TITLE: Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis of randomized trials

AUTHORS: ¹Sapna Oberoi MD, DM, ¹Paula D. Robinson MD, MSc, ²Danielle Cataudella ³Nicole Culos-Reid PhD, ⁴Hailey Davis, ⁴Nathan Duong, ⁵Faith Gibson RN, PhD, ⁶Miriam Götte, PhD, ⁷Pamela Hinds RN, PhD, FAAN, ⁸Sanne L Nijhof MD, PHD, ⁴Deborah Tomlinson RN, ⁸Patrick van der Torre MSc, ¹Sandra Cabral, ^{4,9}L Lee Dupuis MScPhm, PhD and ^{4,10}Lillian Sung MD, PhD

AFFILIATIONS:

¹Pediatric Oncology Group of Ontario, Toronto, ON

²Department of Pediatric Psychology, Children's Hospital, London Health Sciences Centre, London, ON

³Faculty of Kinesiology, University of Calgary, Calgary, AB

⁴Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON

⁵Centre for Outcomes and Experiences Research in Children's Health, Illness, and Disability, Great Ormond Street Hospital for Children NHS Foundation Trust, London, and School of Health Sciences, University of Surrey, Guildford, UK

⁶University Hospital Essen, Center for Child and Adolescent Medicine, Department of Pediatric Hematology/Oncology, Essen, Germany

⁷Department of Nursing Science, Professional Practice, and Quality, Children's National Health System, Washington, District of Columbia, USA; Department of Pediatrics, George Washington University, Washington, District of Columbia, USA.

⁸Division of Pediatrics, Wilhelmina Children's Hospital (part of UMC Utrecht), Utrecht, Netherlands

⁹Department of Pharmacy, The Hospital for Sick Children, Toronto, ON

¹⁰Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON

Corresponding Author:

Lillian Sung, MD, PhD

Division of Haematology/Oncology

The Hospital for Sick Children

555 University Avenue, Toronto, Ontario

M5G1X8

Telephone: 416-813-5287

Fax: 416-813-5979

Email: lillian.sung@sickkids.ca

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ABSTRACT

Purpose: Objective was to determine whether physical activity reduces the severity of fatigue in patients with cancer or hematopoietic stem cell transplant (HSCT) recipients.

Methods: We conducted a meta-analysis of randomized trials comparing physical activity with control interventions for the management of fatigue in patients with cancer or HSCT recipients. .

Results: There were 170 trials included. Physical activity reduced the severity of fatigue when compared to all control groups (standardized mean difference -0.49, 95% confidence interval -0.60 to -0.37; $P < 0.00001$). Aerobic, neuromotor, resistance and combination exercises were all effective in reducing fatigue although smaller effects were observed with resistance exercises (P interaction=0.01). Other intervention and patient characteristics did not influence the effect of physical activity on the severity of fatigue.

Conclusions: Physical activity was effective at reducing fatigue in patients with cancer and HSCT recipients across patient sub-groups. Determining the best approaches for safe implementation should be a priority.

INTRODUCTION

Cancer-related fatigue (CRF) can be defined as a “distressing, persistent, subjective sense of physical, emotional or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”. [1] CRF affects up to 80-90% of adult cancer patients, and can occur prior to diagnosis, during cancer treatment and following the completion of cancer therapies. [2-6] Although the prevalence of CRF is less certain among children with cancer, 50 to 76% of children will experience fatigue. [7-9]

The etiology of CRF is multifactorial and fatigue may result from cancer itself, treatments such as chemotherapy, radiotherapy or surgery, and comorbid medical and psychological conditions. [1, 10] Recipients of hematopoietic stem cell transplantation (HSCT) also experience fatigue, likely related to similar underlying mechanisms. [11, 12] Fatigue adversely affects the physical, mental and social health of patients with cancer, and consequently reduces quality of life. [3, 6, 13] It not only limits the ability to perform daily routines but also affects the desire to continue treatment, participate in social activities, perform cognitive tasks, and retain employment status. [5, 6, 14]

A number of approaches have been investigated for the management of fatigue in cancer patients including physical activity. [1, 15, 16] Physical activity may be effective at reducing fatigue by decreasing inflammation, increasing muscle strength or mass and improving functional capacity and mental health. [17, 18] There are several systematic reviews, which have focused on the effect of physical activity on fatigue. [16, 19-25] However, none has included all randomized trials of physical activity, and thus, they had limited power to identify which patients may benefit from physical activity and which interventions may be more effective. Such analyses are important in order to create recommendations on how physical activity should be used in clinical practice for the management of fatigue.

Consequently, our primary objective was to determine whether physical activity reduces the severity of fatigue in adults and children with cancer or HSCT recipients as compared to control interventions. Our secondary objective was to determine whether the effect of physical activity on fatigue varied by patient, intervention or methodological factors.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for this systematic review. We searched for eligible trials indexed from 1980 to May 11, 2017 in the following electronic databases: MEDLINE, MEDLINE in-process, Embase, Cochrane Central Register of Controlled Trials, CINAHL, and PsychINFO. The search strategy included a combination of Medical Subject Heading terms and text words to identify adults and children with cancer or HSCT recipients who received an intervention to reduce fatigue. The search strategy is available as Appendix 1.

Study Selection and Data Abstraction

We defined inclusion and exclusion criteria *a priori*. Studies were included if participants were adults or children with cancer or HSCT recipients, and if the study was a fully published primary randomized or quasi-randomized trial with a parallel group design. Studies had to evaluate an intervention for the management of fatigue. Studies were excluded if they: (1) were not randomized or quasi-randomized with a parallel group design; (2) were not a full-text publication; (3) included fewer than 75% of patients with cancer or undergoing HSCT; (4) did not include fatigue as an end point; or (5) were a duplicate publication. Included studies were not restricted by language or publication

status. For the purpose of this analysis, we then limited studies to those which evaluated a physical activity intervention.

Three reviewers (SO, PDR or LS) independently evaluated the titles and abstracts of publications identified by the search. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this meta-analysis was determined by agreement of both reviewers.

Discrepancies between the two reviewers were resolved by consensus and adjudication by a third reviewer if required (LLD or LS). The Kappa statistic was used to evaluate agreement in study inclusion between the two reviewers. Strength of agreement was defined as slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00).[26]

Data were abstracted in duplicate by two reviewers (SO and PDR) and any discrepancies were resolved by consensus and adjudication by a third reviewer if required (LS). We contacted authors in the event of missing primary outcome data.

Outcomes

The primary outcome was the severity of self-report fatigue across different fatigue scales at the end of the intervention. For studies that used more than one fatigue scale, we *a priori* defined a hierarchy of which scale to use in the primary analysis. We ordered the scales according to prevalence in this systematic review (Appendix 2), and chose the most commonly used scale. The secondary outcomes were the severity of self-report fatigue using the three most common fatigue scales, namely the Functional Assessment of Cancer Therapy (FACT) (13-item fatigue subscale), the European Organisation for Research and Treatment Quality of Life Questionnaire - C30 (EORTC QLQ-C30) (fatigue subscale) and the Brief Fatigue Inventory (BFI) scale.

Physical Activity Interventions

The intervention was physical activity of any type, intensity, frequency, or duration, used for the management of fatigue. We defined physical activity as any bodily movement produced by skeletal muscles, which results in energy expenditure above resting (basal) levels.[27] Physical activity interventions were categorized using the American College of Sports Medicine[27] approach as follows: (1) aerobic – includes brisk walking, running, cycling, climbing stairs, working out in a gym using a treadmill, stationary bike or elliptical machine, water aerobics, aerobic dance and hiking; (2) neuromotor – includes yoga, tai chi and qigong; (3) resistance – includes use of free weights and dumbbells, machines with stacked weights or pneumatic resistance, elastic tubing and resistance bands; and (4) flexibility – includes ballistic stretches, dynamic stretching, and static stretching. Studies that used two or more discrete modes of physical activity such as combining aerobic or neuromotor were classified as combination. Because aerobic and neuromotor activities often include stretching, flexibility was only categorized if it was used alone. Studies that did not state the type of physical activity intervention were classified as unspecified.

Characteristics of the physical activity interventions were described as follows. The mode of intervention delivery was categorized as supervised when the activity was performed under the direct supervision of an instructor and non-supervised otherwise. The delivery setting was classified as group when the intervention was delivered to more than one target participant at the same time. The number of weeks of physical activity intervention was dichotomized at 12 as this was the median duration of exercise used by the included studies. The minutes of physical activity per week was dichotomized at 150 as this duration has been recommended for low to moderate intensity exercise in healthy adults.[27-29]

Control Groups

We categorized control group type as: (1) usual care or wait list control; (2) physical activity when studies compared two different types of physical activities such as aerobic vs. resistance; (3) non-physical activity, active control (not usual care or wait list control) such as psychological, pharmacological or mind and body interventions; and (4) combination (physical activity and non-physical activity, active control). Among trials comparing two different types of physical activities, the activity of lower intensity was chosen as the control arm. For example, in a study comparing aerobic exercise and yoga, yoga was designated as the control arm.

Study Characteristics and Risk of Bias Assessment

Study-level variables included year of publication and enrollment, country of study, age of participants (adults vs. children), type of cancer (breast, prostate, other cancer and more than one cancer type), cancer stage (non-metastatic, metastatic and both), inclusion of HSCT recipients, timing of intervention (during cancer treatment, following completion of treatment or both during and following treatment), exclusive enrollment of palliative care patients (defined by each study), presence of fatigue as an eligibility criterion for enrollment (threshold varied by study) and characteristics of the intervention and control groups.

We used the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[30] This approach evaluates sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition bias and selective reporting. Calculation of a total quality score and stratification of results by study quality (low vs. high quality) leads to unreliable results.[31] For this reason we chose to adopt the suggestions of the Cochrane Collaboration[32] and forego

calculation of a total quality score and to evaluate quality domains separately.

Data Analysis

We combined data at the study level for this meta-analysis. For fatigue scores with missing summary measures, we made the following assumptions to facilitate data synthesis: the mean can be approximated by the median; the range contains six standard deviations (SDs); the 95% confidence interval (CI) contains four standard errors, and the interquartile range contains 1.35 SDs.

For the primary analysis, we compared physical activity interventions vs. all controls across different fatigue scales and by the three most common fatigue scales. We then stratified these analyses by control group type: physical activity intervention vs. usual care or wait list control, physical activity intervention vs. physical activity control, and physical activity intervention vs non-physical activity, active control (psychological, pharmacological or mind and body interventions). For analyses across different fatigue scales, data were synthesized using the standardized mean difference (SMD) after rescaling such that higher scores reflected more fatigue. For analyses focused on specific fatigue scales, data were synthesized using the weighted mean difference (WMD). A SMD or WMD less than 0 indicate that the mean fatigue scores were lower (better) in the physical activity group as compared to the control group. Effects were weighted by the inverse variance. As we anticipated heterogeneity between studies, a random effects model was used for all analyses. Statistical heterogeneity between trials was assessed using the I^2 value, which describes the percentage of total variation across studies due to heterogeneity rather than chance.

For the secondary objective, which was to determine whether the effect of physical activity varied by patient, intervention or methodological factors, we conducted stratified analyses. These stratified analyses focused on synthesis across fatigue scales

(and thus relied upon SMD) and compared physical activity interventions vs. all control groups and physical activity interventions vs. usual care or wait list controls separately. We evaluated the following factors for stratified analyses: (1) type of cancer, (2) cancer stage, (3) timing of intervention, (4) required fatigue for eligibility, (5) physical activity intervention type, (6) supervised vs. non-supervised physical activity intervention, (7) group vs. non-group delivery setting, (8) number of weeks of physical activity intervention, (9) minutes per week of physical activity intervention, (10) adequate sequence generation, and (11) adequate allocation concealment. We determined whether the physical activity effect varied by subgroups using the P value for interaction.

Potential publication bias was explored by visual inspection of funnel plots when at least 10 studies were available for synthesis.[30] In the event of potential publication bias, the “trim and fill” technique was used to determine the impact of potential bias.[33] With this technique, outlying studies are deleted, and hypothetical negative studies with equal weight are created. Meta-analyses were conducted using Review Manager 5.2 (Cochrane Collaboration, Nordic Cochrane Centre).

RESULTS

The flow diagram of study identification and selection is presented as Figure 1. The search strategy identified 11,793 citations, of which 617 were retrieved for full-text evaluation. Of these citations, 170 met the eligibility criteria and were included in this systematic review. Reasons for exclusion are described in Figure 1. Agreement of study inclusion between the two reviewers was almost perfect ($\kappa = 0.97$, 95% CI 0.95 to 0.99).

Table 1 and Appendix 3 describe the characteristics of the 170 included studies. These studies were conducted in 27 countries. Half of the trials (51.7%) were published after 2013. Only one study was conducted in children and adolescents; it compared

aerobic exercise with usual care. Studies of breast cancer patients were the most common (47.1%). Physical activity intervention types were aerobic (44.7%), neuromotor (16.5%), resistance (8.8%) and combination (27.1%). Five studies (2.9%) did not specify the type of physical activity intervention used. Control group types were usual care or wait list (77.1%), other physical activity (16.5%), non-physical activity, active control (5.3%) and combination (1.2%). The non-physical activity, active controls were relaxation (n=5), psychological therapy (n=3), and breathing exercises (n=1). Fatigue assessment scales used across all the studies are listed in Appendix 2. Among the 27 reported fatigue scales, the three most common were the FACT (13-item fatigue subscale) (n=58), EORTC QLQ-C30 (fatigue subscale) (n=30) and the BFI (n=21).

Table 2 shows the effect of physical activity on fatigue severity across fatigue assessment scales and by specific fatigue scale for all control groups and stratified by control group type. One hundred and thirty-four studies encompassing 8927 patients were included in the comparison of physical activity intervention vs. all controls across fatigue scales. Overall, physical activity reduced the severity of fatigue when compared to all controls when measured using any fatigue scale (SMD -0.49, 95% CI -0.60 to -0.37; $P < 0.00001$, Figure 2) and when measured using FACT (WMD -3.40, 95% CI -5.25 to -1.55; $P = 0.0003$), EORTC QLQ-C30 (WMD -11.07 95% CI -17.79 to -4.36 $P = 0.002$) and the BFI (WMD -0.53, 95% CI -0.93 to -0.13; $P = 0.009$). When stratified by control group type, effects were generally similar irrespective of specific control group.

Table 3 shows the effect of physical activity intervention by patient, intervention and methodological factors stratified by all controls and by usual care or wait list controls. The effect of physical activity did not differ based upon type of cancer, cancer stage, timing of intervention and requirement of fatigue for eligibility. The following features of the intervention also did not influence the physical activity effect: supervised vs. non-supervised, group vs. non-group setting, < 12 vs. ≥ 12 weeks of intervention, and < 150

minutes/week vs. ≥ 150 minutes/week. However, the effect of physical activity on fatigue severity reduction differed by the type of physical activity performed when compared to all controls (P for interaction=0.01) (Figure 2). The effect of resistance exercises (SMD -0.21, 95% CI -0.35 to -0.07; $P=0.004$) was smaller although still statistically significant as compared to aerobic (SMD -0.36, 95% CI -0.52 to -0.21; $P<0.00001$), neuromotor (SMD -0.56, 95% CI -0.97 to -0.14; $P=0.008$), combination (SMD -0.61, 95% CI -0.80 to -0.42; $P<0.00001$) and unspecified (SMD -1.81, 95% CI -4.21 to 0.59; $P=0.14$) interventions. Similar effects were seen when physical activity intervention types were compared to usual care or wait list controls.

Appendix 4 illustrates the funnel plot of all physical activity interventions against all controls across different fatigue scales. There was no suggestion of publication bias.

DISCUSSION

In this meta-analysis, we found that physical activity significantly decreases the severity of fatigue in patients with cancer and HSCT recipients. The effect was significant when all scales were combined and when evaluated by the three most common scales. Aerobic, neuromotor, resistance and combination exercises were all effective in reducing fatigue although smaller effects were observed with resistance exercises compared with the other physical activity approaches. The effect of physical activity did not differ based upon presence of fatigue at the time of the intervention, or whether the intervention was supervised, conducted in a group or its duration in weeks or minutes per week.

The overall impact of physical activity on fatigue was -0.49 SMD which is considered a moderate effect.[34, 35] The effect of physical activity as measured using FACT (13-item fatigue subscale) was 3.40, which is larger than the reported minimum clinically important difference of 3 points.[36] Similarly, an effect of 11.07 units measured

using EORTC QLQ-C30 (fatigue subscale) suggests a clinically relevant improvement in fatigue.[37-39] Together, these data suggest that the impact of physical activity on fatigue severity is important to patients.

We found that all physical activity interventions, namely aerobic, neuromotor, resistance and combination, were significantly associated with improved fatigue severity in comparison to all controls. However, we also found a quantitative interaction with resistance training being less effective compared to the other physical activity interventions. This finding should be viewed cautiously as we performed many tests and there is a chance that the significant interaction test is related to the number of tests performed. However, even if a true interaction exists, these findings suggest that all interventions are effective and that if resistance is a patient's preferred modality, it should be offered if safe. Otherwise, aerobic, neuromotor or combination exercises may be offered preferentially.

We found that the benefits of physical activity were not dependent upon the type or stage of cancer nor did it depend on whether the intervention was administered during or following completion of treatment. In addition, physical activity appeared to be effective whether administered in the prophylactic or therapeutic setting as evidenced by a similar effect based upon studies that required a threshold level of fatigue for study inclusion. These findings suggest that physical activity should be encouraged throughout the treatment course to diverse groups of cancer and HSCT patients although our analysis lacked granularity in evaluating specific patient subgroups. Further, only 12 studies were available for data synthesis in which fatigue was an eligibility criterion and thus, conclusions about similar efficacy in the prophylactic and therapeutic setting should be made cautiously.

In addition, the benefit of physical activity on fatigue was not restricted to studies providing ≥ 12 weeks or ≥ 150 minutes per week of intervention. An important potential

confounder is intensity of physical activity intervention. Unfortunately, we could not abstract data on intensity of physical activity because included studies did not use standardized tools to measure this aspect. The American Society of Sports Medicine recommends 30 to 60 minutes of purposeful moderate intensity aerobic physical activity per day for healthy adults for the purpose of improving physical fitness and health.[27] Our findings suggest that when used for the purpose of fatigue reduction, shorter durations (< 150 minutes per week) may also be effective.

Our meta-analysis improves upon two other systematic reviews that reported the effect of physical activity on CRF.[16, 20] We had broader inclusion criteria and synthesized data from 134 studies as compared to analyses published by Mustain et al and Cramp et al, which synthesized 79 and 38 studies respectively.[16, 20] Our review provides unique insights as we had sufficient power to evaluate sub-group effects and to describe effects by different control group types.

We did not evaluate whether fatigue was the primary outcome of trials as articulation of primary vs. secondary outcomes is often not clear in publications. Further, researchers have described bias in outcome reporting and modifications to outcomes from protocol to publication;[40, 41] these modifications are influenced by study findings. Finally, whether fatigue was identified as a primary or secondary outcome should not have impacted on the efficacy of a specific intervention for fatigue reduction.

The strength of our systematic review was the large number of included studies, which provided precision in describing the effect of physical activity both overall, and among specific subgroups. The sample size also increased power to detect significant interactions by patient, intervention and methodological factors. However, our systematic review must be interpreted in light of its limitations. Studies did not use common endpoints, and as a result, we had to rely upon describing the effects using SMDs, which are harder to interpret than WMDs. In our review, only one pediatric study was identified

and thus, these results may not be applicable to children. Finally, we observed heterogeneity in the effect across analyses and we were not able to explain heterogeneity by our *a priori* specified sub-group analyses. It is possible that a source of heterogeneity was related to different study designs. Thus, our results must be viewed cautiously in view of this issue.

In conclusion, physical activity was effective at reducing fatigue in patients with cancer and HSCT recipients across patient sub-groups. Physical activity should be widely promoted for the management of fatigue in this population. Determining the best approaches for safe implementation should be a priority.

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CONFLICT OF INTEREST STATEMENT AND DISCLOSURES

No authors declare a conflict of interest. All authors have approved the final article

Highlights

- Physical activity is effective at reducing fatigue in patients with cancer
- Benefit of physical activity is similar across patient subgroups
- Aerobic, neuromotor, resistance and combination exercises are all effective
- Effect of resistance is smaller than other physical activity interventions

References

1. Berger, A.M., et al., *Cancer-Related Fatigue, Version 2.2015*. J Natl Compr Canc Netw, 2015. **13**(8): p. 1012-39.
2. Henry, D.H., et al., *Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S.* Support Care Cancer, 2008. **16**(7): p. 791-801.
3. Hofman, M., et al., *Cancer-related fatigue: the scale of the problem*. Oncologist, 2007. **12 Suppl 1**: p. 4-10.
4. Mustian, K.M., et al., *Cancer-Related fatigue interferes with activities of daily living among 753 patients receiving chemotherapy: A URCC CCOP study*. Journal of Clinical Oncology, 2008. **26**(15_suppl): p. 9500-9500.
5. Wang, X.S., et al., *Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors*. Cancer, 2014. **120**(3): p. 425-32.
6. Bower, J.E., et al., *Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life*. J Clin Oncol, 2000. **18**(4): p. 743-53.
7. Baggott, C., et al., *Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy*. J Pediatr Oncol Nurs, 2010. **27**(6): p. 307-15.
8. Collins, J.J., et al., *The measurement of symptoms in children with cancer*. J Pain Symptom Manage, 2000. **19**(5): p. 363-77.
9. Walker, A.J., et al., *Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and one week after the administration of chemotherapy*. J Pediatr Oncol Nurs, 2010. **27**(5): p. 259-65.
10. Wagner, L.I. and D. Cella, *Fatigue and cancer: causes, prevalence and treatment approaches*. Br J Cancer, 2004. **91**(5): p. 822-8.
11. Tonosaki, A., *The long-term effects after hematopoietic stem cell transplant on leg muscle strength, physical inactivity and fatigue*. Eur J Oncol Nurs, 2012. **16**(5): p. 475-82.
12. Graef, D.M., et al., *Sleepiness, Fatigue, Behavioral Functioning, and Quality of Life in Survivors of Childhood Hematopoietic Stem Cell Transplant*. J Pediatr Psychol, 2016. **41**(6): p. 600-9.
13. Curt, G.A., et al., *Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition*. Oncologist, 2000. **5**(5): p. 353-60.
14. Kim, S.H., et al., *Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life*. J Pain Symptom Manage, 2008. **35**(6): p. 644-55.
15. Bower, J.E., et al., *Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation*. J Clin Oncol, 2014. **32**(17): p. 1840-50.
16. Mustian, K.M., et al., *Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis*. JAMA Oncol, 2017.
17. Meneses-Echavez, J.F., et al., *The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review with Meta-analysis*. Cancer Epidemiol Biomarkers Prev, 2016. **25**(7): p. 1009-17.
18. Al-Majid, S. and D.P. Gray, *A biobehavioral model for the study of exercise interventions in cancer-related fatigue*. Biol Res Nurs, 2009. **10**(4): p. 381-91.

19. Puetz, T.W. and M.P. Herring, *Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis*. Am J Prev Med, 2012. **43**(2): p. e1-24.
20. Cramp, F. and J. Byron-Daniel, *Exercise for the management of cancer-related fatigue in adults*. Cochrane Database Syst Rev, 2012. **11**: p. CD006145.
21. Tomlinson, D., et al., *Effect of exercise on cancer-related fatigue: a meta-analysis*. Am J Phys Med Rehabil, 2014. **93**(8): p. 675-86.
22. Mishra, S.I., et al., *Exercise interventions on health-related quality of life for people with cancer during active treatment*. Cochrane Database Syst Rev, 2012(8): p. CD008465.
23. Tian, L., et al., *Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials*. Support Care Cancer, 2016. **24**(2): p. 969-83.
24. Chang, C.W., et al., *The effectiveness of non-pharmacological interventions on fatigue in children and adolescents with cancer: a systematic review*. JBI Libr Syst Rev, 2012. **10**(10): p. 574-614.
25. Lopes-Junior, L.C., et al., *Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review*. Eur J Cancer Care (Engl), 2016. **25**(6): p. 921-935.
26. Koch, G.G., et al., *A general methodology for the analysis of experiments with repeated measurement of categorical data*. Biometrics, 1977. **33**(1): p. 133-58.
27. Garber, C.E., et al., *American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise*. Med Sci Sports Exerc, 2011. **43**(7): p. 1334-59.
28. Haskell, W.L., et al., *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association*. Circulation, 2007. **116**(9): p. 1081-93.
29. Kushi, L.H., et al., *American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity*. CA Cancer J Clin, 2006. **56**(5): p. 254-81; quiz 313-4.
30. Higgins, J.P.T. and S. Green, (editors), *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*2011. Available from www.cochrane-handbook.org. The Cochrane Collaboration.
31. Juni, P., et al., *The hazards of scoring the quality of clinical trials for meta-analysis*. JAMA, 1999. **282**(11): p. 1054-60.
32. Higgins, J.P.T. and S. Green, (editors), *Chapter 8: Assessing risk of bias in included studies*. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.
33. Duval, S. and R. Tweedie, *Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis*. Biometrics, 2000. **56**(2): p. 455-63.
34. Faraone, S.V., *Interpreting estimates of treatment effects: implications for managed care*. P T, 2008. **33**(12): p. 700-11.
35. Cohen, J., *Statistical power analysis for the behavioral sciences*1988, Hillsdale, N.J.: L. Erlbaum Associates.
36. Storey, D.J., et al., *Clinically relevant fatigue in cancer outpatients: the Edinburgh Cancer Centre symptom study*. Ann Oncol, 2007. **18**(11): p. 1861-9.

37. Osoba, D., et al., *Interpreting the significance of changes in health-related quality-of-life scores*. J Clin Oncol, 1998. **16**(1): p. 139-44.
38. Ringash, J., et al., *Interpreting clinically significant changes in patient-reported outcomes*. Cancer, 2007. **110**(1): p. 196-202.
39. Maringwa, J., et al., *Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients*. Ann Oncol, 2011. **22**(9): p. 2107-12.
40. Chan, A.W. and D.G. Altman, *Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors*. BMJ, 2005. **330**(7494): p. 753.
41. Chan, A.W., et al., *Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research*. CMAJ, 2004. **171**(7): p. 735-40.

Table 1: Characteristics of Included Studies in the Systematic Review (N=170)

Characteristic	No. of Studies (%)
Study Population	
Adults	169 (99.4)
Children	1 (0.6)
Type of Cancer	
Breast	80 (47.1)
Prostate	19 (11.2)
More than one cancer	45 (26.5)
Other cancer types	26 (15.3)
Cancer Stage*	
Non-metastatic	93 (54.7)
Metastatic	7 (4.1)
Both	29 (17.1)
Included Hematopoietic Stem Cell Transplant Recipients	13 (7.6)
Timing of Intervention*	
During cancer treatment	93 (54.7)
Following completion of treatment	39 (22.9)
Both during and following treatment	36 (21.2)
Palliative Care Setting Only	2 (1.2)
Required Fatigue for Eligibility	15 (8.8)
Physical Activity Intervention Type	
Aerobic	76 (44.7)
Neuromotor	28 (16.5)
Resistance	15 (8.8)
Flexibility	0 (0)
Combination	46 (27.1)
Unspecified	5 (2.9)
Mode of Physical Activity Intervention Delivery*	
Supervised	110 (64.7)
Non-supervised	58 (34.1)
Delivery Setting	
Group	47 (27.6)
Non-group	73 (42.9)
Number of Weeks - Physical Activity Intervention*	
<12 weeks	56 (32.9)
≥12 weeks	91 (53.5)
Minutes per Week – Physical Activity Intervention*	
<150 minutes	39 (22.9)
≥150 minutes	88 (51.7)
Control Group Type	
Usual care or wait list	131 (77.1)
Physical activity	28 (16.5)
Non-physical activity, active control	9 (5.3)
Combination	2 (1.2)
Risk of Bias	
Adequate sequence generation	109 (64.1)
Adequate allocation concealment	69 (40.6)
Participants and personnel blinded	0 (0)
Outcome assessors blinded	0 (0)
Lack of attrition bias	103 (60.6)
Free of selective reporting	119 (70)

* Does not add to 170 because not all the studies report this information

Table 2: Effect of Physical Activity Intervention on Fatigue Stratified by Fatigue Scale and Control Group Type

Outcome	No. of Studies	No. of Patients	Effect	95% CI	I ² (%)	P Value
All Controls						
Physical Activity Intervention vs. All Controls						
Any fatigue scale	134	8927	-0.49 SMD	-0.60, -0.37	85	<0.00001
FACT (13-item fatigue subscale)	45	3295	-3.40 WMD	-5.25, -1.55	89	0.0003
EORTC QLQ-C30 fatigue scale	25	1693	-11.07 WMD	-17.79, -4.36	91	0.002
Brief fatigue inventory	12	704	-0.53 WMD	-0.93, -0.13	85	0.009
Stratified by Control Group Type						
Physical Activity Intervention vs. Usual Care or Wait List Control						
Any fatigue scale	101	6750	-0.54 SMD	-0.68, -0.39	87	<0.00001
FACT (13-item fatigue subscale)	38	2701	-2.99 WMD	-4.72, -1.27	84	0.0007
EORTC QLQ-C30 fatigue scale	11	732	-14.53 WMD	-28.06, -1.00	95	0.04
Brief fatigue inventory	10	622	-0.53 WMD	-0.95, -0.10	88	0.01
Physical Activity Intervention vs. Physical Activity Control						
Any fatigue scale	23	1463	-0.42 SMD	-0.66, -0.18	78	0.0006
FACT (13-item fatigue subscale)	7	594	-5.49 WMD	-11.64, 0.66	95	0.08
EORTC QLQ-C30 fatigue scale	11	662	-6.38 WMD	-9.75, -3.00	0	0.002
Physical Activity Intervention vs. Non-Physical Activity, Active Control*						
Any fatigue scale	9	651	-0.24 SMD	-0.54, 0.07	72	0.13
EORTC QLQ-C30 fatigue scale	3	299	-10.76 WMD	-20.04, -1.48	62	0.02

Abbreviations: CI – confidence interval; FACT - Functional Assessment of Cancer Therapy; SMD - standardized mean difference; WMD - weighted mean difference

* Non-physical activity, active controls were relaxation (n=5), psychological therapy (n=3), and breathing exercises (n=1)

Table 3: Effect of Physical Activity Intervention by Patient, Intervention and Methodological Factors Stratified by Control Group Type

	Physical Activity Intervention vs. All Control Groups						Physical Activity Intervention vs. Usual Care or Wait List Control Groups					
Subgroup	No. of Studies	No. of Patients	SMD*	95% CI	I ²	P Values	No. of Studies	No. of Patients	SMD*	95% CI	I ²	P Values
Type of cancer						Pint=0.09						Pint=0.25
Breast	57	4110	-0.43	-0.58, -0.28	80	<0.00001	41	2884	-0.53	-0.72, -0.34	83	<0.00001
Prostate	17	1078	-0.92	-1.35, -0.50	90	<0.0001	14	894	-0.77	-1.15, -0.38	86	<0.001
Other cancer types	23	1269	-0.60	-1.11, -0.09	94	0.02	20	1058	-0.70	-1.30, -0.10	94	0.02
More than one cancer	37	2470	-0.37	-0.51, -0.24	59	<0.00001	26	1914	-0.38	-0.56, -0.20	70	<0.0001
Cancer stage						Pint=0.45						Pint=0.53
Non-metastatic	75	5200	-0.56	-0.74, -0.38	89	<0.00001	58	4069	-0.59	-0.80, -0.39	90	<0.00001
Metastatic	4	116	-0.39	-0.85, 0.07	32	0.1	3	80	-0.40	-1.07, 0.27	51	0.24
Both	23	1706	-0.38	-0.61, -0.15	79	0.001	20	1340	-0.41	-0.68, -0.13	83	0.004
Timing of Intervention						Pint=0.51						Pint=0.54
During cancer treatment	74	5127	-0.52	-0.70, -0.34	89	<0.00001	58	4140	-0.51	-0.72, -0.30	90	<0.00001
Following completion of treatment	29	1518	-0.38	-0.58, -0.18	68	0.0002	19	1073	-0.49	-0.76, -0.23	73	0.0002
Both during and following treatment	29	2248	-0.53	-0.73, -0.32	81	<0.00001	22	1503	-0.67	-0.92, -0.43	80	<0.00001
Required Fatigue for Eligibility						Pint=0.74						Pint=0.54
Yes	12	549	-0.55	-0.91, -0.19	75	0.003	8	331	-0.67	-1.10, -0.24	69	0.002
No	122	8378	-0.48	-0.61, -0.36	86	<0.00001	93	6419	-0.53	-0.68, -0.38	87	<0.00001
Physical Activity Intervention Type						Pint=0.01						Pint=0.09
Aerobic	59	3624	-0.36	-0.52, -0.21	80	<0.00001	44	2851	-0.45	-0.64, -0.25	83	<0.00001
Neuromotor	24	1601	-0.56	-0.97, -0.14	93	0.008	20	1337	-0.54	-1.04, -0.04	94	0.04
Resistance	13	761	-0.21	-0.35, -0.07	0	0.004	7	323	-0.20	-0.42, 0.02	0	0.07
Combination exercises	35	2803	-0.61	-0.80, -0.42	83	<0.00001	27	2101	-0.59	-0.78, -0.40	76	<0.00001

Unspecified	3	138	-1.81	-4.21, 0.59	96	0.14	3	138	-1.81	-4.21, 0.59	96	0.14
Mode of Physical Activity Intervention Delivery						Pint=0.35						Pint=0.16
Supervised	95	6353	-0.53	-0.67, -0.38	86	<0.00001	67	4534	-0.56	-0.75, -0.38	88	<0.00001
Non-supervised	38	2623	-0.41	-0.61, -0.21	82	<0.0001	34	2298	-0.50	-0.73, -0.28	87	<0.00001
Delivery setting						Pint=0.85						Pint=0.99
Group	49	3662	-0.57	-0.76, -0.39	85	<0.00001	36	2791	-0.60	-0.80, -0.41	83	<0.00001
Non-group	44	2819	-0.54	-0.81, -0.27	91	<0.0001	38	2233	-0.60	-0.92, -0.29	91	0.0002
Number of Weeks - Physical Activity Intervention						Pint=0.22						Pint=0.16
< 12 weeks	46	2627	-0.59	-0.85, -0.34	89	<0.00001	36	2230	-0.66	-0.97, -0.35	91	<0.0001
≥ 12 weeks	72	5215	-0.41	-0.54, -0.28	79	<0.00001	54	3730	-0.42	-0.57, -0.26	79	<0.00001
Minutes per Week – Physical Activity Intervention						Pint=0.69						Pint=0.70
< 150 minutes	30	1665	-0.50	-0.72, -0.28	75	<0.00001	20	1115	-0.64	-0.94, -0.33	80	<0.0001
≥ 150 minutes	72	5118	-0.56	-0.74, -0.37	89	<0.00001	55	4006	-0.56	-0.78, -0.34	90	<0.00001
Adequate Sequence Generation						Pint=0.52						Pint=0.99
Yes	91	6355	-0.51	-0.66 -0.35	88	<0.00001	70	4857	-0.53	-0.71, -0.35	89	<0.00001
No	43	2572	-0.43	-0.60, -0.26	75	<0.00001	31	1893	-0.53	-0.74, -0.31	79	<0.00001
Adequate Allocation Concealment						Pint=0.20						Pint=0.65
Yes	61	4409	-0.57	-0.77, -0.37	90	<0.00001	48	3424	-0.56	-0.79, -0.34	90	<0.00001
No	73	4518	-0.41	-0.54 -0.28	78	<0.00001	53	3326	-0.50	-0.68, -0.32	82	<0.00001

* Effect reflects SMD using any fatigue scale

Abbreviations: CI – confidence interval; Pint – P value for interaction; SMD – standardized mean difference;

Figure 1: Flow diagram Depicting Study Identification, Selection and Reasons for Exclusion

Figure 2: Forest plot of studies comparing all physical activity interventions vs. all controls stratified by type of physical activity intervention

Squares to the left of the vertical line mean that the physical activity is better than control. Horizontal lines through the squares represent 95% confidence intervals (CIs). The size of the squares reflects each study's relative weight, and the diamond represents the aggregate standardized mean difference (SMD) and 95% CI.