

# The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis

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**Objective:** The objective of the study was to conduct systematic review and meta-analysis to establish the effect of exercise interventions on cancer-related fatigue (CRF) in cancer survivors, compared to non-exercise intervention controls.

**Methods:** Trials published between January 1st 2000 and August 17th 2016 were included through PubMed database search and search of references. Eligible trials compared the effect of an exercise intervention on CRF compared to non-exercise intervention controls, with CRF as primary outcome and measured by validated self-report questionnaire, in cancer survivors not receiving palliative care. We evaluated risk of bias of individual trials following Cochrane Quality criteria. We performed a random-effects meta-analysis in the low risk of bias trials with intervention type, exercise intensity, adherence, and cancer type as moderators, and also performed meta-regression analyses and a sensitivity analysis including the high risk of bias trials.

**Results:** Out of 274 trials, 11 met the inclusion criteria, of which six had low risk of bias. Exercise improved CRF with large effect size (Cohen's  $d$  0.605, 95% CI 0.235–0.975) with no significant difference between types of cancer. Aerobic exercise ( $\Delta$ =1.009, CI 0.222–1.797) showed a significantly greater effect than a combination of aerobic and resistance exercises ( $\Delta$ =0.341, CI 0.129–0.552). Moderator and meta-regression analyses showed high adherence yielding best improvements.

**Conclusion:** Exercise has a large effect on CRF in cancer survivors. Aerobic interventions with high adherence have the best result.

**Keywords:** exercise, cancer-related fatigue, cancer survivors, randomized clinical trials, systematic review, meta analysis

## Introduction Background

Cancer incidence is growing, with an incidence rate of 14.1 million in 2012 and 23.6 million new yearly cases predicted worldwide by 2030.<sup>1</sup> Cancer incidence is highest in Denmark (338 cases per 100,000), followed by France (325/100,000), Australia (323/100,000), the USA (318 cases per 100,000), and South Korea (308/100,000) as top five countries. With growing incidence and current treatment possibilities, a growing number of people live beyond diagnosis. We define a person as a cancer survivor when he or she is living with and beyond a cancer diagnosis (like the US National Coalition for Cancer Survivorship).<sup>2</sup>

One of the major causes of distress in cancer survivors is cancer-related fatigue (CRF).<sup>3</sup> Although in earlier research the prevalence of CRF as reported by patients in the USA ranged from 4% to 99%, depending on the sample and assessment method,<sup>4–6</sup> a recent USA-based study found a prevalence of 45% of moderate to severe CRF

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in cancer survivors.<sup>7</sup> Several factors have been identified in research as contributing to fatigue, such as treatment, emotional distress, inactivity, and decondition.<sup>8</sup> The nature of the fatigue is pervasive, as cancer survivors state “it’s so much more than just feeling tired”.<sup>9</sup> Several trials have shown that exercise has a positive effect on health-related quality of life, physiological and psychological side effects of treatment,<sup>10</sup> and overall fitness,<sup>11</sup> and may even increase survival rates.<sup>12</sup> It has also been suggested that there are similarities<sup>13</sup> among research on chronic fatigue syndrome (CFS), which shows that exercise can alleviate fatigue.<sup>14,15</sup> It is estimated that up to 10% of the world population suffers from chronic fatigue.<sup>10</sup> In all clinical settings including but not limited to oncology care, mental health care, general hospital care, and primary care, chronic fatigue prevalence rates of 40%–63% are reported.<sup>16</sup> With so many people suffering from fatigue, it is important to be able to treat fatigue properly. A large number of studies have been conducted to test the effectiveness of treatments to reduce chronic fatigue, both in patients with and without chronic medical conditions, as it seems that there may be similarities between the chronic fatigue types.

A recent meta-analysis showed that both exercise and psychological treatment have small effect sizes in CRF, whereas medication has no effect.<sup>11</sup> The effect depends on cancer treatment stage,<sup>11</sup> with most effect for exercise during cancer treatment, while psychotherapy has more effect after treatment.

Despite the evidence that exercise is beneficial, many cancer survivors do not engage in sufficient levels of exercise. Survivors report a significant decline in exercise after diagnosis, with less than half (48%) engaging in a beneficial amount of exercise.<sup>17,18</sup> Research on determinants of exercise levels is limited and shows contradictory results. For example, one study found being female and being older to be associated with decreased exercise;<sup>19</sup> another study found the opposite.<sup>20</sup> Whether the nature of cancer treatment influences exercise levels of cancer survivors specifically is also up for debate.<sup>21</sup> It might be that the exercise regimen is too strenuous; an ongoing debate concerns the question if patients should rest, or continue training despite malaise. It has been suggested in CFS patients that exercise improves fatigue but too much exercise has adverse effects, resulting in low adherence;<sup>22</sup> post-exercise malaise is a frequent reason to stop an exercise regimen.<sup>23</sup> Being fatigued is a valid reason for a person without cancer not to exercise, and the larger burden of CRF might make it even harder to exercise.

## Rationale

CRF, because of its persistence and interference with many aspects of daily life,<sup>24</sup> even in cancer survivors with no

evidence of active disease,<sup>25,26</sup> leads to loss of work, limited social functioning including parenting, and even lower treatment adherence. In view of its high prevalence of 45%, combined with growing survival rates, CRF can be considered as a major public health concern. An often dispensed advice is to exercise, but it is not clear how and with which intensity. Research is warranted that aims to clarify this.

A Cochrane systematic review and meta analysis by Cramp and Byron-Daniel<sup>27</sup> examined the effect of exercise on CRF in cancer survivors. Patients received non-palliative treatment or palliative treatment. Also, this review included CRF as secondary outcome. As we intend to establish the effect of exercise on CRF as a primary outcome in a population not suffering from specific end-of-life distress, we have only included trials evaluating exercise interventions versus non-exercise intervention controls, with CRF as a primary outcome measure. Hence, the results of this meta-analysis may provide the clinician with clear-cut information if exercise should be recommended, and what kind of exercise to recommend to cancer survivors not receiving palliative care.

## Objectives

This study aims to provide a systematic review of RCTs evaluating the effect on CRF of exercise interventions versus non-exercise intervention controls in cancer survivors not receiving palliative care in trials evaluating CRF as a primary outcome measure. In our review, both level of exercise intensity and adherence are taken into account. The ensuing meta-analysis will provide a pooled estimate of the effect.

## Methods

### Protocol and registration

The review protocol has been registered in the Prospero Centre for reviews and dissemination<sup>28</sup> under ID CRD42013003670. The systematic review and meta-analysis are performed and presented according to PRISMA Guidelines and with a PRISMA checklist (Figure S1).<sup>29</sup>

### Eligibility criteria

An overview of participants, interventions, comparisons, outcomes, and study design (PICOS) is shown in Table 1. Patients were adults (18 years or older), regardless of sex, living with and beyond any cancer diagnosis. Patients were not receiving palliative care in the sense of symptom reduction in advanced disease, but may receive active treatment such as surgery, chemotherapy, or radiation therapy. Patients with metastatic disease were not included. Any length of follow-up was acceptable for inclusion and included in the data synthesis; however, for comparability of estimate of the

**Table I** PICOS eligibility criteria

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adults > 18 years living with, through, or beyond a cancer diagnosis not receiving palliative care	Patients under 18 years of age Patients receiving palliative care Patients with metastatic cancer
Intervention	Physical activity intervention of sufficient intensity as measured by METs	An information letter/session Education Yoga (of insufficient METs) Stretching
Comparator	Non-exercise control group	Non-exercise control group receiving additional care, such as CBT
Outcomes	Primary outcome: intensity of CRF as measured by self-report questionnaire Secondary outcome: adherence	CRF is not the primary outcome
Study design	Randomized controlled trials published between January 1st 2000 and August 17th 2016 No language restrictions	Non-randomized controlled trials Retrospective, prospective, or concurrent cohort studies Cross-sectional studies Case reports Editorials and opinion pieces

**Abbreviations:** CBT, cognitive behavioral therapy; CRF, cancer-related fatigue; METs, metabolic equivalents of task; PICOS, patients, intervention, comparator, outcomes, study design.

effect, in the meta-analysis similar length of follow-up was chosen between studies.

## Information sources

A PubMed database and a Cochrane Database search were performed. We also hand-searched the references noted by Cramp and Byron-Daniel<sup>27</sup> in their Cochrane review and each included article. Furthermore, we contacted study authors to identify relevant data for the analysis.

## Search

The MeSH terms and free text terms used were “cancer” AND “fatigue” AND (“physical activity” OR “exercise”) AND “randomized controlled trial”. The search string was “cancer”[All Fields] AND “fatigue”[All Fields] AND (“physical activity”[All Fields] OR “exercise”[All Fields]) AND “randomized controlled trial”[All Fields]. For the Cochrane Database, the search was adapted to systematic reviews.

The search was limited to articles published between January 1st 2000 and August 17th 2016. There were no language or other search limitations.

## Study selection

We included RCTs that evaluated any exercise intervention in any setting, individually or in a group, to study the effect on CRF in cancer survivors. The intervention was of sufficient intensity as measured in metabolic equivalent of the task (MET), thus not including stretching exercises. We also excluded yoga; although the majority of yoga sessions

are of very light intensity,<sup>30</sup> quite strenuous yoga exercise also exists and specific characteristics of the yoga intervention are usually not given. Comparisons were with a control group, not receiving any (major) exercise intervention or other intervention (eg, cognitive behavioral therapy). Primary outcome had to be CRF and was expressed in quantitative measures by a validated self-report questionnaire.

Titles and subsequent abstracts of trials were retrieved and screened in duplicate by two independent reviewers (EK and OH) to identify trials that met the inclusion criteria. In case of disagreement, an independent third reviewer (CFC) gave her opinion regarding eligibility and the article was selected based on combination of the three. Subsequently, the full text of potentially eligible trials was retrieved and independently assessed for eligibility in duplicate by two independent reviewers (EK, OH) and the third reviewer in case of disagreement. Thereafter, risk of bias was assessed. For the meta-analysis, only RCTs with low risk of bias assessment were included. A flow chart will be presented in the subsection “Study selection”.

## Data collection process

Data was extracted by two authors (EK, OH). When insufficient data were available in the full text, authors were contacted by email for further information.

## Data items

The main variable for which data was sought is:

- 1) CRF severity, measured by self-report questionnaire validated to assess fatigue in cancer patients.

Other moderating variables for which data were sought are:

- 1) Number of patients in intervention and control groups.
- 2) Type of exercise intervention.
- 3) Type of cancer.
- 4) Current stage of treatment and type of treatment received.
- 5) Intensity of exercise intervention in METs/hour; if MET was not mentioned, it was calculated (OH) based on the described characteristics of the intervention.<sup>31</sup>
- 6) Adherence percentages; we made an assessment based on three aspects: level of reporting, adherence rates as a percentage based on the information in the trials regarding adherence, in terms of sessions attended, and if reporting was done by supervisor or self-report. Adherence level then was determined on a combined assessment of these three aspects, and split into three groups: low (<60%), moderate (60%–80%), and high (>80%). This is indicated in a data extraction table (Table 2).

## Risk of bias in individual trials

Two independent assessors (EK, OH) assessed the risk of bias of included trials on study level (not on outcome level) on the basis of the Cochrane Quality criteria, of which randomization is considered the most important.<sup>32</sup> Any disagreement on eligibility was resolved through discussion with the third reviewer (CFC). Results are shown in a risk-of-bias table (Table 3). Trials with low risk of bias, adequately addressing more than half ( $\geq 4/7$ ) of the items, were included in the meta-analysis.

## Summary measures

The principal summary measure was expressed as standardized difference in means (Cohen *d*) of CRF. These effect sizes indicate by how many standard units the intervention group is better off than the control group. The effect size *d* is calculated by subtracting the average score of the control group ( $M_c$ ) from the average score of the experimental group ( $M_e$ ) and dividing the raw difference score by the pooled standard deviation of the experimental and control group. An effect size of 0.5 indicates that the mean of the experimental group is half a standard unit larger than the mean of the control group. It is generally assumed that an effect size of 0.56–1.2 represents a large clinical effect, 0.33–0.55 is medium, and below 0.33 is small.<sup>33</sup> If trials reported more than one (validated) self-report measure for fatigue, we used only one in the analysis that was preferably also used in other trials. For the benefit of clinical relevance, we chose to use

the outcomes at post-intervention, not at longer follow-up, in the meta-analysis.

## Synthesis of results

We have provided a synthesis of results (Table 2) with an overview of type of cancer, intervention, and outcome. Subsequently, a random-effects meta-analysis was performed. Between-study heterogeneity was assessed by the observed dispersion, reflected by the *Q*-statistic. The *I*<sup>2</sup> statistic shows the percentage of total variation across trials that is the result of heterogeneity rather than chance and was used to quantify this dispersion.<sup>34</sup> The statistical program Comprehensive Meta-Analysis v.2<sup>35</sup> was used for all analyses.

## Risk of bias across trials

A test of publication bias was performed in order to assess evidence for publication bias and if the reported effect was valid. Publication bias was examined by constructing a Begg funnel plot<sup>36</sup> and performing as the fail-safe *N*.<sup>37</sup>

## Additional pre-envisioned moderator analyses

We planned several moderator analyses, which are as follows:

### Type of intervention

Type of intervention was split into three groups: aerobic, resistance, and a combination of resistance and aerobic exercise. Aerobic exercise is physical exercise that depends primarily on the aerobic energy-generating process.<sup>38</sup> This refers to the use of oxygen to adequately meet energy demands during exercise via aerobic metabolism.<sup>39</sup> Examples are walking, running, swimming, and cycling.

Resistance exercise is physical exercise that induces muscular contraction that builds the strength, endurance, and size of skeletal muscles as anaerobic activity associated with lactate production. Training commonly uses the technique of progressively increasing the force output of the muscle by increasing weight and using a variety of exercises to target specific muscle groups.<sup>40</sup> Examples are weightlifting and rowing.

### Type of cancer

Type of cancer was split into four groups: breast cancer, prostate cancer, gynecological cancer, and mixed.

### Intensity of exercise

Intensity of exercise was split into high or low intensity (in METs/hour):<sup>32</sup> high MET was operationalized as at least

Table 2 Data extraction table

Study	– n intervention – n control group – Sample mean age – Setting	Type of cancer	– Outcome instrument – p-value	– MET – Adherence – Effect size	– T1 timing – Outcome compared to non-exercise control group	Intervention	Control group
<b>Trials included in the meta-analysis</b>							
<b>Aerobic exercise intervention (n=2)</b>							
Cantarero-Villanueva et al <sup>42</sup>	– n=34 – n=34 – 48 years – Outpatient clinic	Breast (100%)	– Piper fatigue scale – p<0.001	– 12= low METs – 84% = high – Δ=1.40 (95% CI 0.869 –1.930)	– T1 8 weeks – Improved CRF – Improved strength	Aquatic exercise: warm-up, aerobic and endurance exercises, cool-down.	Usual care: followed the oncologist recommendations for maintaining a healthy lifestyle based on adequate nutrition, energy balance, and maintaining usual activities.
Yeo et al <sup>50</sup>	– n=54 – n=48 – 66.5 years – Thomas Jefferson University Hospital Department of Surgery	Pancreas (91%) and periampullary cancer	– FACIT-FS – p=0.05	– 8= low METs – 80% self-report = moderate – Δ=0.60 (95% CI 0.003 –1.189)	– T1 12–24 weeks – Improved CRF – Less pain – Better overall physical functioning – Better mental functioning	Aerobic: walking program.	Usual care: perform usual activity/exercise.
<b>Combination of aerobic and resistance exercise intervention (n=4)</b>							
Adamsen et al <sup>41</sup>	– n=118 – n=117 – 47.2 years – Copenhagen University Hospital	Mixed (44% breast, 0% prostate, 18% gynecological, 1% pancreatic)	– EORTC QLQ-C30 fatigue subscale – p=0.02	– 43= high METs – 71% = moderate – Δ=0.27 (95% CI 0.015–0.529)	– T1 6 weeks – Improved CRF – Improved vitality and functioning – Improved physical capacity – No significant effects on quality of life	Multimodal exercise intervention: high intensity physical training (warm-up exercises, resistance and cardiovascular training) and low intensity physical training (relaxation, body awareness and restorative training, and massages).	Conventional medical care: allowed to freely increase physical activity.
Donnelly et al <sup>44</sup>	– n=16 – n=17 – 53 years – Gynecological clinics	Gynecological (100%)	– MFSI-SF – p=0.046	– Cannot be determined – 44%–58% = low – Δ=0.21 (95% CI –0.477 to 0.892)	– T1 12 weeks – Improved CRF – Improved sleep quality – Improved quality of life	Walking and strengthening exercises.	Standard care and no advice on how to change physical activity levels during the study period.
Mustian et al <sup>46</sup>	– n=19 – n=19 – 56.6 years – Standard radiation therapy center	Breast (71% and prostate 29%)	– FACIT-FS – p<0.05	– 38= high METs – 79% = moderate – Δ=0.56 (95% CI –0.089 to 1.207)	– T1 4 weeks – Improved CRF – Improved aerobic capacity – Improved quality of life	Aerobic (walking) and progressive resistance (therapeutic resistance bands) exercises.	Instructed not to begin any new formal physical exercise program (eg, joining a gym or a walking group).

(Continued)

Table 2 (Continued)

Study	n intervention n control group Sample mean age Setting	Type of cancer	Outcome instrument p-value	MET Adherence Effect size	T1 timing Outcome compared to non-exercise control group	Intervention	Control group
Rogers et al <sup>47</sup>	n=20 n=24 56.2 years Academic center	Breast (100%)	PROMIS fatigue p<0.01	21.6= high METs 92%= high Δ=0.64 (95% CI 0.030 – 1.247)	T1 12 weeks Improved CRF Higher baseline CRF predicted a greater decline during intervention Fewer anxiety symptoms	Aerobic walking and strength training using resistance bands.	Exercise behaviour at time of study enrollment.
<b>Studies excluded in the meta-analysis</b>							
Aerobic exercise intervention (n=5)							
Dodd et al <sup>43</sup>	n=44 n=39 50.5 years Outpatient clinics	Mixed (100%): breast, colorectal or ovarian	Piper fatigue scale p=0.048	High METs 73%= high Δ=0.39 (95% CI –0.050 to 0.820)	T1 16–24 weeks No effect on CRF or related symptoms	Cardiovascular/aerobic exercise. (Two experimental groups. 1) Exercise prescription throughout the study period [during and after cancer treatment]. 2) Exercise prescription after completed cancer treatment.)	Usual care: no exercise prescription during and after cancer treatment.
Mock et al <sup>45</sup>	n=60 n=59 52 years University teaching centers and community cancer centers	Breast (100%)	Piper fatigue scale p=0.003	Low METs 72%= moderate Δ=0.08 (95% CI –0.280 to 0.439)	T1 6 weeks No group differences due to dilution of treatment effect from exercise adherence Significant effect of exercise if corrected for adherence Improvement in walking distance	Aerobic activity.	Usual care: encouraged to maintain current levels of activity, and no exercise prescriptions or formal programs were offered.
Wang et al <sup>48</sup>	n=30 n=392 50.4 years Chang-Gung Memorial Hospital and National Taiwan University Hospital	Breast (100%)	FACIT-FS p=0.003	Low METs 93%= high Δ<0.01 (95% CI –0.458 to 0.466)	T1 6 weeks Improved CRF Improved quality of life Less sleep disturbances Higher self-efficacy for exercise More exercise behavior Better exercise capacity	Aerobic: walking program.	Usual care.

(Continued)



Table 2 (Continued)

Study	n intervention n control group Sample mean age Setting	Type of cancer	Outcome instrument p-value	MET Adherence Effect size	T1 timing Outcome compared to non-exercise control group	Intervention	Control group
Windsor et al <sup>49</sup>	n=33 n=33 68.8 years Men on the outpatient waiting list	Prostate (100%)	Brief fatigue inventory p=0.18	Low METs 100% = high $\Delta=0.32$ (95% CI -0.165 to 0.807)	T1 8 weeks No improvement in CRF Improvement in walking distance Improvement in physical functioning	Aerobic: walking intervention. (All participants were selected from a waiting list?)	Control group was not discouraged from performing normal activities but was advised to rest and take things easy if they became fatigued.
Yuen and Sword <sup>51</sup>	n=7 n=7 53.9 years Medical University of South Carolina	Breast (100%)	Piper fatigue scale p=0.06 (one-tailed)	Low METs 73% = moderate $\Delta=1.78$ (95% CI 0.542 -3.018)	T1 12 weeks Improved CRF Improved subjective CRF	Aerobic or resistance exercises (two experimental groups)	Usual care: continued with normal activities and received no exercise related instruction.

Note: T1= timing of post-intervention measurement.

Abbreviations: CBT, cognitive behavioral therapy; CRF, cancer-related fatigue; MET, metabolic equivalent of task; FACIT-FS, Functional Assessment of Chronic Illness Therapy - Fatigue Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PROMIS, Patient-Reported Outcomes Measurement Information System.

3.5 METs per day at least 5 days a week, adding up to  $\geq 17.5$ . Low MET was  $<17.5$ . For linear meta-regression, the actual MET scores were used.

## Adherence

Adherence was split into three groups: low ( $<60\%$ ), moderate ( $60\%–80\%$ ), and high ( $>80\%$ ). For linear meta-regression, adherence percentages as reported in the trials were used.

After performing each analysis we examined heterogeneity. We performed a sensitivity analysis also including the articles with high risk of bias.

## Results

### Study selection

The search strategy yielded 274 hits, 246 after checking for duplicates. Searching the Cochrane Database provided one systematic review,<sup>28</sup> of which we hand-searched the references. After independently screening title and abstracts, 35 trials were included for independent full-text screening. We were not able to procure a translated version in English or Dutch for one study published in Korean. Twenty-four trials were excluded and finally 11 trials met the inclusion criteria as stated in the subsection “Study selection” and were included in the systematic review. Five of these were excluded because of high risk of bias and six were included in the meta-analysis. However, all 11 trials were included in the sensitivity analysis. See the PRISMA Flow Diagram (Figure 1) for an overview and exclusion reasons.

### Study characteristics

All 11 trials were RCTs.<sup>41–52</sup> In total, 788 patients were included in the trials, 411 of which received an exercise intervention and 377 were randomized in a non-exercise intervention control group as described in the section “Eligibility criteria”. In five trials,<sup>42,44,46,47,49</sup> patients were still undergoing cancer treatment during the intervention, in one study there was no active cancer treatment,<sup>43</sup> and in the other five trials<sup>45,48,50–52</sup> some patients were still undergoing cancer treatment but outcome reporting of fatigue scores was not differentiated between patients still undergoing cancer treatment or not. Post-intervention follow-up assessments of CRF varied from 4 weeks<sup>34</sup> to 12–24 weeks.<sup>50,51</sup>

### Risk of bias

Risk of bias was determined for 11 trials on study level and is presented in Table 3. Several trials did not adequately address allocation concealment, missing data, and blinding.

Table 3 Risk-of-bias table

Study	Sequence generation	Allocation concealment	Blind outcome assessor	Blind other	Loss to follow-up reported/ITT analysis	Free of selective outcome reporting	Free of other bias	Appraisal of quality	Comment
Trials included in meta-analysis (n=6)									
Adamsen et al <sup>41</sup>	Yes	Yes	Yes	No	No	Yes	Yes	B	Missing data not addressed explicitly, good quality study.
Cantarero-Villanueva et al <sup>42</sup>	Yes	Yes	Yes	No	In part	Yes	Yes	B	Missing data not addressed explicitly, good quality study.
Donnelly et al <sup>44</sup>	Yes	Yes	Yes	No	Yes	Yes	Yes	A	Good quality study.
Mustian et al <sup>46</sup>	Yes	Yes	Yes	No	Yes	Yes	Yes	A	Good quality study.
Rogers et al <sup>47</sup>	Yes	Yes	No	No	Yes	Yes	Yes	B	Blinding not addressed explicitly, good quality study.
Yeo et al <sup>50</sup>	Yes	Yes	No	No	Yes	Yes	Yes	B	Blinding not addressed explicitly, good quality study. Missing data reported.
Trials excluded from meta-analysis (n=6)									
Dodd et al <sup>43</sup>	In part randomization not described	No	No	No	In part	Yes	Yes	C	Randomization not described, most risk of bias not addressed, dropout shown.
Mock et al <sup>45</sup>	No	Yes	No	No	Yes	No	No	C	Blinding not addressed. Selective reporting.
Wang et al <sup>48</sup>	In part randomization not described	No	No	No	Yes	Yes	In part	C	Randomization not described, most risk of bias not addressed. Missing data addressed.
Windsor et al <sup>49</sup>	In part randomization method unclear	No	No	No	Yes	Yes	Yes	C	Unclear what randomization entails, blinding and allocation concealment not addressed.
Yuen and Sword <sup>51</sup>	Yes	No	No	No	Yes	Yes	No	C	Blinding and allocation concealment not addressed, analysis one-sided.

**Note:** A = excellent, B = very good, C = insufficient as in Cochrane handbook of systematic reviews.

**Abbreviation:** ITT, intention-to-treat.



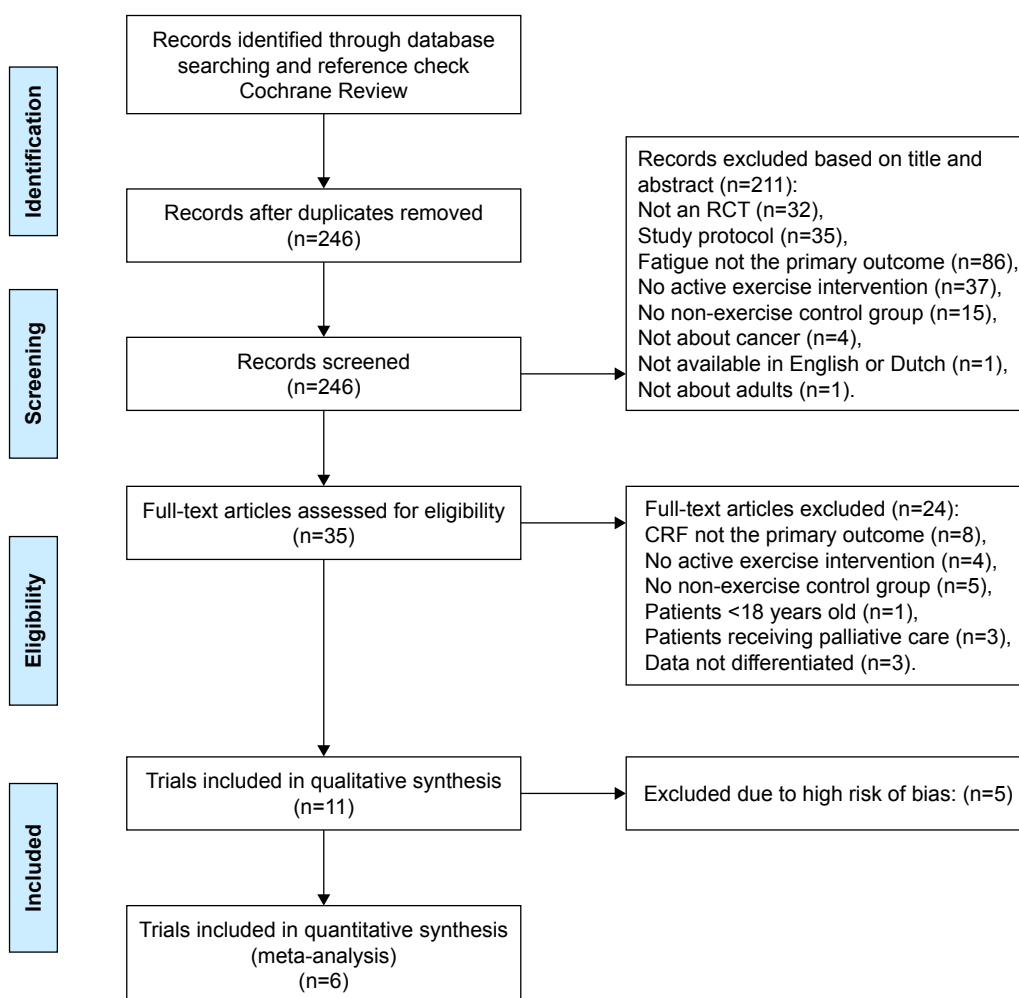
Trials not scoring the maximum may be underestimated due to lack of reporting. Six trials<sup>42,43,45,47,48,51</sup> fulfilled the majority of criteria to eliminate risk of bias and were thus considered of sound quality. Five trials were assessed as being high risk of bias and were excluded from the initial meta-analysis.<sup>44,46,49,50,52</sup> The risk of bias assessment showed that these trials failed to provide important information, such as not adequately describing the randomization procedure,<sup>49</sup> testing one-sided while the research question was clearly two-sided,<sup>52</sup> or otherwise as indicated.

## Results of individual trials

The meta-analysis was performed first with the six low risk of bias trials. Later, a sensitivity analysis was performed with all 11 RCTs. The results are summarized in Table 2.

## Intervention characteristics and supervision

Eight trials found significant improvements in CRF,<sup>42,43,45,47–49,51</sup> and one found a significant effect for exercise after correcting for adherence to the intervention.<sup>46</sup> Two found no effect on CRF.<sup>44,50</sup> Three types of exercise interventions were distinguished: aerobic exercise,<sup>43,44,46,49–51,52</sup> resistance exercise, which was not evaluated as stand-alone exercise intervention in the selected trials; and a mix of both.<sup>42,45,47,48</sup> Three trials offered a fully supervised exercise program at a health care location,<sup>42,43,48</sup> eight offered home-based interventions with monitoring methods like a wristband monitor,<sup>50</sup> follow-up calls,<sup>44,45</sup> or logs.<sup>46,47,49,51,52</sup> Intensity of the exercise interventions in METs varied: the exercise programs combining aerobics and resistance exercises<sup>42,47,48</sup> and one aerobic program<sup>44</sup>



**Figure 1** PRISMA 2009 flow diagram.

**Abbreviation:** CRF, cancer-related fatigue.

were of high intensity, and the other aerobic exercise programs were of low intensity.<sup>43,46,49–52</sup> One study did not provide enough information to determine METs;<sup>45</sup> their patients did not keep detailed records of their home exercise.

## Outcome measure characteristics

The timing of measurements varied and for the benefit of clinical relevance, and to enable us to pool similar results, we chose to use the outcomes at post-intervention, not the outcomes at follow-up, as this differed greatly between trials and long-term follow-up might depend on other factors than the intervention alone.

## Synthesis of results (meta-analysis)

In order to establish the overall effect of exercise on CRF, a first meta-analysis was performed for CRF outcomes of the six low risk of bias trials. See Figure 2 for the forest plot. The effects were presented in terms of standardized effect sizes (Cohen's *d*). The results of the random analysis showed that any exercise improves CRF, compared to controls. The pooled estimate of the effect size was large (0.605, 95% CI 0.235–0.975). Heterogeneity (*Q*-value) of this effect was  $Q(2)=15, p=0.010$ . The *I*<sup>2</sup> statistic was 67%, indicating sufficient heterogeneity to use a random model to fit the data.

## Pre-envisioned moderator analyses

Several pre-envisioned moderator analyses were performed: cancer type, intervention type, MET, and adherence.

### Cancer type

Two trials included patients with breast cancer,<sup>43,48</sup> one included prostate cancer,<sup>47</sup> one included gynecological cancers,<sup>45</sup> and the other two trials were categorized as “mixed cancer”.<sup>42,51</sup> The moderator analysis of type of cancer showed no significant heterogeneity between these four cancer types ( $Q(3)=3.7, p=0.295$  (ns)).

### Type of exercise intervention

A moderator analysis of intervention type was performed. The two aerobic exercise trials<sup>43,51</sup> ( $\Delta=1.009$ , CI 0.222–1.797) show a significantly greater effect than the four trials<sup>42,45,47,48</sup> examining a combination of aerobic and resistance exercises ( $\Delta=0.341$ , CI 0.129–0.552). There was no significant heterogeneity between groups ( $Q(1)=2.6, p=0.108$  (ns)).

### MET

Using MET as a moderator to explore the role of intensity of exercise, one study<sup>45</sup> could not be taken into account as we had insufficient data to calculate MET intensity. We performed a meta-regression analysis that showed better results for low MET intensity; however, this finding was not significant.

### Adherence

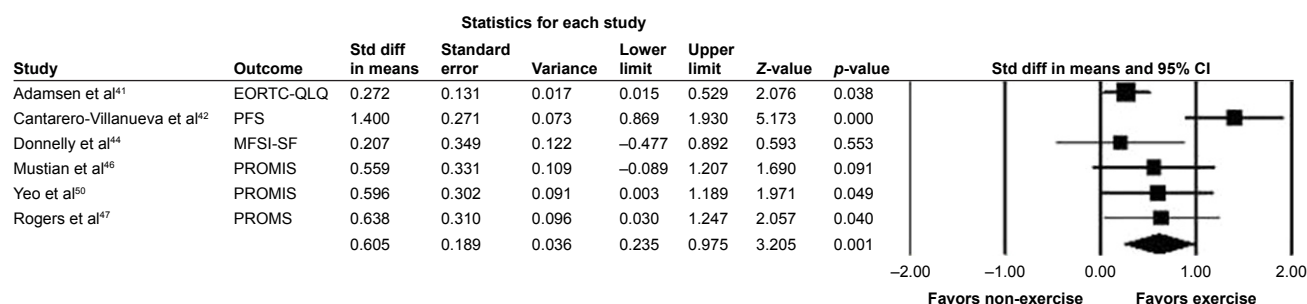
The meta-regression analysis showed a significant effect of adherence on effect size ( $Q(1)=5.925, p=0.01$ ). With low adherence (<56%), the effect size is 0. With high adherence, the effect size becomes large, going up to 0.8 for 100% adherence (see Figure 3).

## Sensitivity analysis

We performed an additional sensitivity analysis, including the five trials with high risk of bias. This did not change the outcome that exercise improves CRF compared to controls. The pooled effect size was diminished slightly, but still medium (0.465, 95% CI 0.217, 0.712). Heterogeneity of this effect was  $Q(10)=26, p\leq 0.01$ . The *I*<sup>2</sup> statistic was 63%.

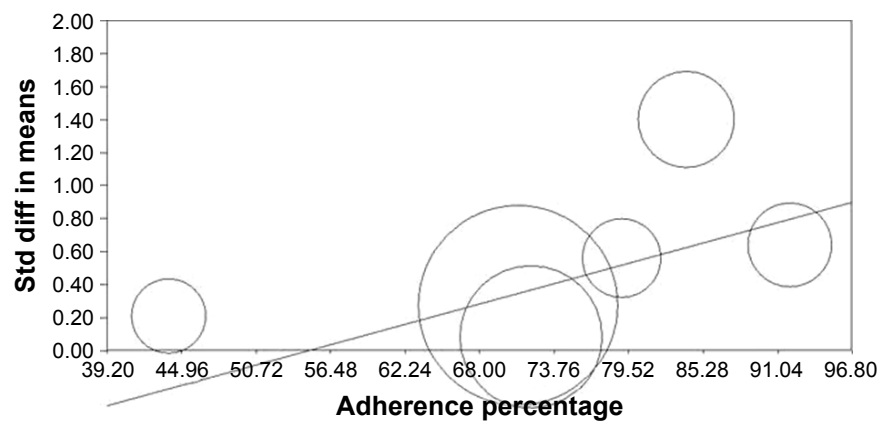
## Publication bias

A test for publication bias was performed. The fail-safe *N* showed that 42 additional trials should be added to the analysis before the cumulative effect would become statistically non-significant. Given the fact that only 11 trials could be identified that specifically looked at the effect of exercise



**Figure 2** Forest plot of effect on CRF.

**Abbreviation:** CRF, cancer-related fatigue; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PFS, Piper Fatigue Scale; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PROMIS, Patient-Reported Outcomes Measurement Information System; Std diff, standard difference.



**Figure 3** Meta-regression plot of adherence.

**Abbreviation:** Std diff in means, standard difference in means.

on CRF as a primary outcome compared to a non-exercise control group, and only six of those addressed risk of bias sufficiently, it is unlikely that 42 trials were missed. This indicates that no significant publication bias seems to be the case and the reported effect is valid.

## Discussion

### Summary of evidence

This study provides us with the possibility to estimate the effect of exercise, the surplus value of aerobic exercise, and the importance of adherence in cancer survivors who may or may not still be under treatment, but not in a terminal phase.

We found a clear improvement in CRF as a result of exercise interventions, with a large effect size. Aerobic exercises showed better improvement than a combination of aerobic and resistance exercises. Adherence to the intervention is important: high adherence resulted in a large effect, whereas low or moderate adherence yielded small effects. These effects were the same for all cancer types in the study. The indication that low-intensity exercise might be more effective than high-intensity exercise was not significant in a meta-regression.

### Comparison with other studies

This finding is in sync with the National Comprehensive Cancer Network guidelines on treating CRF,<sup>8</sup> which note that exercise is one of the most effective non-pharmacological treatments for CRF. Embedding of exercise programs in current oncologic rehabilitation guidelines is, however, still not standard. Our results clearly indicate that this should be considered.

Other studies report that CRF is highly associated with pain, insomnia, and psychological distress factors like

depression;<sup>52</sup> similar findings have been reported in CFS.<sup>53</sup> These symptoms may arise through a common pathway, as previous research on inflammation and CRF suggests that tumours and the treatments used to treat them activate proinflammatory cytokines, leading to CRF and other symptoms.<sup>54</sup> Similar suggestions have been made for CFS,<sup>55</sup> as difficulty in following through with exercise has also been found in chronic fatigue patients. It has been suggested that exercise does improve fatigue; however, too much exercise might have adverse effects resulting in low adherence to the exercise protocol.<sup>56</sup> It might be somewhat surprising that low-intensity exercise is more effective than high-intensity exercise. However, this finding is in sync with findings in CFS that overriding leads to more post-exercise malaise than pacing yourself and grading activities.<sup>57</sup> This may be an indication that for handling fatigue, low exercise may be enough and that strenuous exercise is not needed to get good results. This finding warrants further research in treatment modes for fatigue in general.

Another important factor to address is adherence. Pathophysiological or mental barriers, or fatigue by itself could hinder patients from becoming (more) active.<sup>58</sup> Our results show high adherence rates leading to better CRF outcomes. Information provision by health care professionals might ensure adherence; other methods are sufficient professional support, tailored advice, clear individual goals, and including the support system.<sup>59,60</sup>

### Implications

The finding that exercise leads to lower levels of CRF underlines the importance of focussing upon physical training in the care of cancer patients. Exercise programs can have a direct effect on CRF by increasing muscle strength and physical fitness to counteract physical deconditioning.

However, exercise can also have an indirect effect on CRF. CRF is highly associated with physical distress factors like pain and insomnia and psychological distress factors like depression and anxiety on CRF. Similar findings have been reported in CFS.<sup>54</sup> It may be that these symptoms arise through a common pathway as previous research on inflammation and CRF suggests that tumours and the treatments used to treat them activate proinflammatory cytokines, leading to CRF and other symptoms.<sup>55</sup> Similar suggestions have been made for CFS, which has as characteristic that, apart from the fatigue, other symptoms should be present, such as memory or concentration problems, muscle pain, joint pain, headache, sleeping problems, and malaise after exercise.<sup>56,61</sup> Exercise can reduce CRF indirectly by its beneficial effects on mood, immune functioning, or sleep.<sup>62</sup> In that sense, working mechanisms of exercise might have aspects similar to those in CFS. This should be a topic of further research.

The findings in this review may therefore be relevant not only for cancer survivors, but also, more in general, for people suffering from chronic fatigue, as it provides clinicians with concrete tools to enhance the possibility for adherence to exercise protocols. This should be a topic for future research.

## Limitations

The main limitation of this study is that the number of trials was small and that only six were of low risk of bias. The randomization procedures are not addressed sufficiently to evaluate or reproduce, and allocation concealment/blinding was sometimes not mentioned at all. Moreover, in many trials, active treatment status was not addressed properly. Trials included in the review have different timeframes: some were during active treatment and others were after primary treatment or a combination of the two. There is a need for RCTs of better quality in this field. However, a sensitivity analysis including the high risk of bias trials showed that the effect of exercise versus non-exercise still remained positive.

Furthermore, most patients in our sample were “early” cancer survivors as many were still undergoing treatment during the RCT. It is unclear if our recommendations for exercise are valid for long-term cancer survivors. Research with long-term survivors and longer follow-up is clearly needed.

Furthermore, trials with widely divergent cancer types are included. Although this enables us to estimate the effect as a general intervention in all types of cancer, more trials for specific cancer types would be needed to estimate the effect in specific cancer types and their specific treatments.

## Strengths

Comparison with a previous meta-analysis shows several methodological differences. We only included RCTs with non-exercise intervention controls; the ones that studied CRF as a primary outcome and patients receiving palliative care were not included. In contrast to the study of Cramp and Byron-Daniel,<sup>27</sup> we were able to conduct sub-analyses for type and intensity of exercise, which enabled us to find clear cues for exercise regimens.

## Conclusion

Based on this review, we conclude that exercise effectively improves CRF, especially with high adherence rates. The clinical recommendation is to improve exercise in cancer survivors with an exercise intervention that includes aerobic exercise and with high focus on facilitating adherence. Research implications are that more research of sufficient quality is needed. Future research should preferably assess CRF as a primary outcome.

## Acknowledgment

Mw drs L Ossewaarde was involved in an early stage in setting up the database search. No other contributions were made.

## Disclosure

A poster with preliminary results without pooled estimate was previously presented at the Dutch psychiatry association (NVvP) congress on April 10th 2014. The authors report no conflicts of interest in this work.

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## Supplementary material

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable, background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusion and implications of key findings; systematic review registration number.	3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual trials	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, $I^2$ ) for each meta-analysis.	9
Risk of bias across trials	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual trials	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	14
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	13

Figure S1 (Continued)

Section/topic	#	Checklist item	Reported on page #
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	16
Conclusion	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	2

**Figure S1** PRISMA checklist.

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