Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis
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CRD summary
The authors concluded that exercise reduced cancer-related fatigue among patients both undergoing and following cancer treatment. Exercise had a palliative effect in patients undergoing treatment and a restorative effect following treatment. Limitations of the included studies and the review reporting mean that the reliability of the results is uncertain.

Authors' objectives
To determine the extent to which the effect of exercise on cancer-related fatigue varied across the time course of treatment and recovery.

Searching
Published studies were identified through searches of PubMed, PsycINFO and Web of Science to August 2011. Brief search terms were reported. Reference lists of retrieved articles were searched manually. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared the effects of exercise training on cancer-related fatigue, with a non-exercise comparison, in patients undergoing or having completed treatment were eligible for inclusion. The cancer-related fatigue outcome had to be measured before and during and/or after exercise training. Studies were excluded if they: compared exercise only with an active therapy; examined the effect of acute exercise on cancer-related fatigue; or used education or promotion interventions aimed at increasing physical activity but which did not result in an increase in physical activity.

Summary details of the included studies were given separately for those that measured the exercise outcome during or after the end of treatment. For participants undergoing treatment, mean age was 52 years, 68% were women, mean body mass index (BMI) was 26.8kg/m² and aerobic capacity (VO2max) was 21.1 mL/kg/min. For participants after treatment mean age was 55 years, 87% were women, mean BMI was 27.2kg/m² and VO2max was 24.2 mL/kg/min. The most common cancer sites studied were blood, prostate and breast (during treatment) and breast (after treatment). Treatments were chemotherapy, radiotherapy and hormone therapy. The baseline fatigue T-score was 50.3 during treatment and 41.4 after treatment. Post-treatment measures were made at a mean of 16.3 months post treatment.

Exercise interventions were either supervised or done at home and averaged 2.9 to 3.4 times per week. Sessions lasted between an average of 42.3 and 49.6 minutes. Programmes lasted a mean of 11.7 to 12.6 weeks. Retention rates ranged from 59% to 100% in the intervention group and 50% to 100% in the control group. Mean adherence rate ranged from 78.5% to 87.4%. Outcomes were measured using 14 different scales of tiredness/fatigue.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The methodological quality of included studies was assessed using a 15-item scale of randomisation, sample selection, quality of outcome measures and statistical analysis by Detsky et al.

It was unclear how many reviewers performed the quality assessment but it was more than one as concordance rates were reported.

Data extraction
Data were extracted to calculate effect sizes by subtracting mean change in the control arm from mean change in the exercise arm, divided by the pooled standard deviation of pre-intervention scores. These effect sizes were adjusted
using Hedges’ small-sample bias correction. Where more than one effect was reported within one trial, these were averaged so that each trial contributed only one effect to the analysis. Where precise means were not reported, effect sizes were estimated from t-tests, exact p-values or figures. Where precise standard deviations were not reported, the standard deviation was drawn from published norms or the largest other study that used the same measure.

It was unclear how many authors extracted these data but it was stated that this was done independently and that discrepancies were resolved by consensus.

Methods of synthesis
Random effects meta-analysis was used to estimate mean effect sizes (d) with 95% confidence intervals (CI). A decision to stratify the results according to timing of intervention with respect to treatment was made following inspection of the pooled results.

Statistical heterogeneity and consistency were evaluated with the Q statistic and the I² statistic. Heterogeneity was deemed present where the sampling error accounted for less than 75% of the observed variance. Publication bias was assessed by inspection of funnel plots and quantified with rank correlation (Begg’s test) and regression (Egger test).

Sensitivity analyses investigated the effect of study quality by omitting studies in the lowest quartile of quality and the effect of exercise adherence by omitting studies with less than 80% adherence rates.

Moderating variables were investigated for each model. The Johnson-Neyman procedure was conducted to identify the critical point in significant interactions of categorical and continuous variables to define significance regions.

Results of the review
Seventy studies (4,881 patients) were included in the review. Mean study quality ranged from 10.9 to 11.1 points (maximum 15).

Both during treatment (43 studies, 3,235 patients) and after treatment (27 studies, 1,646 patients) exercise was associated with an improvement in fatigue (d=0.32, 95% CI 0.21 to 0.43 and d=0.38, 95% CI 0.21 to 0.54). There was moderate heterogeneity at both time points (I²=48.4% and 60.7%).

Univariate moderator analysis showed that for the during treatment model, adherence by baseline fatigue score interaction was related to fatigue outcomes. For the post-treatment model, moderating variables were duration post-treatment, length of exercise programme and type of comparison group. Larger effects were found for studies that used a wait-list comparison (d=0.66, 95% CI 0.42 to 0.90) compared with the effect for other comparison types (d=0.19, 95% CI 0.00 to 0.37).

Funnel plot asymmetry suggested potential small-study bias for all models. Begg and Egger tests both showed significant evidence of publication bias for the overall model (p<0.001), the during treatment model (p=0.003 and p=0.004) and the post-treatment model (p=0.025 and p=0.006).

Sensitivity analyses that investigated the effects of study quality and adherence reinforced the results found in the primary meta-analysis.

Authors’ conclusions
Exercise reduced cancer-related fatigue among patients both while undergoing and following cancer treatment. Exercise had a palliative effect in patients undergoing treatment and a restorative effect following treatment.

CRD commentary
The review question was clear. Most inclusion criteria were appropriate, although the definition of eligible control interventions was not clear. The search covered several sources and as no language restriction was applied in the search, the risk of language bias was minimised. No attempts were made to locate unpublished data and there was evidence of publication bias in the results. It was not clear what steps were taken to reduce error and bias during the review process. No description of individual studies was given and the generalisability of the results was unclear.

Study quality was assessed. Omitting low quality studies did not affect the results of the review. Combining studies in a
meta-analysis appeared appropriate although sources of heterogeneity were not fully explored. The authors noted that reporting, design and outcome measurements in the included studies were poor.

The authors’ conclusions reflect the evidence presented; the limited quality of the included studies and the review reporting mean that the reliability of the results is uncertain.

Implications of the review for practice and research

**Practice:** The authors stated that the review provided evidence to support prescribing exercise during and following cancer treatment for cancer-related fatigue.

**Research:** The authors stated that future trials were required to: better characterise the exercise intervention (frequency, intensity, session duration, programme length, mode); examine the effects of exercise on neurobiologic and psychological measures of cancer-related fatigue; examine the relationships of exercise with cancer-related fatigue and mood; and investigate mechanisms and interactions between exercise training protocols, psychosocial interventions and pharmacologic treatments in cancer-related fatigue. Guidelines should be followed to improve the reporting of future trials.

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