)	2.80 [-2.88, 8.48]
21 Weight sensitivity analysis: high risk of bias versus low risk of bias	4	964	Mean Difference (IV, Random, 95% CI)	0.44 [-1.94, 2.82]
21.1 Low Risk	4	964	Mean Difference (IV, Random, 95% CI)	0.44 [-1.94, 2.82]
21.2 High Risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
22 Lean body mass	3	290	Mean Difference (IV, Random, 95% CI)	1.26 [-1.22, 3.74]
23 Lean body mass: SCT versus no SCT	3	290	Mean Difference (IV, Random, 95% CI)	1.26 [-1.22, 3.74]
23.1 SCT	1	131	Mean Difference (IV, Random, 95% CI)	0.20 [-3.57, 3.97]
23.2 no SCT	2	159	Mean Difference (IV, Random, 95% CI)	2.06 [-1.22, 5.35]
24 Lean body mass sensitivity analysis: high risk of bias versus low risk of bias	3	290	Mean Difference (IV, Random, 95% CI)	1.26 [-1.22, 3.74]
24.1 High Risk	1	37	Mean Difference (IV, Random, 95% CI)	0.80 [-5.69, 7.29]
24.2 Low Risk	2	253	Mean Difference (IV, Random, 95% CI)	1.34 [-1.34, 4.02]
25 Serious adverse events (SAEs)	6	435	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.94, 2.06]
26 Serious adverse events (SAEs): SCT versus no SCT	6	435	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.94, 2.06]
26.1 SCT	3	254	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.94, 2.09]
26.2 no SCT	3	181	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.21]
27 Serious adverse events (SAEs) sensitivity analysis: high risk of bias versus low risk of bias	6	435	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.94, 2.06]
27.1 High Risk	5	313	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.94, 2.06]
27.2 Low Risk	1	122	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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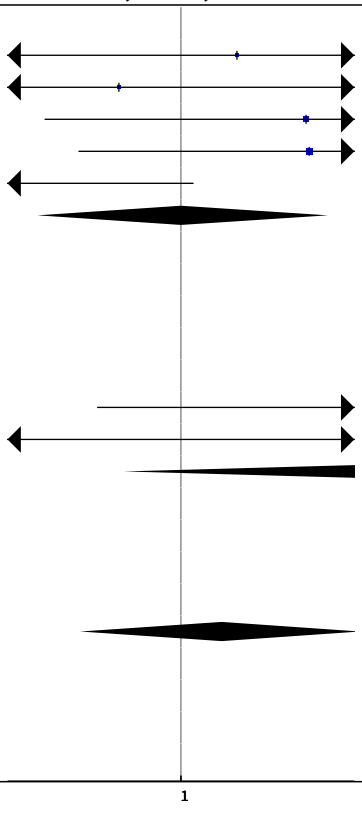
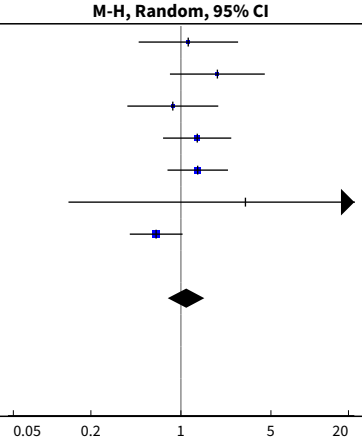
Analysis 1.1. Comparison 1 Physical exercise versus no physical exercise, Outcome 1 Mortality: SCT versus no SCT.

Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 SCT					
Baumann 2010	8/32	7/32		10.68%	1.14[0.47,2.78]
DeFor 2007	9/51	10/49		12.31%	0.86[0.38,1.95]
Jacobsen 2014a	22/180	16/175		18.38%	1.34[0.73,2.46]
Jacobsen 2014b	27/178	20/178		21.33%	1.35[0.79,2.32]
Wiskemann 2015	17/52	27/53		24.77%	0.64[0.4,1.03]
Subtotal (95% CI)	**493**	**487**		**87.47%**	**1[0.71,1.41]**
Total events: 83 (physical exercise), 80 (no exercise)					
Heterogeneity: Tau^2=0.05; Chi^2=5.78, df=4(P=0.22); I^2=30.81%					
Test for overall effect: Z=0.01(P=0.99)					
1.1.2 no SCT					
Courneya 2009	13/60	7/62		11.49%	1.92[0.82,4.48]
Jarden 2016	1/34	0/36		1.04%	3.17[0.13,75.28]
Subtotal (95% CI)	**94**	**98**		**12.53%**	**1.98[0.88,4.5]**
Total events: 14 (physical exercise), 7 (no exercise)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=1.64(P=0.1)					
Total (95% CI)	**587**	**585**		**100%**	**1.1[0.79,1.52]**
Total events: 97 (physical exercise), 87 (no exercise)					
Heterogeneity: Tau^2=0.05; Chi^2=8.47, df=6(P=0.21); I^2=29.17%					
Test for overall effect: Z=0.55(P=0.59)					
Test for subgroup differences: Chi^2=2.28, df=1 (P=0.13), I^2=56.21%					



Analysis 1.2. Comparison 1 Physical exercise versus no physical exercise, Outcome 2 Mortality.

Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baumann 2010	8/32	7/32		10.68%	1.14[0.47,2.78]
Courneya 2009	13/60	7/62		11.49%	1.92[0.82,4.48]
DeFor 2007	9/51	10/49		12.31%	0.86[0.38,1.95]
Jacobsen 2014a	22/180	16/175		18.38%	1.34[0.73,2.46]
Jacobsen 2014b	27/178	20/178		21.33%	1.35[0.79,2.32]
Jarden 2016	1/34	0/36		1.04%	3.17[0.13,75.28]
Wiskemann 2015	17/52	27/53		24.77%	0.64[0.4,1.03]
Total (95% CI)	**587**	**585**		**100%**	**1.1[0.79,1.52]**
Total events: 97 (physical exercise), 87 (no exercise)					
Heterogeneity: Tau^2=0.05; Chi^2=8.47, df=6(P=0.21); I^2=29.17%					
Test for overall effect: Z=0.55(P=0.59)					



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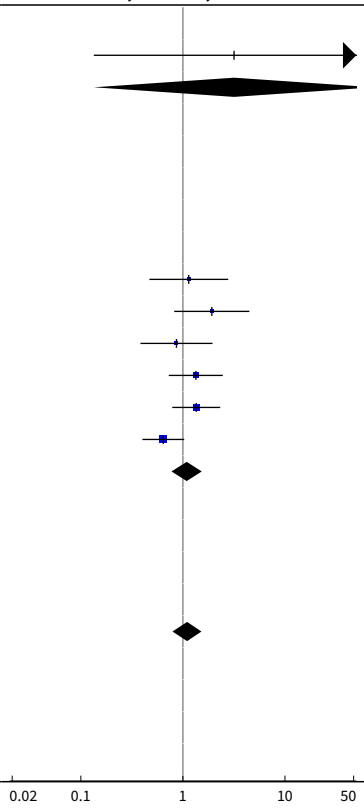
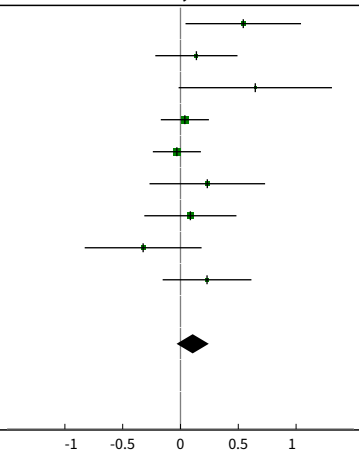
Analysis 1.3. Comparison 1 Physical exercise versus no physical exercise, Outcome 3 Mortality sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 High Risk					
Jarden 2016	1/34	0/36		1.04%	3.17[0.13,75.28]
Subtotal (95% CI)	**34**	**36**		**1.04%**	**3.17[0.13,75.28]**
Total events: 1 (physical exercise), 0 (no exercise)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
1.3.2 Low Risk					
Baumann 2010	8/32	7/32		10.68%	1.14[0.47,2.78]
Courneya 2009	13/60	7/62		11.49%	1.92[0.82,4.48]
DeFor 2007	9/51	10/49		12.31%	0.86[0.38,1.95]
Jacobsen 2014a	22/180	16/175		18.38%	1.34[0.73,2.46]
Jacobsen 2014b	27/178	20/178		21.33%	1.35[0.79,2.32]
Wiskemann 2015	17/52	27/53		24.77%	0.64[0.4,1.03]
Subtotal (95% CI)	**553**	**549**		**98.96%**	**1.09[0.77,1.53]**
Total events: 96 (physical exercise), 87 (no exercise)					
Heterogeneity: Tau²=0.07; Chi²=7.98, df=5(P=0.16); I²=37.37%					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**587**	**585**		**100%**	**1.1[0.79,1.52]**
Total events: 97 (physical exercise), 87 (no exercise)					
Heterogeneity: Tau²=0.05; Chi²=8.47, df=6(P=0.21); I²=29.17%					
Test for overall effect: Z=0.55(P=0.59)					
Test for subgroup differences: Chi²=0.43, df=1 (P=0.51), I²=0%					



Analysis 1.4. Comparison 1 Physical exercise versus no physical exercise, Outcome 4 Quality of life (QoL).

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Baumann 2010	32	57.5 (21.4)	32	45.2 (23.3)		6.64%	0.54[0.04,1.04]
Courneya 2009	60	151.4 (21.7)	62	148.1 (25.7)		11.46%	0.14[-0.22,0.49]
Furzer 2016	18	90.2 (10.1)	19	82.7 (12.4)		4.02%	0.65[-0.02,1.31]
Jacobsen 2014a	180	50.8 (10.4)	175	50.4 (10.7)		22.44%	0.04[-0.17,0.25]
Jacobsen 2014b	178	52.1 (9.7)	178	52.4 (9.4)		22.48%	-0.03[-0.24,0.18]
Jarden 2016	32	85.2 (14.2)	30	81.2 (19.6)		6.63%	0.23[-0.27,0.73]
Persoon 2017	50	75 (18.7)	47	73.4 (18.4)		9.62%	0.09[-0.31,0.48]
Streckmann 2014	30	58.3 (25)	31	66.3 (23.9)		6.51%	-0.32[-0.83,0.18]
Wiskemann 2015	52	61.7 (22.2)	53	57.1 (17.3)		10.2%	0.23[-0.15,0.61]
Total ***	**632**		**627**			**100%**	**0.11[-0.03,0.24]**
Heterogeneity: Tau²=0.01; Chi²=10.85, df=8(P=0.21); I²=26.3%							
Test for overall effect: Z=1.48(P=0.14)							



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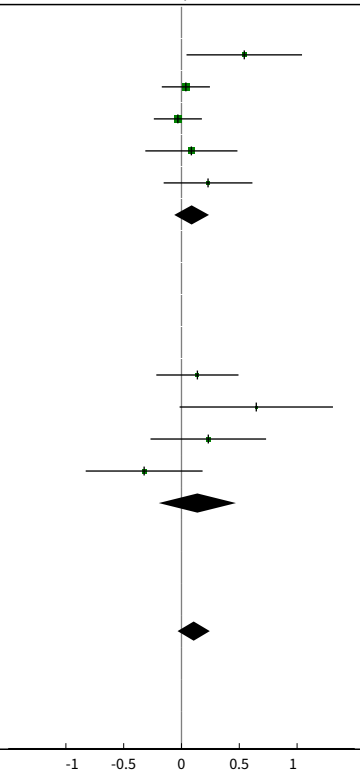
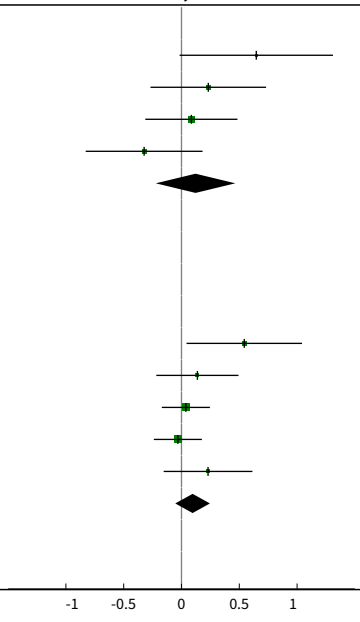
Analysis 1.5. Comparison 1 Physical exercise versus no physical exercise, Outcome 5 QoL: SCT versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.5.1 SCT							
Baumann 2010	32	57.5 (21.4)	32	45.2 (23.3)		6.64%	0.54[0.04,1.04]
Jacobsen 2014a	180	50.8 (10.4)	175	50.4 (10.7)		22.44%	0.04[-0.17,0.25]
Jacobsen 2014b	178	52.1 (9.7)	178	52.4 (9.4)		22.48%	-0.03[-0.24,0.18]
Persoon 2017	50	75 (18.7)	47	73.4 (18.4)		9.62%	0.09[-0.31,0.48]
Wiskemann 2015	52	61.7 (22.2)	53	57.1 (17.3)		10.2%	0.23[-0.15,0.61]
Subtotal ***	**492**		**485**			**71.38%**	**0.09[-0.06,0.24]**
Heterogeneity: Tau^2=0.01; Chi^2=5.12, df=4(P=0.27); I^2=21.93%							
Test for overall effect: Z=1.14(P=0.25)							
1.5.2 no SCT							
Courneya 2009	60	151.4 (21.7)	62	148.1 (25.7)		11.46%	0.14[-0.22,0.49]
Furzer 2016	18	90.2 (10.1)	19	82.7 (12.4)		4.02%	0.65[-0.02,1.31]
Jarden 2016	32	85.2 (14.2)	30	81.2 (19.6)		6.63%	0.23[-0.27,0.73]
Streckmann 2014	30	58.3 (25)	31	66.3 (23.9)		6.51%	-0.32[-0.83,0.18]
Subtotal ***	**140**		**142**			**28.62%**	**0.14[-0.2,0.47]**
Heterogeneity: Tau^2=0.05; Chi^2=5.58, df=3(P=0.13); I^2=46.23%							
Test for overall effect: Z=0.81(P=0.42)							
Total ***	**632**		**627**			**100%**	**0.11[-0.03,0.24]**
Heterogeneity: Tau^2=0.01; Chi^2=10.85, df=8(P=0.21); I^2=26.3%							
Test for overall effect: Z=1.48(P=0.14)							
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%							



Analysis 1.6. Comparison 1 Physical exercise versus no physical exercise, Outcome 6 QoL sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.6.1 High Risk							
Furzer 2016	18	90.2 (10.1)	19	82.7 (12.4)		4.02%	0.65[-0.02,1.31]
Jarden 2016	32	85.2 (14.2)	30	81.2 (19.6)		6.63%	0.23[-0.27,0.73]
Persoon 2017	50	75 (18.7)	47	73.4 (18.4)		9.62%	0.09[-0.31,0.48]
Streckmann 2014	30	58.3 (25)	31	66.3 (23.9)		6.51%	-0.32[-0.83,0.18]
Subtotal ***	**130**		**127**			**26.78%**	**0.12[-0.22,0.47]**
Heterogeneity: Tau^2=0.06; Chi^2=5.58, df=3(P=0.13); I^2=46.21%							
Test for overall effect: Z=0.69(P=0.49)							
1.6.2 Low Risk							
Baumann 2010	32	57.5 (21.4)	32	45.2 (23.3)		6.64%	0.54[0.04,1.04]
Courneya 2009	60	151.4 (21.7)	62	148.1 (25.7)		11.46%	0.14[-0.22,0.49]
Jacobsen 2014a	180	50.8 (10.4)	175	50.4 (10.7)		22.44%	0.04[-0.17,0.25]
Jacobsen 2014b	178	52.1 (9.7)	178	52.4 (9.4)		22.48%	-0.03[-0.24,0.18]
Wiskemann 2015	52	61.7 (22.2)	53	57.1 (17.3)		10.2%	0.23[-0.15,0.61]
Subtotal ***	**502**		**500**			**73.22%**	**0.1[-0.05,0.25]**
Heterogeneity: Tau^2=0.01; Chi^2=5.25, df=4(P=0.26); I^2=23.75%							
Test for overall effect: Z=1.26(P=0.21)							



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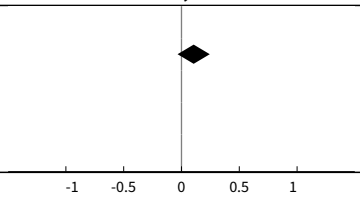
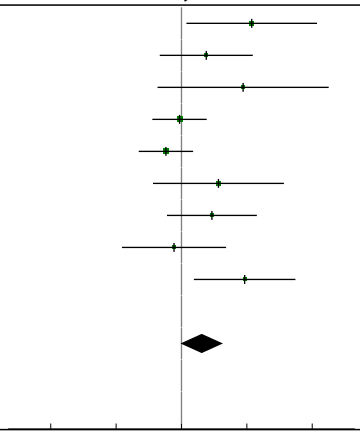
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Total ***	**632**		**627**			**100%**	**0.11[-0.03,0.24]**
Heterogeneity: Tau²=0.01; Chi²=10.85, df=8(P=0.21); I²=26.3%							
Test for overall effect: Z=1.48(P=0.14)							
Test for subgroup differences: Chi²=0.02, df=1 (P=0.89), I²=0%							



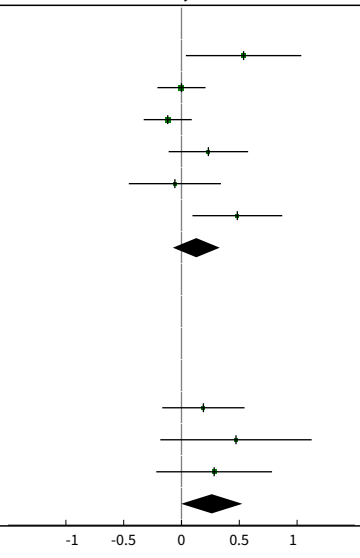
Analysis 1.7. Comparison 1 Physical exercise versus no physical exercise, Outcome 7 Physical functioning/QoL.

Study or subgroup	Favours no exercise N	Favours no exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Baumann 2010	32	61.6 (22.7)	32	48.7 (24.7)		7.49%	0.54[0.04,1.04]
Courneya 2009	60	109.3 (18.7)	62	105.4 (22)		11.5%	0.19[-0.17,0.55]
Furzer 2016	18	52 (6)	19	48 (10)		4.97%	0.47[-0.18,1.13]
Jacobsen 2014a	180	42.2 (20.8)	175	42.5 (19.4)		18.06%	-0.01[-0.22,0.19]
Jacobsen 2014b	178	40.6 (10.5)	178	41.8 (9.6)		18.07%	-0.12[-0.33,0.09]
Jarden 2016	32	22.8 (4.7)	30	21.2 (6.4)		7.46%	0.28[-0.22,0.78]
Knols 2011	64	83.7 (14.2)	67	80.4 (14)		11.94%	0.23[-0.11,0.58]
Persoon 2017	50	83.1 (19.1)	47	84.1 (15.3)		10.09%	-0.06[-0.46,0.34]
Wiskemann 2015	52	73.7 (19.6)	53	63.5 (22.2)		10.41%	0.48[0.09,0.87]
Total ***	**666**		**663**			**100%**	**0.15[-0.01,0.32]**
Heterogeneity: Tau²=0.03; Chi²=15.24, df=8(P=0.05); I²=47.5%							
Test for overall effect: Z=1.87(P=0.06)							



Analysis 1.8. Comparison 1 Physical exercise versus no physical exercise, Outcome 8 Physical functioning/QoL: SCT versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.8.1 SCT							
Baumann 2010	32	61.6 (22.7)	32	48.7 (24.7)		7.44%	0.54[0.04,1.04]
Jacobsen 2014a	180	42.2 (20.8)	175	42.2 (19.4)		18.2%	0[-0.21,0.21]
Jacobsen 2014b	178	40.6 (10.5)	178	41.8 (9.6)		18.21%	-0.12[-0.33,0.09]
Knols 2011	64	83.7 (14.2)	67	80.4 (14)		11.93%	0.23[-0.11,0.58]
Persoon 2017	50	83.1 (19.1)	47	84.1 (15.3)		10.06%	-0.06[-0.46,0.34]
Wiskemann 2015	52	73.7 (19.6)	53	63.5 (22.2)		10.37%	0.48[0.09,0.87]
Subtotal ***	**556**		**552**			**76.2%**	**0.13[-0.07,0.33]**
Heterogeneity: Tau²=0.04; Chi²=12.54, df=5(P=0.03); I²=60.13%							
Test for overall effect: Z=1.24(P=0.22)							
1.8.2 no SCT							
Courneya 2009	60	109.3 (18.7)	62	105.4 (22)		11.48%	0.19[-0.17,0.55]
Furzer 2016	18	52 (6)	19	48 (10)		4.91%	0.47[-0.18,1.13]
Jarden 2016	32	22.8 (4.7)	30	21.2 (6.4)		7.41%	0.28[-0.22,0.78]
Subtotal ***	**110**		**111**			**23.8%**	**0.26[-0,0.53]**



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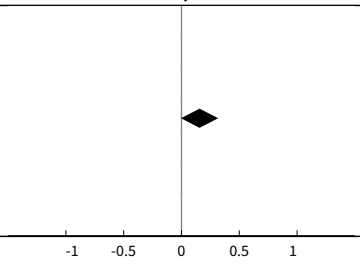
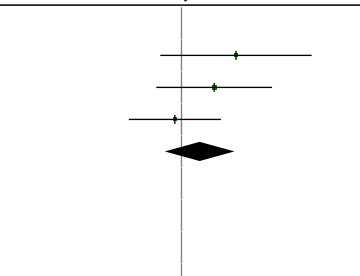
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.56, df=2(P=0.76); I²=0%							
Test for overall effect: Z=1.94(P=0.05)							
Total ***	**666**		**663**			**100%**	**0.16[-0,0.32]**
Heterogeneity: Tau²=0.03; Chi²=14.98, df=8(P=0.06); I²=46.6%							
Test for overall effect: Z=1.9(P=0.06)							
Test for subgroup differences: Chi²=0.62, df=1 (P=0.43), I²=0%							



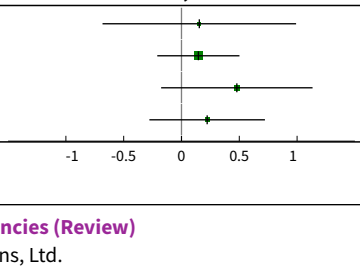
Analysis 1.9. Comparison 1 Physical exercise versus no physical exercise, Outcome 9 Physical functioning/QoL sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.9.1 High Risk							
Furzer 2016	18	52 (6)	19	48 (10)		4.91%	0.47[-0.18,1.13]
Jarden 2016	32	22.8 (4.7)	30	21.2 (6.4)		7.41%	0.28[-0.22,0.78]
Persoon 2017	50	83.1 (19.1)	47	84.1 (15.3)		10.06%	-0.06[-0.46,0.34]
Subtotal ***	**100**		**96**			**22.37%**	**0.16[-0.14,0.46]**
Heterogeneity: Tau²=0.01; Chi²=2.24, df=2(P=0.33); I²=10.53%							
Test for overall effect: Z=1.02(P=0.31)							
1.9.2 Low Risk							
Baumann 2010	32	61.6 (22.7)	32	48.7 (24.7)		7.44%	0.54[0.04,1.04]
Courneya 2009	60	109.3 (18.7)	62	105.4 (22)		11.48%	0.19[-0.17,0.55]
Jacobsen 2014a	180	42.2 (20.8)	175	42.2 (19.4)		18.2%	0[-0.21,0.21]
Jacobsen 2014b	178	40.6 (10.5)	178	41.8 (9.6)		18.21%	-0.12[-0.33,0.09]
Knols 2011	64	83.7 (14.2)	67	80.4 (14)		11.93%	0.23[-0.11,0.58]
Wiskemann 2015	52	73.7 (19.6)	53	63.5 (22.2)		10.37%	0.48[0.09,0.87]
Subtotal ***	**566**		**567**			**77.63%**	**0.16[-0.04,0.36]**
Heterogeneity: Tau²=0.04; Chi²=12.57, df=5(P=0.03); I²=60.22%							
Test for overall effect: Z=1.59(P=0.11)							
Total ***	**666**		**663**			**100%**	**0.16[-0,0.32]**
Heterogeneity: Tau²=0.03; Chi²=14.98, df=8(P=0.06); I²=46.6%							
Test for overall effect: Z=1.9(P=0.06)							
Test for subgroup differences: Chi²=0, df=1 (P=0.98), I²=0%							



Analysis 1.10. Comparison 1 Physical exercise versus no physical exercise, Outcome 10 Depression/QoL.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Chang 2008	11	-1.2 (1.2)	11	-1.5 (1.5)		4.97%	0.15[-0.68,0.99]
Courneya 2009	60	-5.4 (4.5)	62	-6.1 (5)		27.6%	0.15[-0.21,0.5]
Furzer 2016	18	-2.4 (2.2)	19	-3.9 (3.7)		8.13%	0.48[-0.18,1.13]
Jarden 2016	32	-3.3 (3.2)	30	-4.1 (3.9)		13.96%	0.22[-0.28,0.72]



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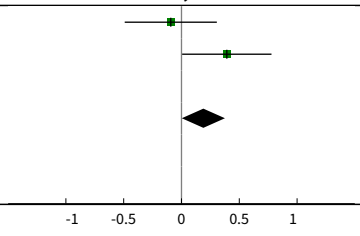
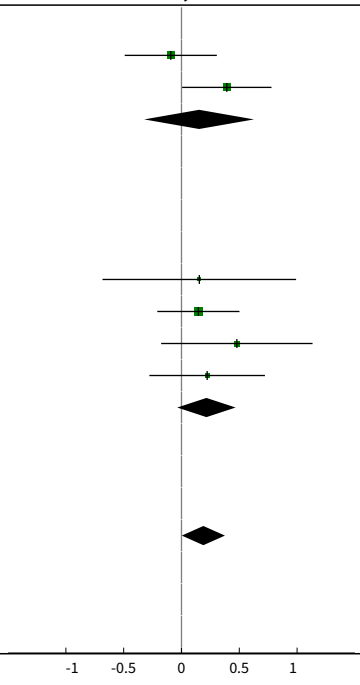
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Persoon 2017	50	-3.2 (3.4)	47	-2.9 (3)		21.97%	-0.09[-0.49,0.31]
Wiskemann 2015	52	-15.6 (1.7)	53	-16.4 (2.3)		23.36%	0.39[0.01,0.78]
Total ***	**223**		**222**			**100%**	**0.19[0,0.38]**
Heterogeneity: Tau²=0; Chi²=3.81, df=5(P=0.58); I²=0%							
Test for overall effect: Z=1.99(P=0.05)							



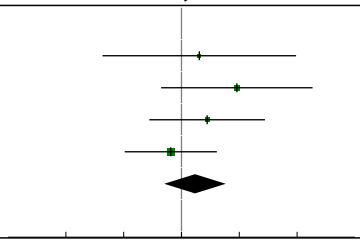
Analysis 1.11. Comparison 1 Physical exercise versus no physical exercise, Outcome 11 Depression/QoL: SCT versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.11.1 SCT							
Persoon 2017	50	-3.2 (3.4)	47	-2.9 (3)		21.97%	-0.09[-0.49,0.31]
Wiskemann 2015	52	-15.6 (1.7)	53	-16.4 (2.3)		23.36%	0.39[0.01,0.78]
Subtotal ***	**102**		**100**			**45.33%**	**0.15[-0.32,0.63]**
Heterogeneity: Tau²=0.08; Chi²=2.93, df=1(P=0.09); I²=65.88%							
Test for overall effect: Z=0.63(P=0.53)							
1.11.2 no SCT							
Chang 2008	11	-1.2 (1.2)	11	-1.5 (1.5)		4.97%	0.15[-0.68,0.99]
Courneya 2009	60	-5.4 (4.5)	62	-6.1 (5)		27.6%	0.15[-0.21,0.5]
Furzer 2016	18	-2.4 (2.2)	19	-3.9 (3.7)		8.13%	0.48[-0.18,1.13]
Jarden 2016	32	-3.3 (3.2)	30	-4.1 (3.9)		13.96%	0.22[-0.28,0.72]
Subtotal ***	**121**		**122**			**54.67%**	**0.22[-0.04,0.47]**
Heterogeneity: Tau²=0; Chi²=0.79, df=3(P=0.85); I²=0%							
Test for overall effect: Z=1.67(P=0.09)							
Total ***	**223**		**222**			**100%**	**0.19[0,0.38]**
Heterogeneity: Tau²=0; Chi²=3.81, df=5(P=0.58); I²=0%							
Test for overall effect: Z=1.99(P=0.05)							
Test for subgroup differences: Chi²=0.05, df=1 (P=0.82), I²=0%							



Analysis 1.12. Comparison 1 Physical exercise versus no physical exercise, Outcome 12 Depression/QoL sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.12.1 High Risk							
Chang 2008	11	-1.2 (1.2)	11	-1.5 (1.5)		4.97%	0.15[-0.68,0.99]
Furzer 2016	18	-2.4 (2.2)	19	-3.9 (3.7)		8.13%	0.48[-0.18,1.13]
Jarden 2016	32	-3.3 (3.2)	30	-4.1 (3.9)		13.96%	0.22[-0.28,0.72]
Persoon 2017	50	-3.2 (3.4)	47	-2.9 (3)		21.97%	-0.09[-0.49,0.31]
Subtotal ***	**111**		**107**			**49.04%**	**0.12[-0.15,0.38]**
Heterogeneity: Tau²=0; Chi²=2.41, df=3(P=0.49); I²=0%							



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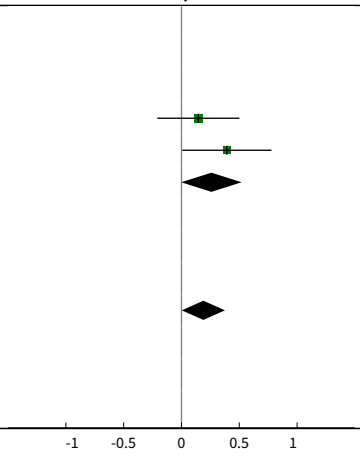
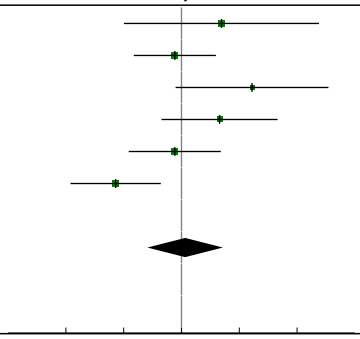
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Test for overall effect: Z=0.86(P=0.39)							
1.12.2 Low Risk							
Courneya 2009	60	-5.4 (4.5)	62	-6.1 (5)		27.6%	0.15[-0.21,0.5]
Wiskemann 2015	52	-15.6 (1.7)	53	-16.4 (2.3)		23.36%	0.39[0.01,0.78]
Subtotal ***	**112**		**115**			**50.96%**	**0.26[-0,0.52]**
Heterogeneity: Tau²=0; Chi²=0.84, df=1(P=0.36); I²=0%							
Test for overall effect: Z=1.94(P=0.05)							
Total ***	**223**		**222**			**100%**	**0.19[0,0.38]**
Heterogeneity: Tau²=0; Chi²=3.81, df=5(P=0.58); I²=0%							
Test for overall effect: Z=1.99(P=0.05)							
Test for subgroup differences: Chi²=0.56, df=1 (P=0.46), I²=0%							



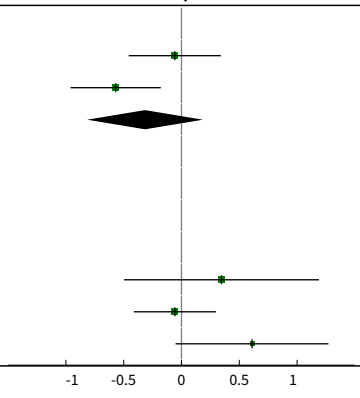
Analysis 1.13. Comparison 1 Physical exercise versus no physical exercise, Outcome 13 Anxiety/QoL.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Chang 2008	11	-1.1 (1.3)	11	-1.7 (1.7)		9.75%	0.35[-0.5,1.19]
Courneya 2009	60	-16.5 (5.2)	62	-16.2 (5.2)		20.92%	-0.06[-0.41,0.3]
Furzer 2016	18	-5 (3.9)	19	-7.4 (3.8)		13%	0.61[-0.05,1.27]
Jarden 2016	32	-3.6 (3.9)	30	-5 (4.5)		16.79%	0.33[-0.17,0.83]
Persoon 2017	50	-4.1 (4.1)	47	-3.9 (2.5)		19.66%	-0.06[-0.46,0.34]
Wiskemann 2015	52	-20.3 (2)	53	-19 (2.5)		19.89%	-0.57[-0.96,-0.18]
Total ***	**223**		**222**			**100%**	**0.03[-0.3,0.36]**
Heterogeneity: Tau²=0.1; Chi²=13.67, df=5(P=0.02); I²=63.42%							
Test for overall effect: Z=0.19(P=0.85)							



Analysis 1.14. Comparison 1 Physical exercise versus no physical exercise, Outcome 14 Anxiety/QoL: SCT versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.14.1 SCT							
Persoon 2017	50	-4.1 (4.1)	47	-3.9 (2.5)		19.66%	-0.06[-0.46,0.34]
Wiskemann 2015	52	-20.3 (2)	53	-19 (2.5)		19.89%	-0.57[-0.96,-0.18]
Subtotal ***	**102**		**100**			**39.55%**	**-0.32[-0.82,0.19]**
Heterogeneity: Tau²=0.09; Chi²=3.23, df=1(P=0.07); I²=69.03%							
Test for overall effect: Z=1.23(P=0.22)							
1.14.2 no SCT							
Chang 2008	11	-1.1 (1.3)	11	-1.7 (1.7)		9.75%	0.35[-0.5,1.19]
Courneya 2009	60	-16.5 (5.2)	62	-16.2 (5.2)		20.92%	-0.06[-0.41,0.3]
Furzer 2016	18	-5 (3.9)	19	-7.4 (3.8)		13%	0.61[-0.05,1.27]



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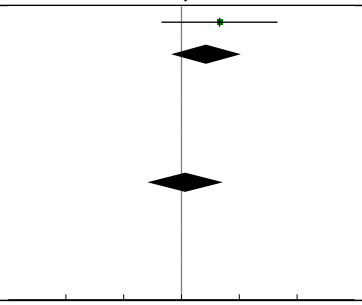
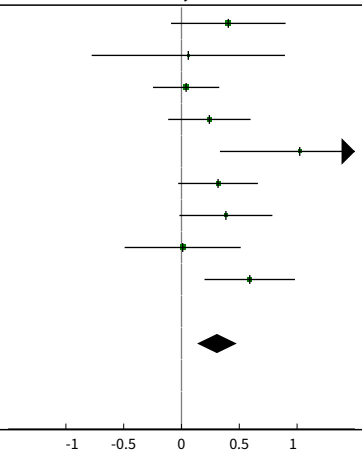
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Jarden 2016	32	-3.6 (3.9)	30	-5 (4.5)		16.79%	0.33[-0.17,0.83]
Subtotal ***	**121**		**122**			**60.45%**	**0.21[-0.09,0.51]**
Heterogeneity: Tau²=0.02; Chi²=3.83, df=3(P=0.28); I²=21.66%							
Test for overall effect: Z=1.37(P=0.17)							
Total ***	**223**		**222**			**100%**	**0.03[-0.3,0.36]**
Heterogeneity: Tau²=0.1; Chi²=13.67, df=5(P=0.02); I²=63.42%							
Test for overall effect: Z=0.19(P=0.85)							
Test for subgroup differences: Chi²=3.11, df=1 (P=0.08), I²=67.88%							



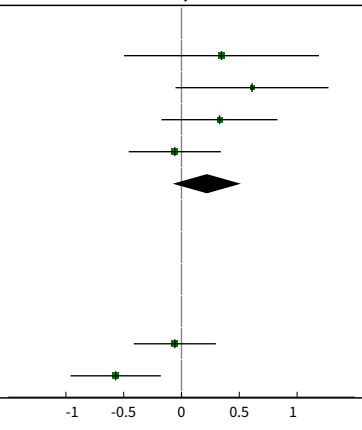
Analysis 1.15. Comparison 1 Physical exercise versus no physical exercise, Outcome 15 Fatigue.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Baumann 2010	32	-51 (23.2)	32	-61.3 (26.9)		9.12%	0.41[-0.09,0.9]
Chang 2008	11	-4.6 (3)	11	-4.8 (3.5)		3.79%	0.06[-0.78,0.89]
Coleman 2012	95	-10.6 (7.2)	92	-10.9 (7.2)		18.41%	0.04[-0.25,0.33]
Courneya 2009	60	40.5 (9.4)	62	38 (11.1)		14.39%	0.24[-0.12,0.6]
Furzer 2016	18	-9.3 (2)	19	-12.5 (3.8)		5.32%	1.02[0.33,1.71]
Knols 2011	64	-31.6 (22.1)	67	-38.3 (20)		14.98%	0.32[-0.03,0.66]
Persoon 2017	50	-10 (4.5)	47	-11.8 (4.8)		12.3%	0.38[-0.02,0.79]
Streckmann 2014	30	-40.8 (27.8)	31	-41.1 (29.5)		8.93%	0.01[-0.49,0.51]
Wiskemann 2015	52	-11 (4.1)	53	-13.5 (4.3)		12.76%	0.59[0.2,0.98]
Total ***	**412**		**414**			**100%**	**0.31[0.13,0.48]**
Heterogeneity: Tau²=0.02; Chi²=11.51, df=8(P=0.17); I²=30.52%							
Test for overall effect: Z=3.5(P=0)							



Analysis 1.16. Comparison 1 Physical exercise versus no physical exercise, Outcome 16 Anxiety/QoL sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.16.1 High Risk							
Chang 2008	11	-1.1 (1.3)	11	-1.7 (1.7)		9.75%	0.35[-0.5,1.19]
Furzer 2016	18	-5 (3.9)	19	-7.4 (3.8)		13%	0.61[-0.05,1.27]
Jarden 2016	32	-3.6 (3.9)	30	-5 (4.5)		16.79%	0.33[-0.17,0.83]
Persoon 2017	50	-4.1 (4.1)	47	-3.9 (2.5)		19.66%	-0.06[-0.46,0.34]
Subtotal ***	**111**		**107**			**59.2%**	**0.22[-0.08,0.51]**
Heterogeneity: Tau²=0.01; Chi²=3.46, df=3(P=0.33); I²=13.28%							
Test for overall effect: Z=1.46(P=0.14)							
1.16.2 Low Risk							
Courneya 2009	60	-16.5 (5.2)	62	-16.2 (5.2)		20.92%	-0.06[-0.41,0.3]
Wiskemann 2015	52	-20.3 (2)	53	-19 (2.5)		19.89%	-0.57[-0.96,-0.18]



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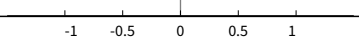
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Subtotal ***	**112**		**115**			**40.8%**	**-0.31[-0.81,0.2]**
Heterogeneity: Tau²=0.09; Chi²=3.62, df=1(P=0.06); I²=72.35%							
Test for overall effect: Z=1.2(P=0.23)							
Total ***	**223**		**222**			**100%**	**0.03[-0.3,0.36]**
Heterogeneity: Tau²=0.1; Chi²=13.67, df=5(P=0.02); I²=63.42%							
Test for overall effect: Z=0.19(P=0.85)							
Test for subgroup differences: Chi²=3.14, df=1 (P=0.08), I²=68.14%							

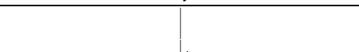


Analysis 1.17. Comparison 1 Physical exercise versus no physical exercise, Outcome 17 Fatigue: SCT versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.17.1 SCT							
Baumann 2010	32	-51 (23.2)	32	-61.3 (26.9)		9.12%	0.41[-0.09,0.9]
Coleman 2012	95	-10.6 (7.2)	92	-10.9 (7.2)		18.41%	0.04[-0.25,0.33]
Knols 2011	64	-31.6 (22.1)	67	-38.3 (20)		14.98%	0.32[-0.03,0.66]
Persoon 2017	50	-10 (4.5)	47	-11.8 (4.8)		12.3%	0.38[-0.02,0.79]
Wiskemann 2015	52	-11 (4.1)	53	-13.5 (4.3)		12.76%	0.59[0.2,0.98]
Subtotal ***	**293**		**291**			**67.57%**	**0.31[0.12,0.51]**
Heterogeneity: Tau²=0.01; Chi²=5.62, df=4(P=0.23); I²=28.84%							
Test for overall effect: Z=3.11(P=0)							
1.17.2 no SCT							
Chang 2008	11	-4.6 (3)	11	-4.8 (3.5)		3.79%	0.06[-0.78,0.89]
Courneya 2009	60	40.5 (9.4)	62	38 (11.1)		14.39%	0.24[-0.12,0.6]
Furzer 2016	18	-9.3 (2)	19	-12.5 (3.8)		5.32%	1.02[0.33,1.71]
Streckmann 2014	30	-40.8 (27.8)	31	-41.1 (29.5)		8.93%	0.01[-0.49,0.51]
Subtotal ***	**119**		**123**			**32.43%**	**0.3[-0.09,0.69]**
Heterogeneity: Tau²=0.08; Chi²=5.87, df=3(P=0.12); I²=48.88%							
Test for overall effect: Z=1.52(P=0.13)							
Total ***	**412**		**414**			**100%**	**0.31[0.13,0.48]**
Heterogeneity: Tau²=0.02; Chi²=11.51, df=8(P=0.17); I²=30.52%							
Test for overall effect: Z=3.5(P=0)							
Test for subgroup differences: Chi²=0, df=1 (P=0.97), I²=0%							

Analysis 1.18. Comparison 1 Physical exercise versus no physical exercise, Outcome 18 Fatigue sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.18.1 High Risk							
Chang 2008	11	-4.6 (3)	11	-4.8 (3.5)		3.79%	0.06[-0.78,0.89]
Coleman 2012	95	-10.6 (7.2)	92	-10.9 (7.2)		18.41%	0.04[-0.25,0.33]



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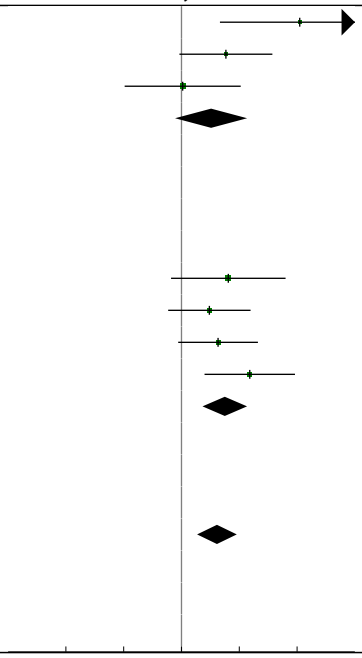
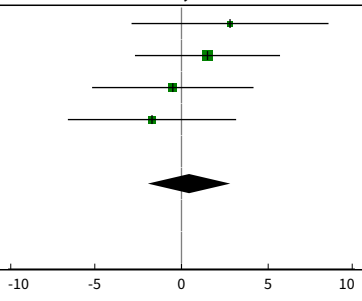
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Furzer 2016	18	-9.3 (2)	19	-12.5 (3.8)		5.32%	1.02[0.33,1.71]
Persoon 2017	50	-10 (4.5)	47	-11.8 (4.8)		12.3%	0.38[-0.02,0.79]
Streckmann 2014	30	-40.8 (27.8)	31	-41.1 (29.5)		8.93%	0.01[-0.49,0.51]
Subtotal ***	**204**		**200**			**48.75%**	**0.26[-0.06,0.57]**
Heterogeneity: Tau²=0.06; Chi²=8.12, df=4(P=0.09); I²=50.73%							
Test for overall effect: Z=1.61(P=0.11)							
1.18.2 Low Risk							
Baumann 2010	32	-51 (23.2)	32	-61.3 (26.9)		9.12%	0.41[-0.09,0.9]
Courneya 2009	60	40.5 (9.4)	62	38 (11.1)		14.39%	0.24[-0.12,0.6]
Knols 2011	64	-31.6 (22.1)	67	-38.3 (20)		14.98%	0.32[-0.03,0.66]
Wiskemann 2015	52	-11 (4.1)	53	-13.5 (4.3)		12.76%	0.59[0.2,0.98]
Subtotal ***	**208**		**214**			**51.25%**	**0.37[0.18,0.57]**
Heterogeneity: Tau²=0; Chi²=1.83, df=3(P=0.61); I²=0%							
Test for overall effect: Z=3.81(P=0)							
Total ***	**412**		**414**			**100%**	**0.31[0.13,0.48]**
Heterogeneity: Tau²=0.02; Chi²=11.51, df=8(P=0.17); I²=30.52%							
Test for overall effect: Z=3.5(P=0)							
Test for subgroup differences: Chi²=0.4, df=1 (P=0.53), I²=0%							



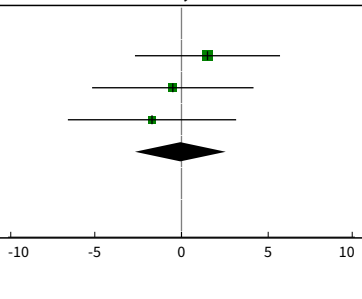
Analysis 1.19. Comparison 1 Physical exercise versus no physical exercise, Outcome 19 Weight.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Courneya 2009	60	81.5 (16)	62	78.7 (16)		17.54%	2.8[-2.88,8.48]
Jacobsen 2014a	180	84 (20.8)	175	82.5 (19.4)		32.33%	1.5[-2.68,5.68]
Jacobsen 2014b	178	87.4 (22.1)	178	87.9 (22.7)		26.11%	-0.5[-5.15,4.15]
Knols 2011	64	70.8 (14.5)	67	72.5 (13.8)		24.03%	-1.7[-6.55,3.15]
Total ***	**482**		**482**			**100%**	**0.44[-1.94,2.82]**
Heterogeneity: Tau²=0; Chi²=1.81, df=3(P=0.61); I²=0%							
Test for overall effect: Z=0.36(P=0.72)							



Analysis 1.20. Comparison 1 Physical exercise versus no physical exercise, Outcome 20 Weight SCT: versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.20.1 SCT							
Jacobsen 2014a	180	84 (20.8)	175	82.5 (19.4)		32.33%	1.5[-2.68,5.68]
Jacobsen 2014b	178	87.4 (22.1)	178	87.9 (22.7)		26.11%	-0.5[-5.15,4.15]
Knols 2011	64	70.8 (14.5)	67	72.5 (13.8)		24.03%	-1.7[-6.55,3.15]
Subtotal ***	**422**		**420**			**82.46%**	**-0.07[-2.68,2.55]**
Heterogeneity: Tau²=0; Chi²=1.01, df=2(P=0.6); I²=0%							
Test for overall effect: Z=0.05(P=0.96)							



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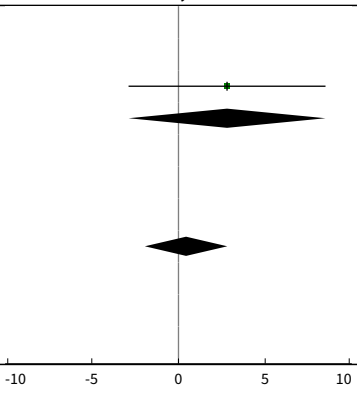
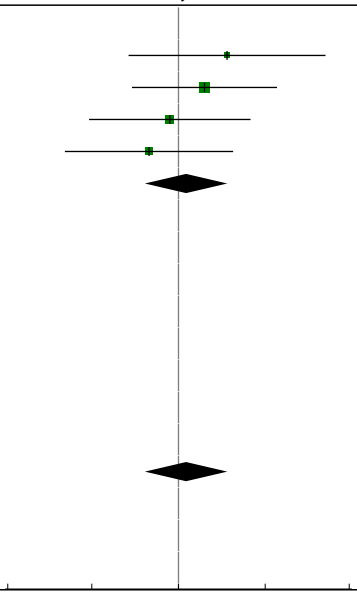
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.20.2 no SCT							
Courneya 2009	60	81.5 (16)	62	78.7 (16)		17.54%	2.8[-2.88,8.48]
Subtotal ***	**60**		**62**			**17.54%**	**2.8[-2.88,8.48]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.97(P=0.33)							
Total ***	**482**		**482**			**100%**	**0.44[-1.94,2.82]**
Heterogeneity: Tau²=0; Chi²=1.81, df=3(P=0.61); I²=0%							
Test for overall effect: Z=0.36(P=0.72)							
Test for subgroup differences: Chi²=0.81, df=1 (P=0.37), I²=0%							



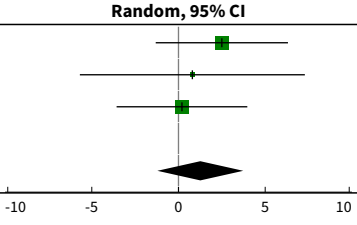
Analysis 1.21. Comparison 1 Physical exercise versus no physical exercise, Outcome 21 Weight sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no physical exercise N	no physical exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.21.1 Low Risk							
Courneya 2009	60	81.5 (16)	62	78.7 (16)		17.54%	2.8[-2.88,8.48]
Jacobsen 2014a	180	84 (20.8)	175	82.5 (19.4)		32.33%	1.5[-2.68,5.68]
Jacobsen 2014b	178	87.4 (22.1)	178	87.9 (22.7)		26.11%	-0.5[-5.15,4.15]
Knols 2011	64	70.8 (14.5)	67	72.5 (13.8)		24.03%	-1.7[-6.55,3.15]
Subtotal ***	**482**		**482**			**100%**	**0.44[-1.94,2.82]**
Heterogeneity: Tau²=0; Chi²=1.81, df=3(P=0.61); I²=0%							
Test for overall effect: Z=0.36(P=0.72)							
1.21.2 High Risk							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**482**		**482**			**100%**	**0.44[-1.94,2.82]**
Heterogeneity: Tau²=0; Chi²=1.81, df=3(P=0.61); I²=0%							
Test for overall effect: Z=0.36(P=0.72)							
Test for subgroup differences: Not applicable							



Analysis 1.22. Comparison 1 Physical exercise versus no physical exercise, Outcome 22 Lean body mass.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Courneya 2009	60	52.3 (11.5)	62	49.8 (9.9)		42.21%	2.5[-1.31,6.31]
Furzer 2016	19	49.3 (10.9)	18	48.5 (9.2)		14.58%	0.8[-5.69,7.29]
Knols 2011	64	52.2 (11.1)	67	52 (10.9)		43.2%	0.2[-3.57,3.97]
Total ***	**143**		**147**			**100%**	**1.26[-1.22,3.74]**



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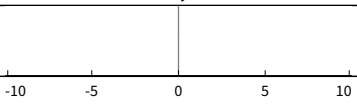
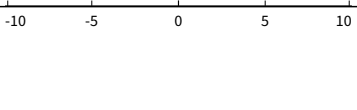
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.73, df=2(P=0.69); I²=0%							
Test for overall effect: Z=1(P=0.32)							



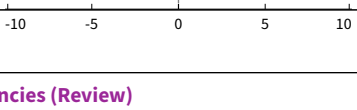
Analysis 1.23. Comparison 1 Physical exercise versus no physical exercise, Outcome 23 Lean body mass: SCT versus no SCT.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.23.1 SCT							
Knols 2011	64	52.2 (11.1)	67	52 (10.9)		43.2%	0.2[-3.57,3.97]
Subtotal ***	**64**		**67**			**43.2%**	**0.2[-3.57,3.97]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.1(P=0.92)							
1.23.2 no SCT							
Courneya 2009	60	52.3 (11.5)	62	49.8 (9.9)		42.21%	2.5[-1.31,6.31]
Furzer 2016	19	49.3 (10.9)	18	48.5 (9.2)		14.58%	0.8[-5.69,7.29]
Subtotal ***	**79**		**80**			**56.8%**	**2.06[-1.22,5.35]**
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.66); I²=0%							
Test for overall effect: Z=1.23(P=0.22)							
Total ***	**143**		**147**			**100%**	**1.26[-1.22,3.74]**
Heterogeneity: Tau²=0; Chi²=0.73, df=2(P=0.69); I²=0%							
Test for overall effect: Z=1(P=0.32)							
Test for subgroup differences: Chi²=0.53, df=1 (P=0.47), I²=0%							



Analysis 1.24. Comparison 1 Physical exercise versus no physical exercise, Outcome 24 Lean body mass sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.24.1 High Risk							
Furzer 2016	19	49.3 (10.9)	18	48.5 (9.2)		14.58%	0.8[-5.69,7.29]
Subtotal ***	**19**		**18**			**14.58%**	**0.8[-5.69,7.29]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.24(P=0.81)							
1.24.2 Low Risk							
Courneya 2009	60	52.3 (11.5)	62	49.8 (9.9)		42.21%	2.5[-1.31,6.31]
Knols 2011	64	52.2 (11.1)	67	52 (10.9)		43.2%	0.2[-3.57,3.97]
Subtotal ***	**124**		**129**			**85.42%**	**1.34[-1.34,4.02]**
Heterogeneity: Tau²=0; Chi²=0.71, df=1(P=0.4); I²=0%							
Test for overall effect: Z=0.98(P=0.33)							
Total ***	**143**		**147**			**100%**	**1.26[-1.22,3.74]**



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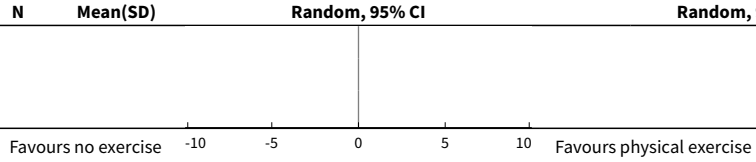
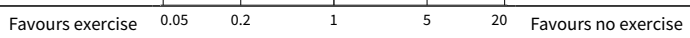
Study or subgroup	physical exercise N	physical exercise Mean(SD)	no exercise N	no exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.73, df=2(P=0.69); I²=0%							
Test for overall effect: Z=1(P=0.32)							
Test for subgroup differences: Chi²=0.02, df=1 (P=0.88), I²=0%							



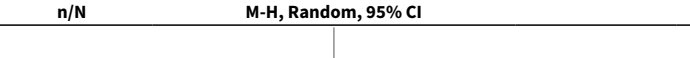
Analysis 1.25. Comparison 1 Physical exercise versus no physical exercise, Outcome 25 Serious adverse events (SAEs).

Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alibhai 2014	0/20	0/17			Not estimable
Chang 2008	1/12	1/12		2.2%	1[0.07,14.21]
Coleman 2012	30/58	22/62		88.99%	1.46[0.96,2.21]
Courneya 2009	0/60	0/62			Not estimable
Furzer 2016	0/18	0/17			Not estimable
Persoon 2017	4/50	4/47		8.81%	0.94[0.25,3.55]
Total (95% CI)	**218**	**217**		**100%**	**1.39[0.94,2.06]**
Total events: 35 (physical exercise), 27 (no exercise)					
Heterogeneity: Tau²=0; Chi²=0.46, df=2(P=0.8); I²=0%					
Test for overall effect: Z=1.64(P=0.1)					



Analysis 1.26. Comparison 1 Physical exercise versus no physical exercise, Outcome 26 Serious adverse events (SAEs): SCT versus no SCT.

Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.26.1 SCT					
Alibhai 2014	0/20	0/17			Not estimable
Coleman 2012	30/58	22/62		88.99%	1.46[0.96,2.21]
Persoon 2017	4/50	4/47		8.81%	0.94[0.25,3.55]
Subtotal (95% CI)	**128**	**126**		**97.8%**	**1.4[0.94,2.09]**
Total events: 34 (physical exercise), 26 (no exercise)					
Heterogeneity: Tau²=0; Chi²=0.39, df=1(P=0.53); I²=0%					
Test for overall effect: Z=1.66(P=0.1)					
1.26.2 no SCT					
Chang 2008	1/12	1/12		2.2%	1[0.07,14.21]
Courneya 2009	0/60	0/62			Not estimable
Furzer 2016	0/18	0/17			Not estimable
Subtotal (95% CI)	**90**	**91**		**2.2%**	**1[0.07,14.21]**
Total events: 1 (physical exercise), 1 (no exercise)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



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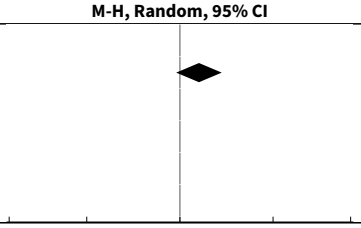
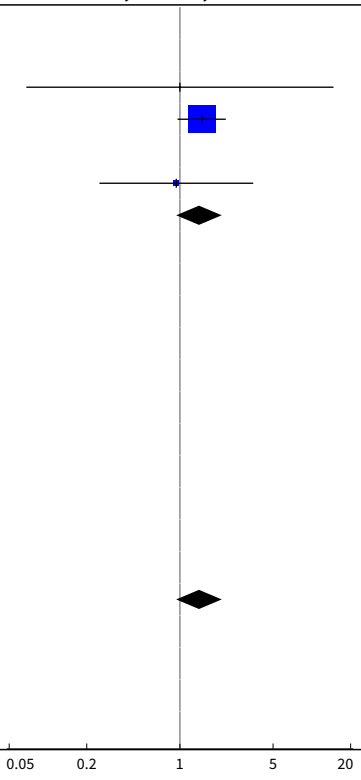
Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**218**	**217**		**100%**	**1.39[0.94,2.06]**
Total events: 35 (physical exercise), 27 (no exercise)					
Heterogeneity: Tau²=0; Chi²=0.46, df=2(P=0.8); I²=0%					
Test for overall effect: Z=1.64(P=0.1)					
Test for subgroup differences: Chi²=0.06, df=1 (P=0.81), I²=0%					



Analysis 1.27. Comparison 1 Physical exercise versus no physical exercise, Outcome 27 Serious adverse events (SAEs) sensitivity analysis: high risk of bias versus low risk of bias.

Study or subgroup	physical exercise n/N	no exercise n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 High Risk					
Alibhai 2014	0/20	0/17			Not estimable
Chang 2008	1/12	1/12		2.2%	1[0.07,14.21]
Coleman 2012	30/58	22/62		88.99%	1.46[0.96,2.21]
Furzer 2016	0/18	0/17			Not estimable
Persoon 2017	4/50	4/47		8.81%	0.94[0.25,3.55]
Subtotal (95% CI)	**158**	**155**		**100%**	**1.39[0.94,2.06]**
Total events: 35 (physical exercise), 27 (no exercise)					
Heterogeneity: Tau²=0; Chi²=0.46, df=2(P=0.8); I²=0%					
Test for overall effect: Z=1.64(P=0.1)					
1.27.2 Low Risk					
Courneya 2009	0/60	0/62			Not estimable
Subtotal (95% CI)	**60**	**62**			**Not estimable**
Total events: 0 (physical exercise), 0 (no exercise)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**218**	**217**		**100%**	**1.39[0.94,2.06]**
Total events: 35 (physical exercise), 27 (no exercise)					
Heterogeneity: Tau²=0; Chi²=0.46, df=2(P=0.8); I²=0%					
Test for overall effect: Z=1.64(P=0.1)					
Test for subgroup differences: Not applicable					



APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor Exercise Movement Techniques explode all trees

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(Continued)

#2	MeSH descriptor Exercise explode all trees
#3	MeSH descriptor Exercise Therapy explode all trees
#4	MeSH descriptor Physical Education and Training explode all trees
#5	MeSH descriptor Physical Fitness explode all trees
#6	MeSH descriptor Physical Exertion explode all trees
#7	MeSH descriptor Physical Endurance explode all trees
#8	physical therap* modalit*
#9	physiotherap*
#10	(human NEAR/1 physical NEAR/1 conditioning*)
#11	(training NEAR/1 program*)
#12	(muscular* NEAR/ fitness*)
#13	exertion*
#14	(physical NEAR/1 (activit* or behaviour* or behavior* or conditioning* or education* or exercis* or habit* or intervention* or program* or recreation* or stud* or train* or effort* or exertion* or fitness*))
#15	(physical NEAR/1 (activit* or behaviour* or behavior* or conditioning* or education* or exercis* or habit* or intervention* or program* or recreation* or stud* or train* or effort* or exertion* or fitness*))
#16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17	MeSH descriptor Gymnastics explode all trees
#18	gymnastic*
#19	(calisthenic* or callisthenic*)
#20	pilates*
#21	(resistanc* NEAR/2 (training* or exercise*))
#22	(muscular* NEAR/ fitness*)
#23	(physical* NEAR/ (activit* or fitness* or exercise*))
#24	(physical* NEAR/ (condition* or effort4 or train*))
#25	MeSH descriptor Tai Ji explode all trees
#26	MeSH descriptor Yoga explode all trees
#27	(tai chi or tai ji or ji quan tai)

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(Continued)

#28	yoga*
#29	(aerobic* NEAR/ train*)
#30	stretching*
#31	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
#32	MeSH descriptor Sports explode all trees
#33	MeSH descriptor Running explode all trees
#34	MeSH descriptor Walking explode all trees
#35	MeSH descriptor Walking explode all trees
#36	MeSH descriptor Swimming explode all trees
#37	MeSH descriptor Bicycling explode all trees
#38	MeSH descriptor Dancing explode all trees
#39	MeSH descriptor Mountaineering explode all trees
#40	sport*
#41	athletic*
#42	running*
#43	running*
#44	ambulation*
#45	jogging*
#46	swimming*
#47	bicycling*
#48	cycling*
#49	mountaineer*
#50	danc*
#51	(ramble* or rambling*)
#52	rowing*
#53	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52
#54	(#16 OR #31 OR #53)
#55	MeSH descriptor Hematologic Diseases explode all trees

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(Continued)

#56	MeSH descriptor Hematologic Neoplasms explode all trees
#57	(hematolog* NEAR/1 malignan*)
#58	(hematolog* NEAR/1 neoplas*)
#59	(haematolog* NEAR/1 malignan*)
#60	(haematolog* NEAR/1 neoplas*)
#61	MeSH descriptor Bone Marrow Diseases explode all trees
#62	MeSH descriptor Lymphoma explode all trees
#63	MeSH descriptor Leukemia explode all trees
#64	MeSH descriptor Leukemia explode all trees
#65	hodgkin*
#66	lymphogranulomato*
#67	lymphom*
#68	histiocy*
#69	granulom*
#70	non-hodgkin*
#71	nonhodgkin*
#72	reticulosis
#73	reticulosarcom*
#74	(burkitt* NEAR/ (lymph* or tumor* or tumour*))
#75	lymphosarcom*
#76	brill-symmer*
#77	plasm**ytom*
#78	myeloma*
#79	sezary
#80	(leukem* or leukaem*)
#81	myelodysplas*
#82	(aplast* NEAR/ (anem* or anaem*))

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(Continued)

#83	(#55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82)
#84	(#54 AND #83)

Update search: Cochrane Central Register of Controlled Trials 30.07.2018

ID Search

#1 MeSH descriptor: [Exercise Movement Techniques] explode all trees

#2 MeSH descriptor: [Exercise] explode all trees

#3 MeSH descriptor: [Exercise Therapy] explode all trees

#4 MeSH descriptor: [Physical Education and Training] explode all trees

#5 MeSH descriptor: [Physical Fitness] explode all trees

#6 (muscular* near/1 fitness*)

#7 exertion*

#8 MeSH descriptor: [Gymnastics] explode all trees

#9 gymnastic*

#10 (calisthenic* or callisthenic*)

#11 pilates*

#12 (resistanc* near/2 (training* or exercise*))

#13 (muscular* near/1 fitness*)

#14 (physical* near/1 (activit* or fitness* or exercise*))

#15 (physical* near/2 (condition* or effort* or train*))

#16 ((aerobic* or isometric*) near/2 exercise*)

#17 MeSH descriptor: [Sports] explode all trees

#18 sport*

#19 MeSH descriptor: [Walking] explode all trees

#20 walking*

#21 MeSH descriptor: [Jogging] explode all trees

#22 jogging*

#23 MeSH descriptor: [Swimming] explode all trees

#24 swimming*

#25 MeSH descriptor: [Bicycling] explode all trees

#26 bicycling* or cycling*

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#27 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26

#28 MeSH descriptor: [Neoplasms by Histologic Type] explode all trees

#29 MeSH descriptor: [Neoplasms by Site] explode all trees

#30 neoplas*

#31 tumor* or tumour*

#32 Krebs or cancer*

#33 malignan*

#34 (carcino* or karzino*)

#35 karzinom*

#36 sarcom*

#37 leukaem* or leukem* or leucem*

#38 lymphom*

#39 melano*

#40 metastas*

#41 mesothelio* or mesotelio*

#42 carcinomatos*

#43 (gliom* or glioblastom*)

#44 osteo*sarcom*

#45 (blastom* or neuroblastom*)

#46 #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45

#47 #27 and #46 in Trials

#48 #47 Publication Year from 2014 to 2017

Appendix 2. MEDLINE search strategy

1	exp EXERCISE MOVEMENT TECHNIQUES/
2	exp EXERCISE/
3	EXERCISE THERAPY/
4	exp "PHYSICAL EDUCATION AND TRAINING"/
5	PHYSICAL FITNESS/
6	PHYSICAL EXERTION/
7	exp PHYSICAL ENDURANCE/
8	physical therap$ modalit$.tw,kf,ot.

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(Continued)

9	physiotherap$.tw,kf,ot.
10	(human adj1 physical adj1 conditioning$).tw,kf,ot.
11	(training adj1 program$).tw,kf,ot.
12	(muscular$ adj fitness$).tw,kf,ot.
13	exertion$.tw,kf,ot.
14	(physical adj1 (activit$ or behaviour$ or behavior$ or conditioning$ or education$ or exercis$ or habit$ or intervention$ or program$ or recreation$ or stud$ or train$ or effort$ or exertion$ or fitness$)).tw,kf,ot.
15	((activit$ behaviour$ or behavior$ or education$ or intervention$ or lifestyle$ or program$ or recreation$ or stud$ or therap$ or train$ or aerobic$ or isometric$ or physical$ or warm-up$ or habit$) adj2 exercise$).tw,kf,ot.
16	or/1-15
17	GYMNASTICS/
18	gymnastic$.tw,kf,ot.
19	(calisthenic$ or callisthenic$).tw,kf,ot.
20	pilates$.tw,kf,ot.
21	(resistanc$ adj2 (training$ or exercise$)).tw,kf,ot.
22	(muscular$ adj fitness$).tw,kf,ot.
23	(physical$ adj (activit$ or fitness$ or exercise$)).tw,kf,ot.
24	(physical$ adj (condition$ or effort4 or train$)).tw,kf,ot.
25	TAI JI/
26	YOGA/
27	(tai chi or tai ji or ji quan tai).tw,kf,ot.
28	yoga.tw,kf,ot.
29	(aerobic$ adj train$).tw,kf,ot.
30	stretching$.tw,kf,ot.
31	or/17-30
32	exp SPORTS/
33	RUNNING/
34	exp WALKING/

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(Continued)

35	JOGGING/
36	SWIMMING/
37	BICYCLING/
38	DANCING/
39	MOUNTAINEERING/
40	sport$.tw,kf,ot.
41	athletic$.tw,kf,ot.
42	running$.tw,kf,ot.
43	walking$.tw,kf,ot.
44	ambulation$.tw,kf,ot.
45	jogging$.tw,kf,ot.
46	swimming$.tw,kf,ot.
47	bicycling$.tw,kf,ot.
48	cycling$.tw,kf,ot.
49	mountaineer$.tw,kf,ot.
50	danc$.tw,kf,ot.
51	(ramble$ or rambling$).tw,kf,ot.
52	rowing$.tw,kf,ot.
53	or/32-52
54	16 or 31 or 53
55	HEMATOLOGIC DISEASES/
56	exp HEMATOLOGIC NEOPLASMS/
57	(hematolog$ adj1 malignan$).tw,kf,ot.
58	(hematolog$ adj1 neoplas$).tw,kf,ot.
59	(haematolog$ adj1 malignan$).tw,kf,ot.
60	(haematolog$ adj1 neoplas$).tw,kf,ot.
61	exp BONE MARROW DISEASES/
62	exp LYMPHOMA/

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(Continued)

63	exp LEUKEMIA/
64	hodgkin$.tw,kf,ot.
65	lymphogranulomato$.tw,kf,ot.
66	lymphom$.tw,kf,ot.
67	histiocy$.tw,kf,ot.
68	granulom$.tw,kf,ot.
69	non-hodgkin$.tw,kf,ot.
70	nonhodgkin$.tw,kf,ot.
71	reticulosis.tw,kf,ot.
72	reticulosarcom$.tw,kf,ot.
73	(burkitt$ adj (lymph$ or tumo?r$)).tw,kf,ot.
74	lymphosarcom$.tw,kf,ot.
75	brill-symmer$.tw,kf,ot.
76	plasm##ytom$.tw,kf,ot.
77	myeloma$.tw,kf,ot.
78	sezary.tw,kf,ot.
79	leuk?em$.tw,kf,ot.
80	myelodysplas$.tw,kf,ot.
81	aplast$ an?em$.ti,kf,ot.
82	or/55-81
83	randomized controlled trial.pt.
84	controlled clinical trial.pt.
85	randomized.ab.
86	placebo.ab.
87	drug therapy.fs.
88	randomly.ab.
89	trial.ab.
90	groups.ab.

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(Continued)

91	or/83-90
92	humans.sh.
93	91 and 92
94	54 and 82
95	54 and 82 and 93

Update search: 30.07.2018

#	Searches
1	exp Exercise/
2	exp Exercise Movement Techniques/
3	exp Exercise Therapy/
4	exp "Physical Education and Training"/
5	exp Physical Fitness/
6	exp Sports/
7	sport$.tw,kf,ot.
8	exp Walking/
9	walking$.tw,kf,ot.
10	exp jogging/
11	jogging$.tw,kf,ot.
12	exp swimming/
13	swimming$.tw,kf,ot.
14	exp Bicycling/
15	(bicycling$ or cycling$).tw,kf,ot.
16	exp Gymnastics/
17	gymnastic$.tw,kf,ot.
18	(calisthenic$ or callisthenic$).tw,kf,ot.
19	(resistan$ adj2 (training$ or exercise$)).tw,kf,ot.

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(Continued)

20	(pilates$ adj5 exercise$).tw,kf,ot.
21	(resistanc$ adj2 (training$ or exercise$)).tw,kf,ot.
22	((aerobic$ or isometric$) adj2 exercise$).tw,kf,ot.
23	(muscular$ adj fitness$).tw,kf,ot.
24	exertion$.tw,kf,ot.
25	pilates$.tw,kf,ot.
26	(physical$ adj (activit$ or fitness$ or exercise$)).tw,kf,ot.
27	(physical$ adj (conditioning$ or effort$)).tw,kf,ot.
28	or/1-27
29	exp NEOPLASMS BY HISTOLOGIC TYPE/
30	exp NEOPLASMS BY SITE/
31	neoplas$.tw,kf,ot.
32	tumo?r$.tw,kf,ot.
33	(Krebs or cancer$).tw,kf,ot.
34	malignan$.tw,kf,ot.
35	(carcino$ or karzino$).tw,kf,ot.
36	karzinom$.tw,kf,ot.
37	sarcom$.tw,kf,ot.
38	leuk#?m$.tw,kf,ot.
39	lymphom$.tw,kf,ot.
40	melano$.tw,kf,ot.
41	metastas$.tw,kf,ot.
42	(mesothelio$ or mesotelio$).tw,kf,ot.
43	carcinomatos$.tw,kf,ot.
44	(gliom$ or glioblastom$).tw,kf,ot.
45	osteo?sarcom$.tw,kf,ot.
46	(blastom$ or neuroblastom$).tw,kf,ot.
47	or/29-46

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(Continued)

48	randomized controlled trial.pt.
49	controlled clinical trial.pt.
50	randomi?ed.ab.
51	placebo.ab.
52	drug therapy.fs.
53	randomly.ab.
54	trial.ab.
55	groups.ab.
56	or/48-55
57	exp animals/ not humans/
58	56 not 57
59	28 and 47 and 58
60	limit 59 to ed=20140129-20172008

WHAT'S NEW

Date	Event	Description
3 December 2018	New citation required but conclusions have not changed	New citation, nine new trials included to the nine trials of the first version, three new ongoing studies added and one study awaiting assessment
3 December 2018	New search has been performed	Updated, update search 01.07.2018

CONTRIBUTIONS OF AUTHORS

- Linus Knips: development and writing of updated review
- Nils Bergenthal: development and writing of review
- Fiona Streckmann: content input, provided unpublished data
- Ina Monsef: development of the search strategy
- Thomas Elter: clinical expertise and content input
- Nicole Skoetz: clinical, statistical and methodological expertise and advice

DECLARATIONS OF INTEREST

- Linus Knips: none known
- Nils Bergenthal: none known
- Fiona Streckmann: none known
- Ina Monsef: none known
- Thomas Elter: none known

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- Nicole Skoetz: none known

SOURCES OF SUPPORT

Internal sources

- Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title and added "aerobic" to reflect that we only included trials that evaluated physical exercise intended to improve the oxygen system.

As our primary outcome overall survival was reported in one trial only, we also analysed mortality.

In meta-analyses with at least 10 trials, we would have explored potential publication bias by generating a funnel plot and by using a linear regression test (Sterne 2011). We would have considered a P value of less than 0.1 significant for this test.

NOTES

Some parts of the methods are taken from the Cochrane Haematological Malignancies template.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise; Exercise Tolerance; Feasibility Studies; Hematologic Neoplasms [complications] [mortality] [*rehabilitation]; Physical Conditioning, Human; Qigong; Quality of Life; Randomized Controlled Trials as Topic; Resistance Training; Tai Ji; Yoga

MeSH check words

Adult; Female; Humans; Male

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