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Exercise Effects on Cancer Survivors

Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression

KEY WORDS

Exercise therapy
Cancer
Fatigue
Mobility
Physical therapy (specialty)

ABSTRACT

Question: Is there a dose-response effect of exercise on inflammation, fatigue and activity in cancer survivors? Design: Systematic review with meta-regression analysis of randomised trials. Participants: Adults diagnosed with cancer, regardless of specific diagnosis or treatment. Intervention: Exercise interventions including aerobic and/or resistance as a key component. Outcome measures: The primary outcome measures were markers ofinflammation (including C-reactive protein and interleukins) and various measures offatigue. The secondary outcomes were: measures of activity, as defined by the World Health Organization's International Classification of Functioning, Disability and Health, including activities of daily living and measures offunctional mobility (eg, 6-minute walk test, timed sit-to-stand and stair-climb tests). Risk of bias was evaluated using the PEDro scale, and overall quality of evidence was assessed using the Grades of Research, Assessment, Development and Evaluation (GRADE) approach. Results: Forty-two trials involving 3816 participants were included. There was very low-quality to moderate-quality evidence that exercise results in significant reductions in fatigue (SMD 0.32, 95% CI 0.13 to 0.52) and increased walking endurance (SMD 0.77, 95% CI 0.26 to 1.28). A significant negative association was found between aerobic exercise intensity and fatigue reduction. A peak effect was found for moderate-intensity aerobic exercise for improving walking endurance. No dose-response relationship was found between exercise and markers ofinflammation or exercise duration and outcomes. Rates of adherence were typically high and few adverse events were reported. Conclusions: Exercise is safe, reduces fatigue and increases endurance in cancer survivors. The results support the recommendation of prescribing moderate-intensity aerobic exercise to reduce fatigue and improve activity in people with cancer.

Introduction

Cancer is a leading cause of burden of disease globally [1] and is responsible for approximately three in 10 deaths. [2] However, with improved screening and advancing treatment options, survival rates are improving. As a result, cancer is now recognised as a chronic disease. [3,4] While treatment may improve survival, the side-effects on physical and psychological function often reduce quality oflife. There is an increasing need for rehabilitation to address these issues.

Exercise is an effective treatment for many chronic diseases. Recent systematic reviews have demonstrated that exercise used as part of cancer care reduces cancer-related fatigue and improves cardiovascular function, strength and quality oflife. [5–9] There is also emerging evidence that exercise can reduce recurrence and mortality in some cancer populations. [10–16]

Despite these benefits of exercise, there is a lack of evidence on the safety and efficacy of exercise in relation to dose. [6,17] The ideal mode and intensity of exercise for people with cancer is unclear, and exercise guidelines are based largely on expert clinical opinion and adaptations of guidelines for healthy people. Current recommendations suggest that cancer survivors complete at least 150 minutes of moderate-intensity physical activity per week. [6] However, these recommendations may not recognise the specific health needs of cancer survivors. Recent reviews have reported a low number of adverse events in relation to exercise trials, [6,7,18–20] suggesting that exercise is generally safe for cancer survivors. However, in these reviews, there has been variable reporting of the dose of prescribed exercise.

The association between inflammation and cancer is well documented. [21–23] Chronic inflammation plays a role in the pathogenesis ofinsulin resistance and tumour growth, and has been linked to cancer risk and mortality. [23–26] Inflammatory cytokines have also been implicated in the development of cancer-related fatigue. [27–29] Exercise plays a role in mediating the effects of chronic inflammation, reducing inflammatory

markers such as C-reactive protein (CRP), tumour necrosis factor-alpha, and various types ofinterleukin (IL), including IL6, in people with and without cancer. [30–32] Furthermore, the protective effects of exercise have been attributed to the creation of an anti-inflammatory environment through increasing anti-inflammatory cytokines such as ILRa and IL10 in healthy people. [26,33,34] The relationship between exercise dose and inflammatory markers in people with cancer needs to be considered because strenuous exercise can induce pro-inflammatory cytokines in healthy people. [35] Therefore, it is important to know how much exercise can be safely tolerated in this immune-compromised population of people with cancer.

Cancer-related fatigue affects 80 to 100% of patients. [36] Fatigue is a complex multi-dimensional construct related to reduced physical function and reduced health-related quality oflife. [27,37] Recent reviews have concluded that exercise reduces cancer-related fatigue, [19,38–40] but the optimal dose to achieve this has not been established. It has been suggested that patients undergoing treatment may need to exercise at a lower intensity or for a shorter duration than those who have completed primary treatment. [41] However, others have suggested that higher-intensity exercise may be better. [42,43] For example, Brown et al [40] found that moderate-intensity resistance exercise may be more effective than low-intensity exercise for reducing cancer-related fatigue. The most effective duration and intensity of exercise remain unclear.

Therefore, the research questions that we sought to answer with this systematic review were:

1. Is there a dose-response effect of exercise on inflammation and fatigue in adult cancer survivors?
2. Is there a dose-response effect of exercise for improving functional activity in this population?

Method

This systematic review was reported in accordance with PRISMA guidelines. [44,45]

Search strategy

The Medline, EMBASE and CINAHL databases were searched from the earliest records to April 2015. PubMed was also searched from 2010 for more recent publications. The search strategy was based around synonyms and MeSH subject headings of the key concepts of exercise and cancer combined with the primary outcomes of fatigue and inflammation . These terms were combined with relevant filters to identify randomised, controlled trials. [46] The detailed search strategy is presented in Appendix 1 (see eAddenda). The database searches were supplemented by citation tracking ofincluded articles using Google Scholar and checking the reference lists ofincluded studies.

Eligibility criteria

The eligibility of papers identified by the searches was assessed by two reviewers who independently considered information from the titles and abstracts against predetermined eligibility criteria (Box 1). Disagreements were resolved by discussion, with a third reviewer consulted when necessary. Where eligibility was unclear from the title and abstract, the full-text version was obtained and examined by both reviewers.

To be included, studies had to be randomised, controlled trials that: examined the effect of exercise in adults who had been diagnosed with cancer, reported at least one of the primary outcomes (fatigue or inflammation) and were published in English. The exercise intervention had to meet the definition 'physical activity that is planned, structured and repetitive and has a final or intermediate objective of the improvement or maintenance of physical fitness' [47] with aerobic or resistance training as a key component, because these modes of exercise are expected to result in significant physiological changes that may affect inflammation and fatigue, and are quantifiable. Furthermore, the intensity (eg, percentage of maximum heart rate, repetition maximum, etc) or duration of completed exercise needed to be reported. For studies using a combined exercise intervention (ie, aerobic and resistance training), the intensity or total duration for both components must have been specified. Studies were excluded if only a single bout of exercise was used or ifit was combined with a co-intervention such as diet or education.

Box 1. Inclusion criteria.

Design
- Randomised trial
- Published in English

Participants
- Adults with cancer

Intervention
- Exercise intervention with aerobic or resistance exercise as a key component
- Sufficient reporting of dose (ie, the intensity or duration must be reported). For combined modalities, the intensity or total duration for both components must be specified.

Outcome measures
- Must report at least one measure offatigue or inflammation

Comparisons
- Exercise versus control
- Exercise plus usual care versus usual care only
- One exercise dose compared to another (eg, high versus low intensity)

Quality assessment

The studies were assessed by two reviewers, who independently rated the 11 criteria on the PEDro scale as yes or no. One criterion relates to external validity; the remaining 10 criteria contribute 1 point each, if met, to give a score out of 10. The PEDro score is a valid measure ofinternal validity and completeness of reporting. It has undergone Rasch analysis and has moderate levels ofinter-rater reliability (ICC 0.68, 95% CI 0.57 to 0.76). [48,49] Trials scoring < 6 were deemed to be oflow quality. [50]

Synthesis of results

A standardised mean difference (SMD) was calculated for each outcome from post-intervention means and SDs to compare the control and treatment groups and to account for different scales of measurement between studies. Where only change scores were reported, the post-intervention mean was estimated in reference to the baseline mean and the SD based on baseline data. If only a range was given, the SD was calculated. [51] Authors were contacted if there was insufficient published data for analysis. Data from outcome measures were classified into three categories to address the primary and secondary aims of the review: inflammation, fatigue and activity. Activity was defined according to the World Health Organization International Classification of Functioning as 'the execution of a task or action by an individual', which included measures of activities of daily living and functional mobility. [52]

Meta-analysis was completed using the R statistics package 'metafor' [53] to provide evidence of the pooled effect size of the exercise intervention. Data were combined if clinically homogenous for more than two trials. Random effects models and a restricted maximum likelihood estimator for the random effect variance parameter were used. [54] A meta-analysis of the ratio of sample variances [55] provided evidence of unequal variances

between the control and treatment groups. Consequently, Glass' D[56] was employed where the difference in means was standardised using the control-group sample SD. Subgroup analyses were completed to determine the effect of tumour stream, treatment status and exercise modality. The Grades of Research, Assessment, Development and Evaluation (GRADE) approach was applied to each meta-analysis to evaluate the evidence across trials.[57] The approach involved downgrading the evaluation based on these predetermined criteria: the PEDro score was < 6 for the majority of trials used in the meta-analysis; there was greater than low levels of statistical heterogeneity between trials (I^2 > 25%); there were large confidence intervals (ie, > 0.8 SMD); and if there was asymmetry of a funnel plot when more than 10 trials were included in the meta-analysis, demonstrating evidence of publication bias.

Meta-regression analysis assessed the pooled dose-response relationship between exercise dose and outcomes. To standardise dose for analysis, duration of exercise per week and intensity were evaluated separately, with intensity quantified as maximum oxygen consumption (VO_{2max}) or a percentage of one repetition maximum (1RM). Meta-regression models were fitted to both factor and numeric variables to obtain subgroup estimates (for the factor variables) and estimated increases in effect sizes for one-unit changes of numeric covariates. Analysing exercise dose by volume in metabolic equivalents (METs)/minute/week was considered; however, there were inadequate data. Exercise intensity was categorised as low (< 40% VO_{2max}, < 60% 1RM), moderate (40 to 60% VO_{2max}, 60 to 80% 1RM) or vigorous/high (> 60% VO_{2max}, > 80% 1RM).[58,59] Where outcome data could not be included in the meta-analysis or meta-regression, results were summarised descriptively.

Results

Study selection

The electronic database search resulted in a yield of 874 articles, which was reduced to 677 after the duplicates were removed. Additional articles were identified through citation tracking (n = 2) and reference list scanning (n = 4). Eighty-two articles were obtained in full text and further assessment reduced the yield to 49 articles. There was good inter-rater agreement about eligibility based on title and abstract (k = 0.695) and full texts (k = 0.691). Fourteen articles reported data from seven trials; therefore, 42 trials were included for review (Figure 1).

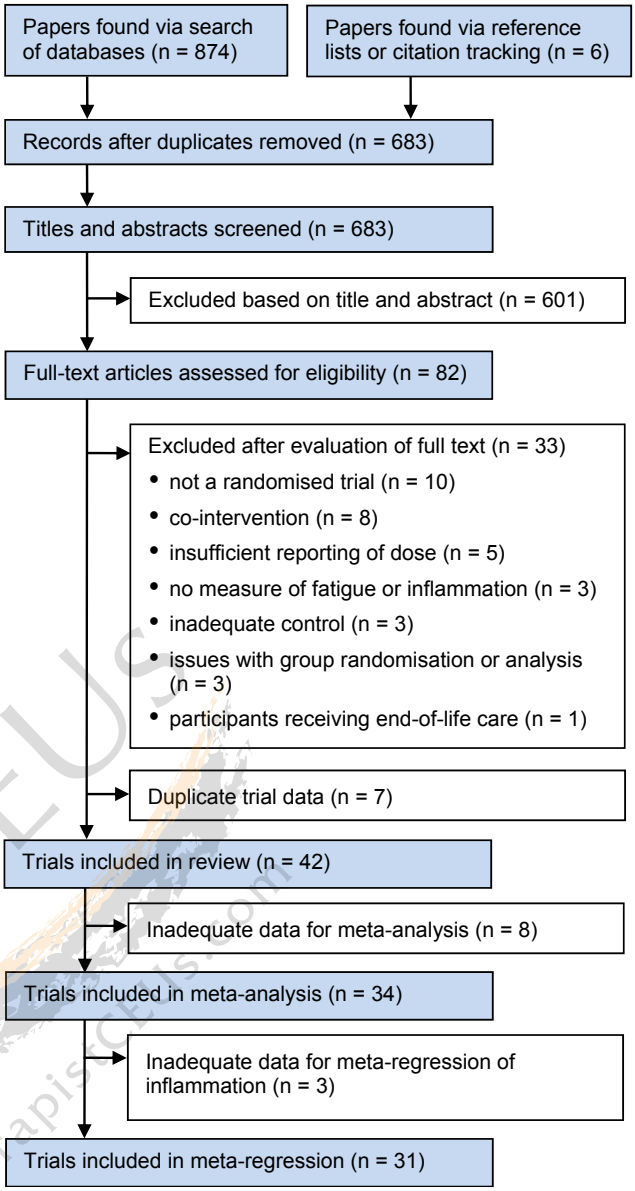

Figure 1. Flow of trials through the review.

Quality

The mean score of the included trials was 5.7 (SD 1.4) on the PEDro scale (Table 1). Inter-rater agreement on quality criteria was very good (k = 0.848). Three trials[60–62] scored 8 on the PEDro scale, which was the highest possible score given the nature of the intervention that was studied, where it would be unfeasible to blind clinicians or participants. Less than half of the trials had blinding of assessment and concealed allocation.

Study characteristics

Participants

Data from 3816 participants were included. The majority of participants were female (70%), with a mean age of 55 years (SD 9) and a mean body mass index of 27 kg/m^2. Solid tumours were investigated in 34 trials (81%), haematological cancers were investigated in four trials,[63–66] with an additional four trials investigating a combination of solid and haematological cancers.[67–70] Breast cancer was the most frequently reported (27 trials, 64%),[30,60–62,68–94] followed by prostate cancer (14 trials, 24%).[85,88,90,92,95–104] Interventions were commonly completed during the treatment phase (30 trials, 71%), with 12 trials completed in the post-treatment phase (Table 2).

Intervention

Trials included aerobic exercise (19 trials),[30,60,61,63,68,70,72,78,80–84,86,87,89,91,92,101,104–106] resistance exercise (five trials),[68,88,93,98,99,102,107] a combination of aerobic and resistance exercise (14 trials)[62,64–67,69,71,73,74,79,85,90,95–97,100] and four trials[75–77,94,103] compared one exercise modality to another (eg, aerobic versus resistance exercise). The interventions were usually completed in an outpatient rehabilitation or fitness centre (20 trials),[30,60,61,68,69,71–80,82,95,97–103,105] at home (13 trials)[64,70,81,84–87,90–92,94,96,104,106] or a combination of home and centre-based exercise (five trials).[62,83,88,89,93] The remaining four trials were completed while participants were inpatients.[63,65–67] Of the 23 trials that reported using supervision, 11 were supervised by an exercise specialist,[30,60,62,66,71,75,85,90,95,97,98,100,103,105] six by physiotherapists,[68,69,74,80,88,89,96] four by a fitness trainer,[70,83,93,99,102] one by a kinesiotherapist and physician,[101] and one by a trained research assistant.[63]

The duration of the intervention ranged from 15 days[65] to 1 year,[89,93] with most trials of at least 12 weeks duration. The exercise sessions were 10 to 90 minutes long, and completed two to three times per week. The average amount of exercise completed each week across the trials was 104 minutes. The intensity of the interventions varied from moderate, between 60% of maximal heart rate[86,91] for aerobic exercise and 60% of 1RM for

Table 1
PEDro scores of the included studies.

Study	Random allocation	Allocation concealed	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor binding	< 15% dropout	Intention to treat	Between-group comparisons reported	Point measures and variability reported	Total (0 to 10)
Battaglini 2008 [71]	Y	N	N	N	N	N	N	N	Y	Y	3
Baumann 2010 [67]	Y	N	Y	N	N	N	N	Y	Y	Y	5
Broderick 2013 [68 a]	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Guinan 2013 [80]	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Buffart 2014 [95 a]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Galvao 2010 [100]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Burnham 2002 [72]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Campbell 2005 [73]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Cantarero-Villanueva 2013 [74]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Chang 2008 [63]	Y	N	N	Y	N	N	Y	Y	N	Y	5
Cheville 2013 [96]	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Christensen 2014 [107]	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Coleman 2012 [64]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Cormie 2013 [98]	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Cormie 2015 [97]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Courneya 2004 [99 a]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Segal 2003 [102]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Courneya 2007 [76 a]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Courneya 2007 [77]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Courneya 2009 [105]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Courneya 2013 [75]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Daley 2007 [78]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Fairey 2005 [30 a]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Fairey 2005 [60]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Gomez 2011 [79]	Y	N	Y	N	N	N	N	N	Y	Y	4
Headley 2004 [81]	Y	N	Y	N	N	N	N	N	Y	Y	4
Hornsby 2014 [61 a]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Jones 2013 [82]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Jones 2013 [83]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Mock 2005 [84]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Monga 2007 [101]	Y	N	N	N	N	N	N	N	Y	Y	3
Mustian 2009 [85 a]	Y	Y	N	N	N	N	Y	Y	Y	Y	6
Sprod 2010 [90]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Mutrie 2007 [62]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Naraphong 2015 [86]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Oechsle 2014 [65]	Y	N	Y	N	N	N	Y	N	Y	N	4
Oldervoll 2011 [69]	Y	N	Y	N	N	N	N	Y	Y	Y	5
Payne 2008 [87]	Y	N	N	N	N	N	Y	N	Y	N	3
Rief 2014 [88]	Y	Y	N	N	N	N	N	N	Y	Y	4
Saarto 2012 [89]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Segal 2009 [103]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Thorsen 2005 [70]	Y	Y	N	N	N	N	N	Y	Y	Y	5
Wang 2011 [91]	Y	N	N	N	N	N	Y	N	Y	Y	4
Wenzel 2013 [92]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Winters-Stone 2012 [93]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Windsor 2004 [104]	Y	Y	Y	N	N	N	Y	N	Y	Y	5
Wiskemann 2011 [66]	Y	N	Y	N	N	N	N	N	Y	Y	4
Yeo 2012 [106]	Y	Y	Y	N	N	N	Y	N	Y	N	5
Yuen 2007 [94]	Y	N	Y	N	N	N	N	N	N	Y	3

N = no, Y = yes
[a] reports data on some or all of the same participants as the study below.

resistance exercise, [65] to high intensity, 100% of peak workload as interval training for aerobic exercise [61,82,105] and 85% of 1RM for resistance exercise [97] (Table 3). No trials implemented low-intensity exercise.

Adverse events and adherence

The exercise interventions appeared to be safe and well tolerated. Of the 22 trials [9,55,60,61,65,67–69,72–75,77–79,84,88,91,96–98,103,105] reporting an adverse event, 19 of the 1888 exercise participants

Table 2
Summary of trial characteristics.

Study	N	Gender (% F)	Age (y) mean (SD)	Tumour stream	Time period relative to treatment and type(s) of therapy	Outcome measure		
						Inflammation	Fatigue	Activity
Battaglini 2008 [71]	20	100	57 (17)	Breast	On: chemotherapy ± surgery ± radiotherapy		• Revised PFS	
Baumann 2010 [67]	64	45	45 (12)	Lymphoma, leukaemia, solid tumour [b]	On: HSCT 100%		• EORTC QLQ-C30	
Broderick 2013 [68 a]	43	86	51 (9)	Breast, colon, lymphoma, oesophageal, gynaecological	Post: time post-chemotherapy 4 (S SD 1) mth; surgery 93%, chemotherapy 100%, radiotherapy 72%		• FACIT-F	
Guinan 2013 [80]	26	100	48 (9)	Breast	Post: time post-chemotherapy 4 (SD 1) mth; chemotherapy 100% radiotherapy 32.4%, hormone therapy 76.9%, surgery 100%	• CRP		
Buffart 2014 [95 a] Galvao 2010 [100]	57	0	70 (3)	Prostate	On: ADT + previous radiotherapy 39%, chemotherapy 25%	• CRP	• EORTC QLQ-C30	• 400-m walk • 6-m walk • Timed STS
Burnham 2002 [72]	18	83	54 (9)	Breast, colon	Post: average 10 mth; surgery 61%, chemotherapy 78%, radiotherapy 56%		• LASA	
Campbell 2005 [73]	22	100	48 (8)	Breast	On: chemotherapy 73% radiotherapy 73%, combination 45%		• Revised PFS	• 12-MWT
Cantarero-Villanueva 2013 [74]	61	100	48 (15)	Breast	Post: surgery 100% chemotherapy 97%, radiotherapy 90%, hormone 100%		• PFS	• Timed STS x 10
Chang 2008 [63]	22	45	51 (55)	Acute myelogenous leukaemia	On: chemotherapy 100%		• BFI	• 12-MWT
Cheville 2013 [96]	66	47	65 (18)	Lung, colon	On: chemotherapy ± radiotherapy		• FACT-F	• AM-PAC SF
Christensen 2014 [107]	30	0	35 (11)	Germ cell	On: average 158 days, surgery 100%, chemotherapy 100%	• IL: 1b, 2, 6, 8, 10, 12	• EORTC QLQ-C30	
Coleman 2012 [64]	187	42	56 (4)	Multiple myeloma	On: chemotherapy, hormone therapy, stem cell treatment		• FACT-F	• 6-MWT
Cormie 2013 [98]	20	0	72 (13)	Prostate	Post: AST 100%, radiation 55%, surgery 20%		• MFI	• 400-m walk • 6-m walk
Cormie 2015 [97]	63	0	68 (17)	Prostate	On: ADT 100%, previous radiotherapy 5%, chemotherapy 2%	• CRP	• FACIT-F	• Timed STS • Timed stair climb • 6-m walk
Courneya 2004 [99 a] Segal 2003 [102]	155	0	68 (4)	Prostate	On: ADT 100%, previous surgery + radiotherapy		• FACT-F	
Courneya 2007 [76 a] Courneya 2007 [77]	242	100	49 (15)	Breast	On: chemotherapy 100% ± previous surgery		• FACT-An	
Courneya 2009 [105]	120	42	53 (18)	Lymphoma	On: chemotherapy 44%		• FACT-An	
Courneya 2013 [75]	301	100	50 (9)	Breast	On: chemotherapy		• TOI Fatigue	
Daley 2007 [78]	108	100	51 (9)	Breast	Post: average 7.5 mth: chemotherapy 74%, radiotherapy 79%, hormone therapy 73%, surgery 100%		• Revised PFS	
Fairey 2005 [30 a] Fairey 2005 [60]	52	100	59 (6)	Breast	Post: average 14 (SD 6) mth; surgery 100%, radiotherapy 71%, chemotherapy 40%, hormone therapy 46%	• IL: 1a, 4, 6, 10 • TNF a		
Gomez 2011 [79]	16	100	49 (6)	Breast	Post: average 36 (SD 12) mth; chemotherapy 100%, surgery 100%	• IL: 1a, 1b, 1Ra, 2, 2Ra, 3, 4, 6 to 10, 12, 13, 15 to 18 • TNF a		
Headley 2004 [81]	32	100	51 (21)	Breast	On: chemotherapy 100%		• FACIT-F	
Hornsby 2014 [61 a] Jones 2013 [82]	20	100	49 (43)	Breast	On: chemotherapy 100%		• FACIT-F	
Jones 2013 [83]	75	100	56 (9)	Breast	Post: no therapy 8% radiotherapy 63%, chemotherapy 52%	• CRP • IL6 • TNF a		
Mock 2005 [84]	119	100	52 (9)	Breast	On: chemotherapy 42% radiotherapy 58%		• PFS	• 12-MWT

Table 2 (Continued)

Study	N	Gender (% F)	Age (y) mean (SD)	Tumour stream	Time period relative to treatment and type(s) of therapy	Outcome measure		
						Inflammation	Fatigue	Activity
Monga 2007 [101]	21	0	69 (12)	Prostate	On: radiotherapy 100%		• Revised PFS	
Mustian 2009 [85] [a] Sprod 2010 [90]	38	71	60 (12)	Prostate, breast	On: radiotherapy 100%, current hormone 8%, previous chemotherapy 50%, surgery 84%		• BFI • FACIT-F	• 6-MWT
Mutrie 2007 [62]	203	100	52 (10)	Breast	On: surgery 100% chemotherapy only 8%, radiotherapy only 28%, combined 64%		• FACT-F	• 12-MWT
Naraphong 2015 [86]	23	100	47 (7)	Breast	On: chemotherapy 100%		• Revised PFS	
Oechsle 2014 [65]	48	29	52 (17)	Acute myeloid leukaemia, non-Hodgkin's lymphoma, germ cell tumour, multiple myeloma	On: chemotherapy + HSCT 100%		• MFIS	
Oldervoll 2011 [69]	231	62	62 (4)	Gastrointestinal, breast, lung, urological, gynaecological, haematological	On: chemotherapy 55%, radiotherapy 6%, hormone 19%, targeted therapies 4%		• Fatigue questionnaire	• Timed STS • SWT
Payne 2008 [87]	20	100	65 (6)	Breast	On: hormone 100%	• IL6	• Revised PFS	
Rief 2014 [88]	60	45	63 (29)	Lung, breast, prostate, melanoma, kidney, other	On: radiotherapy 100%, hormone 43%, immunotherapy 22%, chemotherapy 75%		• EORTC QLQ-FA13	
Saarto 2012 [89]	500	100	52 (1)	Breast	Post: chemotherapy 100% radiotherapy 78%, endocrine 84%, hormone 84%		• FACIT-F	• 2-km walk
Segal 2009 [103]	121	0	66 (7)	Prostate	On: radiotherapy 100%, ADT 61%		• FACT-F	
Thorsen 2005 [70]	139	54	39 (1)	Breast, gynaecological, lymphoma, testicular	Post: average 28 d; surgery 82%, chemotherapy 100%, radiotherapy 57%		• EORTC QLQ-C30	
Wang 2011 [91]	72	100	50 (10)	Breast	On: surgery 100% chemotherapy 100%, radiation 44%		• FACIT-F	• 6-m walk
Wenzel 2013 [92]	126	39	60 (11)	Breast, colorectal, prostate, other solid tumour [c]	On: radiotherapy 52%, chemotherapy 35%, combined 7%, brachytherapy 6%		• PFS	• 12-MWT
Winters-Stone 2012 [93]	106	100	62 (1)	Breast	Post: chemotherapy 60% radiotherapy 88%		• SCFS	• Timed STS • 4-m walk
Windsor 2004 [104]	66	100	69 (1)	Prostate	On: radiotherapy 100%, hormone 29%		• BFI	• Modified SWT
Wiskemann 2011 [66]	105	33	49 (15)	Leukaemia, lymphoma (various)	On: Allo-HSCT 100%		• EORTC QLQ-C30 • MFI	• 6-MWT
Yeo 2012 [106]	102	44	67 (13)	Pancreas	On: surgery 100%, chemotherapy /radiotherapy 73%		• FACIT-F	
Yuen 2007 [94]	29	100	41 (13)	Breast	Post: 9 d to 35 mth; Surgery 100% chemotherapy 82%, radiotherapy 77%		• PFS	• 6-MWT

ADT = Androgen deprivation therapy, AM-PAC SF = Activity Measure for Post-Acute Care Inpatient Mobility Short Form, AST = Androgen suppression thera py, BFI = Brief Fatigue Inventory, CRP = C-reactive protein, EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (C 30 or FA13 versions), FACIT-F = Functional Assessment of Chronic Illness Therapy - Fatigue, FACT-F/An = Functional Assessment of Cancer Therapy-Fatigue/Anaemia, HSCT = Haematopoietic stem cell transplantation, IL = interleukin, LASA = Linear Analogue Self Assessment, MFI = Multi-dimensional Fatigue Inventory, MWT = minute walk test, P FS = Piper Fatigue Scale, SCFS = Schwartz Cancer Fatigue Scale, STS = sit to stand, SWT = Shuttle Walk Test, TNF a = Tumour Necrosis Factor-alpha, TOI = Trial Outcome Index.

[a] reports data on some or all of the same participants as the study below.

[b] n = 3.

[c] n = 8.

had adverse events. Of these, six participants withdrew from the trials because of adverse event(s), including: dizziness, fatigue, bone pain, chest pain, acute myocardial infarction, anaemia, dyspnoea and knee pain. The adverse events that did not affect exercise participation were back pain, lower limb pain, post-exercise discomfort and a fall at home that was unrelated to the intervention. A meta-analysis found moderate-quality evidence that exercise did not increase the risk of an adverse event compared with usual care and there was no difference between exercise modalities or intensities (Table 4).

Adherence was reported in 30 trials. Twenty-two trials [30,60,61,66,68,72,74,75,78–80,82,85,89–91,93–100,102–105] reported adherence of > 75% attendance of exercise sessions or adherence to the prescribed exercise protocol (in the case of non-supervised, home-based exercise). Fifteen trials were supervised outpatient sessions (14 centre-based, [30,60,61,68,72,74,75,78–80,82,97,98,100,105] one home-based), [96] two were a combination of home and centre-based training [89,93] and four were unsupervised interventions completed at home. [85,90,91,94,104] Twenty-two trials included strategies to help improve exercise adherence and support behaviour change, such

Table 3
Summary of exercise interventions.

Study	Program setting	Exercise mode	Session duration (min)	Frequency (sessions/wk)	Program duration (wk)	Intensity
Battaglini 2008 [71]	Supervised, centre-based, individual	Combined aerobic, resistance and flexibility	21 to 32	2	15	40 to 60% VO_{2max}
Baumann 2010 [67]	Supervised, inpatient hospital-based	Combined aerobic and flexibility	10 to 20	10	Duration of therapy (mean 4, SD 2)	80% patient-achieved watt load
Broderick 2013 [68 a] Guinan 2013 [80]	Supervised, centre-based group and individual home	Aerobic	21 to 42	2	8	Poor 55 to 75% HRR Fair 60 to 80% HRR Average 65 to 85% HRR (based on initial fitness level)
Buffart 2014 [95 a] Galvao 2010 [100]	Supervised, centre-based, group	Combined aerobic and resistance	15 to 20 (aerobic)	2	12	Aerobic: 65 to 80% HRmax, 11 to 13 Borg RPE Resistance: 6 to 12 RM, 2 to 4 sets
Burnham 2002 [72]	Supervised, centre-based, group	Aerobic	32	3	10	Low group: 40% HRR Moderate group: 60% HRR by week 10
Campbell 2005 [73]	Supervised, centre-based, group	Combined aerobic and resistance	10 to 20	2	12	60 to 75% age-adjusted HRmax
Cantarero-Villanueva 2013 [74]	Supervised, centre-based, group	Combined aerobic and resistance (aquatic)	40	3	8	Moderate RPE, 8 to 12 RM, 2 to 3 sets,
Chang 2008 [63]	Supervised, inpatient hospital-based, individual	Aerobic	12	5	3	Target HR = resting HR + 30
Cheville 2013 [96]	Unsupervised, home-based, individual [b]	Combined aerobic and resistance	20 (aerobic)	4	8	Moderate RPE, 10 to 15 RM, 3.5 MET
Christensen 2014 [107]	Supervised, hospital-based outpatient, individual	Resistance	NR	3	9	10 to 12 RM, 4 sets
Coleman 2012 [64]	Unsupervised, home-based, individual	Combined aerobic, resistance and flexibility	NR	3	15	Aerobic: 65 to 80% HRmax, 11 to 13 Borg RPE Resistance: 60 to 80% 1RM, 15 to 17 Borg
Cormie 2013 [98]	Supervised, centre-based, group	Resistance	45	2	12	8 to 12 RM, 2 to 4 sets
Cormie 2015 [97]	Supervised, centre-based, group	Combined aerobic and resistance	45	2	12	Aerobic: 70 to 85% HRmax Resistance: 6 to 12, 1 to 4 sets, 60 to 85% 1RM
Courneya 2004 [99 a] Segal 2003 [102]	Unsupervised, centre-based, individual	Resistance	NR	3	12	8 to 12, 2 sets, 60 to 70% 1RM
Courneya 2007 [76 a] Courneya 2007 [77]	Supervised, centre-based, group	Aerobic	15 to 45	3	Duration of chemotherapy (> 12, median 17)	60 to 80% VO_{2max}
		Resistance	NR			8 to 12, 2 sets, 60 to 70% 1RM
Courneya 2009 [105]	Supervised, centre-based, individual	Aerobic	40 to 45	3	12	60 to 75% VO_{2peak} + 1 session/wk interval at VO_{2peak} from wk 9
Courneya 2013 [75]	Supervised, centre-based, individual	Standard aerobic	25 to 30	3	Mean 16	Aerobic: 55 to 60% VO_{2peak} Resistance: 10 to 12, 2 sets, 60 to 75% 1RM
		High-dose aerobic	50 to 60			
		Combined resistance and aerobic	50 to 60			
Daley 2007 [78]	Supervised, centre-based, individual	Aerobic	50	3	8	65 to 85% age-adjusted HRmax, RPE 12 to 13
Fairey 2005 [30 a] Fairey 2005 [60]	Supervised, centre-based, group	Aerobic	15 to 35	3	15	70 to 75% VO_{2peak}
Gomez 2011 [79]	Supervised, centre-based, individual	Combined aerobic and resistance	90	3	8	Aerobic: 70 to 80% HRmax Resistance: 8 to 10 RM, 2 to 3 sets
Headley 2004 [81]	Unsupervised, home-based individual	Aerobic	20	3	Duration of therapy	NR
Hornsby 2014 [61 a] Jones 2013 [82]	Supervised, centre-based, individual	Aerobic	20 to 30	3	12	Initial: 60% baseline peak Target: 2 sessions of 60 to 70% and 1 interval session 100%
Jones 2013 [83]	Supervised, centre-based, individual and unsupervised, home-based	Aerobic	30	3 (centre) + 2 (home)	26	50 to 80% HRmax
Mock 2005 [84]	Unsupervised, home-based, individual	Aerobic	30	5 to 6	Duration of therapy (6 wk to 6 mth)	50 to 70% HRmax
Monga 2007 [101]	Supervised, centre-based, group	Aerobic	30	3	8	65% HRmax

Table 3 (Continued)

Study	Program setting	Exercise mode	Session duration (min)	Frequency (sessions/wk)	Program duration (wk)	Intensity
Mustian 2009 [85] [a] Sprod 2010 [90]	Unsupervised, home-based, individual [b]	Combined aerobic and resistance	NR	7	4	60 to 70% HRR, 3 to 5 RPE
Mutrie 2007 [62]	Supervised, group and unsupervised, home-based	Combined aerobic and resistance	20	2 (group) + 1 (home)	12	50 to 75% HRmax
Naraphong 2015 [86]	Un-supervised, home-based, individual [b]	Aerobic	20 to 30	3 to 5	12	40 to 60% HRmax, 12 to 14 Borg RPE
Oechsle 2014 [65]	Supervised, hospital-based, inpatient	Combined aerobic and resistance	40	5	median 2	40 to 60% 1RM
Oldervoll 2011 [69]	Supervised, centre-based, group	Combined aerobic, resistance, and flexibility	30	2	8	NR
Payne 2008 [87]	Unsupervised, home-based, individual	Aerobic	20	4	14	'Moderate' walking activity
Rief 2014 [88]	Supervised, centre-based, individual and unsupervised, home-based, individual	Resistance	30	3	24	NR
Saarto 2012 [89]	Supervised, centre-based, group and unsupervised, home-based, individual	Aerobic	45 to 50	1 (group) + 2 to 3 (home)	52	14 to 16 RPE, 86 to 92% HRmax, 76 to 85% VO_{2max}
Segal 2009 [103]	Supervised, centre-based, individual	Aerobic	45	3	24	70 to 75% VO_{2max}
		Resistance	NR			8 to 12, 2 sets, 60 to 70% 1RM
Thorsen 2005 [70]	Supervised, home-based, individual	Aerobic	30	2	14	60 to 70% HRmax, 13 to 15 Borg RPE
Wang 2011 [91]	Unsupervised, home-based, individual	Aerobic	30	3 to 5	6	40 to 60% HRmax, 0.5 to 3 Borg RPE
Wenzel 2013 [92]	Unsupervised, home-based, individual	Aerobic	20 to 30	5	Duration of therapy (5 to 35)	50 to 70% HRmax
Winters-Stone 2012 [93]	Supervised, centre-based, group and unsupervised, home-based, individual	Resistance	60	3	52	8 to 10, 1 to 3 sets, 60 to 70% 1RM
Windsor 2004 [104]	Unsupervised, home-based, individual	Aerobic	30	3	4	60 to 70% HRmax
Wiskemann 2011 [66]	Partly supervised, inpatient hospital-based, individual and home-based	Combined aerobic and resistance	20 to 40 (aerobic)	3 (aerobic) + 2 (resistance)	1 to 4 pre-hospital + inpatient stay + 6 to 8 post-hospital	Aerobic: 12 to 14 Borg RPE Resistance: 8 to 20 RM, 2 to 3 sets, 14 to 16 Borg RPE
Yeo 2012 [106]	Unsupervised, home-based, individual	Aerobic	30	3 to 5	6	'Brisk walk'
Yuen 2007 [94]	Un-supervised, home-based, individual	Aerobic	20 to 40	3	12	8 to 12 RM, 10 to 13 Borg RPE
		Resistance	NR			

HRmax = maximum heart rate, HR = heart rate, HRR = heart rate reserve, MET = metabolic equivalents, NR = not reported, RM repetition maximum, RPE = Rating of Perceived Exertion, VO_{2max} = maximum volume of oxygen consumption, VO_{2peak} = volume of oxygen consumption at peak exercise.

[a] Reports data on some or all of the same participants as the study below.

[b] With initial supervised instructional session.

Table 4
Meta-analysis of adverse events in exercise trials compared with usual care.

Outcome	Subgroup (modality or intensity)	Trials (n)	Participants (n)	Risk difference (95% CI)	Quality of the evidence (GRADE)
Adverse events	Aerobic	10 [60,61,68,72,77,78,84,91,103,105]	748	0.01 (−0.02 to 0.05)	moderate [a]
	Resistance	3 [76,98,103]	265	0.01 (−0.02 to 0.03)	high
	Combined	9 [65,67,69,73,79,96–98,100]	466	0.01 (−0.01 to 0.04)	moderate [b]
	Low-moderate intensity	8 [65,72,74,75,84,91,96,98]	495	0.01 (−0.01 to 0.04)	high
	Moderate-high intensity	11 [60,61,67,68,73,77–79,97,100,103,105]	807	0.01 (−0.02 to 0.03)	moderate [a]
	Overall	21	1710	0.01 (−0.01 to 0.02)	moderate [a]

GRADE = Grades of Research, Assessment, Development and Evaluation.
One trial [72] was not included in the analysis due to no usual-care comparison.
GRADE working group grades of evidence (see reason for downgrade).
PEDro score < 6 was considered lower quality.

[a] Reason for downgrade: evidence of publication bias.

[b] Reason for downgrade: seven trials [65,67,69,73,79,96,97] were rated lower quality.

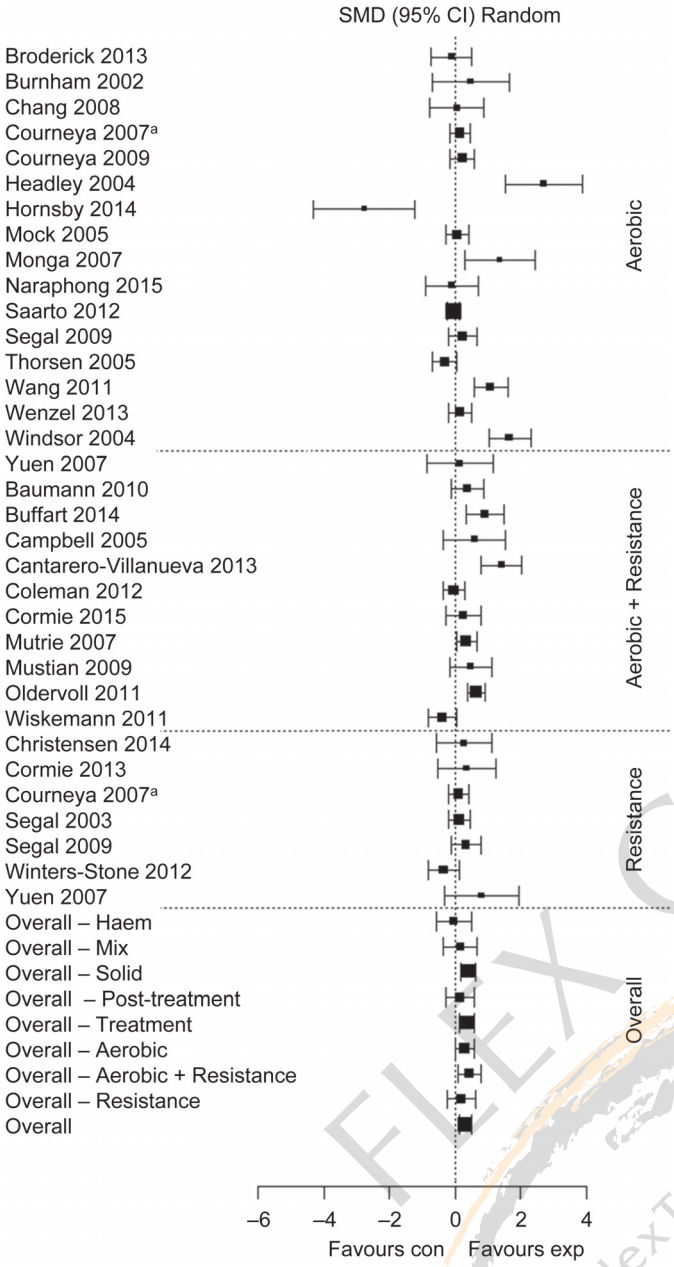

Figure 2. SMD (95% CI) of effect of exercise compared with usual care, on fatigue by pooling data from 33 trials with subgroup analysis by tumour type (haematological, mixed, solid), treatment phase (post-treatment, during treatment) and exercise modality (aerobic, combined aerobic and resistance, resistance).
[a] Courneya et al. [77].

as use of telephone monitoring, exercise diaries, use of pedometers and supervised 'booster' sessions. [30,60,62,64,68,73,78,80,81,83–87,89–92,94–98,100,103,104,106]

Effects of exercise on health outcomes: meta-analysis

Fatigue

Meta-analysis provided moderate-quality evidence that exercise had a positive effect on fatigue when compared with usual care (SMD 0.32, 95% CI 0.13 to 0.52) (Figure 2 , Table 5). When adjusting for tumour type in subgroup analyses, there was insufficient evidence to suggest that exercise was effective for haematological or mixed tumour types. There was strong evidence in favour of exercise with respect to solid tumours and those undergoing treatment (Table 6). With respect to mode of exercise, a combination of aerobic and resistance training provided the largest treatment effect, with smaller and similar estimated effects for aerobic and resistance exercise alone (Table 6). Further meta-analysis provided moderate-quality evidence that a reduction in fatigue was maintained up to 6 months after the intervention when compared with usual care (Table 5). One trial was not included in the meta-analysis because it did not have a usual-care control group. [75] This trial found no differences in fatigue when comparing different exercise modalities and dose (with respect to duration).

Inflammation

A meta-analysis of five trials [30,80,83,97,100] provided high-quality evidence of a non-significant reduction in levels of plasma CRP following exercise when compared with usual care. A meta-analysis offour trials [79,83,90,107] provided moderate-quality evidence that there was no significant difference in plasma IL6 levels; and meta-analysis of two trials [79,107] provided moderate-quality evidence that there was no difference in IL8 or IL10 levels following exercise (Table 5).

Two trials that were not included in the meta-analysis due to insufficient data did not show a significant difference between IL6 levels [87] or any of the cytokines tested. [60] Another trial that was also not included in the meta-analysis due to insufficient data demonstrated a significant reduction in IL b and IL2 in the exercise group during chemotherapy, and a significant increase in IL8 levels during the exercise intervention compared with usual care. [82]

Activity

Of the included trials, 18 reported on outcomes offunctional mobility and one reported on activities of daily living. A meta-analysis of 15 trials provided very low-quality evidence of improvement in walking endurance following exercise when compared with usual care (Table 5 , Figure 3). Sensitivity analysis was completed because a single trial demonstrated a significantly larger effect than other trials. When this study was removed, there was still a moderate effect in favour of the intervention, with high levels of heterogeneity (61%), which was unable to be explained by the study characteristics. There was evidence that exercise had a significant effect on walking endurance for solid tumour types (Table 6). Moderate-quality evidence offour trials demonstrated no difference in usual walking speed following exercise when compared with usual care. There was also no difference in sit-to-stand or stair climbing ability (Table 5). One trial found no differences in patient-reported activities of daily living when comparing combined exercise to usual care. [96]

Dose-response analysis: meta-regression

A total of 31 trials were included in a meta-regression analysis of the dose-response effect ofintensity and duration of exercise programs on fatigue and walking endurance.

Meta-regression analysis demonstrated a significant effect of exercise intensity on fatigue. Aerobic exercise intensity was negatively associated with treatment effect using linear regression models. For every 1% increase in intensity (from moderate to high) there was an estimated reduction of SMD 0.029 (95% CI 0.001 to 0.056) in the positive effect of exercise on fatigue (Figure 4 , top panel, solid line). However, there was no evidence of this for the aerobic exercise component of the combined exercise studies (estimated reduction per 1% increase SMD 0.005 (95% CI –0.038 to 0.048) (Figure 4 , top panel, dotted line). With respect to resistance intensity (Figure 4 , bottom panel) and exercise duration (Figure 5), the meta-regression analyses did not detect any significant associations.

For walking endurance, only the intensity of aerobic exercise was analysed using data from the aerobic and the aerobic component of combined intervention trials. A quadratic meta-regression model demonstrated that moderate-intensity aerobic exercise (70% relative intensity) led to a peak effect (Figure 6). This association was close to significant. There was no association detected for exercise duration (Figure 7).

Meta-regression analysis was not completed for markers of inflammation because there were insufficient data. All studies measuring CRP and IL6 levels were moderate-intensity exercise.

Table 5
Meta-analysis, overall effect of exercise on outcomes.

Outcome	Trials (n)	Participants (n)	Time of assessment	SMD (95%CI) I^2	Quality of the evidence (GRADE)
Inflammation					
IL6	4 [79,83,90,107]	148	immed	0.15 (−0.79 to 1.08) 84%	moderate [a]
IL8	2 [79,107]	43	immed	−0.03 (−0.64 to 0.57) 0%	moderate [b]
IL10	2 [79,107]	43	immed	−0.31 (−0.92 to 0.30) 0%	moderate [b]
CRP	5 [30,80,83,97,100]	264	immed	−0.15 (−0.39 to 0.10) 0%	high [c]
Fatigue [d]	33 [61–64,66–74,77,81,84–87,89,91–98,101–105,107]	3336	immed	0.32 (0.13 to 0.52) 82%	moderate [a]
	7 [62,68,74,77,85,104,107]	721	2 to 6 mth post	0.39 (0.08 to 0.71) 71%	moderate [a]
Activity					
walking endurance [e]	14 [62–64,69,73,84,85,91,93,94,98,100,104]	1032	immed	0.77 (0.26 to 1.28) 93%	very low [f]
usual walking speed [g]	4 [93,97,98,100]	207	immed	0.22 (−0.32 to 0.77) 70%	moderate [a]
sit to stand	5 [69,74,93,97,100]	479	immed	0.25 (−0.30 to 0.80) 87%	moderate [a]
stair climb	2 [97,100]	120	immed	−0.18 (−0.54 to 0.18)	high

GRADE = Grades of Research, Assessment, Development and Evaluation, IL = interleukin, immed = immediate.
GRADE working group grades of evidence (see reasons for downgrade).
PEDro score < 6 was considered lower quality.
[a] Reason for downgrade: heterogeneity.
[b] Reason for downgrade: one trial [79] was rated lesser quality.
[c] Reason for downgrade: five trials [63,64,66,72,91] were rated lesser quality without blinded outcome measures and allocation concealment.
[d] Fatigue measures: Brief Fatigue Inventory, European Organisation for Research and Treatment of Cancer C30/FA13 Questionnaires, Functional Asses sment of Chronic Illness Therapy - Fatigue, Functional Assessment of Cancer Therapy - Fatigue/Anaemia, Fatigue Questionnaire, Linear Analogue Self Assessment, Mu lti-dimensional Fatigue Inventory, Revised Piper Fatigue Scale, Trial Outcome Index - Fatigue.
[e] Walking endurance measures: 6-min and 12-min walk tests; 400-m and 2-km walk time; Shuttle Walk Test.
[f] Reason for downgrade: seven trials [63,64,69,73,94,95,104] were without blinded outcome measures and allocation concealment, evidence of publication bias and heterogeneity.
[g] Gait speed measures: 4-m and 6-m walk tests.

Table 6
Meta-analysis, effect of exercise (post-intervention) on outcomes by subgroup.

Outcome	Subgroup	Trials (n)	Participants (n)	SMD (95% CI) I^2	Quality of the evidence (GRADE)
Subgroup analysis by tumour stream					
Fatigue	Solid	23 [61,62,72–75,77,81,84–87,89,91–94,97,98,101–104,107]	2168	0.37 (0.16 to 0.58) 82%	moderate [a]
	Haematological	4 [63,64,66,105]	360	−0.03 (−0.56 to 0.49) 82%	low [b]
	Mixed	4 [67–70]	446	0.17 (−0.34 to 0.68) 82%	very low [c]
Endurance	Solid	10 [62,73,84,85,91,94,95,97,98,104]	650	0.92 (0.26 to 1.59) 93%	very low [d]
	Hematological	3 [63,64,66]	288	0.41 (−0.87 to 1.68) 93%	very low [e]
Subgroup analysis by treatment phase					
Fatigue	Treatment	26 [61–64,66,67,69,73,75,77,81,84–86,91,92,95,97,101–105,107]	1909	0.33 (0.12 to 0.53) 81%	moderate [a]
	Post-treatment	7 [68,70,72,74,89,93,94,98]	833	0.19 (−0.19 to 0.58) 81%	moderate [a]
Subgroup analysis by exercise modality					
Fatigue	Aerobic	18 [61,63,68,70,72,75,77,81,84,87,89,91,92,94,101,103–105]	1491	0.27 (0.00 to 0.54) 82%	low [f]
	Resistance	8 [67,77,93,94,98,102,103,107]	508	0.19 (−0.24 to 0.62) 82%	moderate [a]
	Combined	11 [62,64,66,67,69,73–75,85,94,95,97]	975	0.41 (0.06 to 0.75) 82%	low [f]
Endurance	Aerobic	4 [63,91,94,104]	293	1.28 (0.36 to 2.20) 94%	very low [g]
	Resistance	2 [97,101]	29	0.18 (−1.36 to 1.72) 94%	very low [h]
	Combined	8 [65,68,69,72,76,88,97,98,100]	790	0.61 (−0.10 to 1.31) 94%	moderate [a]

GRADE = Grades of Research, Assessment, Development and Evaluation.
GRADE working group grades of evidence (see reasons for downgrade).
PEDro score < 6 was considered lower quality.
[a] Reason for downgrade: heterogeneity.
[b] Reason for downgrade: three trials [63,64,66] were rated lower quality, heterogeneity.
[c] Reason for downgrade: heterogeneity, all trials were rated lower quality, without blinded outcome measures and allocation concealment.
[d] Reason for downgrade: heterogeneity, five trials [70,73,88,91,101] were rated lower quality, evidence of publication bias.
[e] Reason for downgrade: heterogeneity, all trials were rated lower quality, without blinded outcome measures and allocation concealment, wide confid ence intervals.
[f] Reason for downgrade: heterogeneity, evidence of publication bias.
[g] Reason for downgrade: heterogeneity, four trials were rated lower quality [63,91,94,104], wide confidence intervals.
[h] Reason for downgrade: heterogeneity, one trial was rated lower quality [94], without blinded outcome measures and allocation concealment, wide confidence intervals.

Discussion

This systematic review provided moderate-quality evidence that exercise reduces fatigue in cancer survivors and very low-quality evidence that exercise improves walking endurance in this group. It also provided evidence of a negative dose-response relationship of aerobic exercise intensity and fatigue, and of a peak treatment effect of moderate-intensity aerobic exercise for improving walking endurance. No significant dose-response was evident for the duration of weekly exercise. There was also moderate-quality to high-quality evidence that there is no significant difference in inflammatory markers after completion of an exercise program compared with usual care and no significant difference in usual walking-speed, sit-to-stand ability or stair climbing ability.

These findings support previous meta-analyses [7,18,38–40] suggesting that exercise can play a significant role in reducing fatigue, particularly in people with solid tumours. Consistent with previous evidence, these effects may not be generalisable to haematological cancers. [38,40] Patients with haematological malignancies can experience many complications during treatment, including muscle atrophy, cachexia, anaemia, physical deconditioning and psychological distress. [64,108,109] In particular, anaemia has been shown to affect people with haematological cancers more than those with solid tumours [110] and this is a known contributor to cancer-related fatigue. [27] Therefore, this complication may be less able to be resolved through exercise.

Our review also demonstrated a significant effect of exercise in reducing fatigue in people undergoing treatment, but not after treatment. A possible explanation could be a ceiling effect

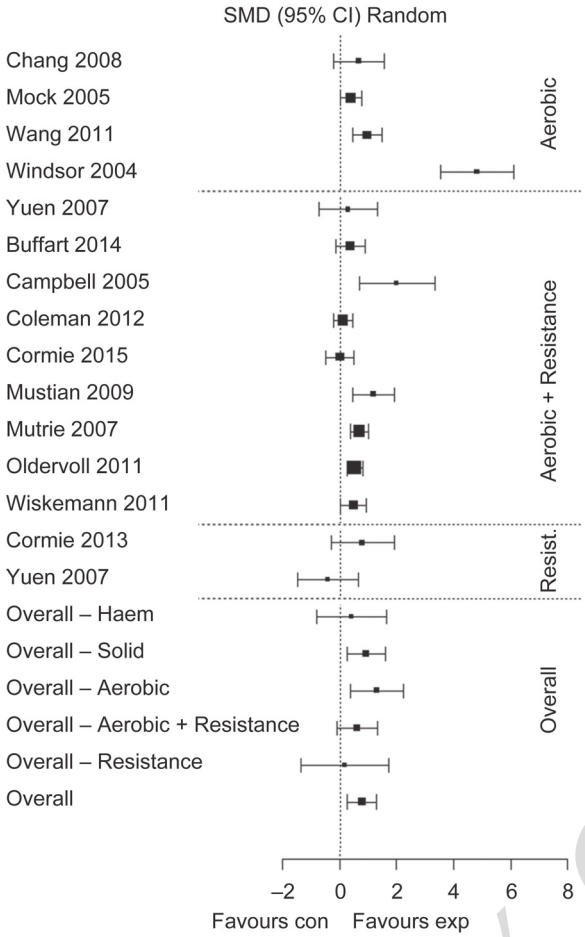

Figure 3. SMD (95% CI) of effect of exercise, compared with usual care, on walking endurance by pooling data from 14 trials with subgroup analysis by tumour type (haematological, solid) and exercise modality (aerobic, combined aerobic and resistance, resistance).

occurring after treatment, when fatigue may be less severe. Previously, reductions in fatigue were not found to be maintained after completion of the exercise program. [19,40] However, in this review, reduction in fatigue was maintained at follow-up. This may be explained by a larger number of studies that included a specified exercise dose, which is important because people need to exercise with sufficient duration and intensity to be able to induce long-term physiological change to their health.

The significant reductions in fatigue were accompanied by significant improvements in walking endurance. It has been hypothesised that the physical dimension offatigue has an organic cause. [111] Cancer survivors have low physical activity levels, [112] which in turn reduce physical performance and impair skeletal muscle function and cardiovascular fitness. This cycle of deconditioning, which perpetuates fatigue, can be broken through the physical adaptations of exercise training. Exercise may also provide the additional benefits ofimproved mood and reduced anxiety and fear, which are known contributors of cancer-related fatigue. [111,113,114]

The safety of exercise in people with cancer was re-enforced by this review, and evidenced by a low number of adverse events and a non-significant reduction in the inflammatory marker CRP. There was also no difference in the levels of the interleukins assessed. These inflammatory markers have previously been linked to tumour development and recurrence, as well as contributing to the development offatigue. The results in this review suggest that exercise does not increase any pro-inflammatory markers, which contribute to cancer risk and tumour development.

Moderate-intensity exercise has a greater effect on reducing fatigue and increasing walking endurance than high-intensity exercise. This is a plausible outcome, given the nature of the mechanism of physiological changes as a result of exercise. Regular exercise induces stress on the cardiovascular and muscular systems in order for physical adaptation to occur. [115] However, in people with cancer, baseline exercise tolerance is reduced secondary to the effects of disease and treatment-related factors. Some tumours may directly disrupt pulmonary mechanics and may also be accompanied by side effects such as weight loss, anaemia and muscle wasting. [116] Treatment such as chemotherapy and radiotherapy can further exacerbate issues with oxygen delivery by inducing pulmonary and cardiovascular damage as well as increasing inflammation and reactive oxygen species; such changes are correlated with change in myocardial strain. [111,116] Therefore, while physical activity is important to relieve fatigue, a balance in the amount of physical activity is also required. However, it should be considered that other training factors such as interval period, duration and length of the program might

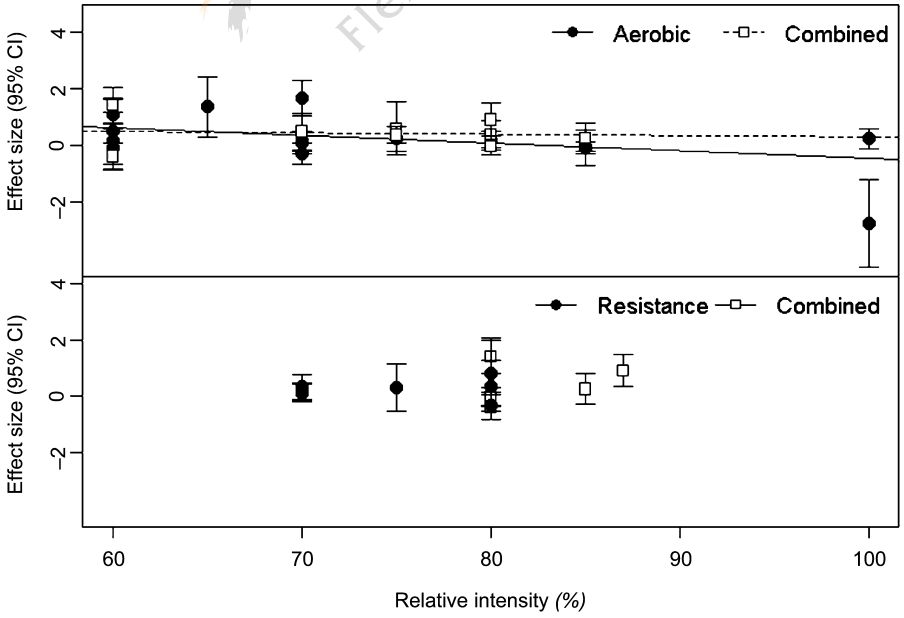

Figure 4. Top panel: Meta-regression scatter plot of 25 trials showing the relationship between aerobic exercise intensity (% relative intensity) and the eff ect on fatigue (effect size, 95% CI), fitted with linear regression lines: solid line – aerobic; dotted line – combined. Bottom panel: Meta-regression scatter plot of 13 tria ls showing the relationship between resistance exercise intensity (% of 1 repetition maximum) and the effect on fatigue (effect size, 95% CI).

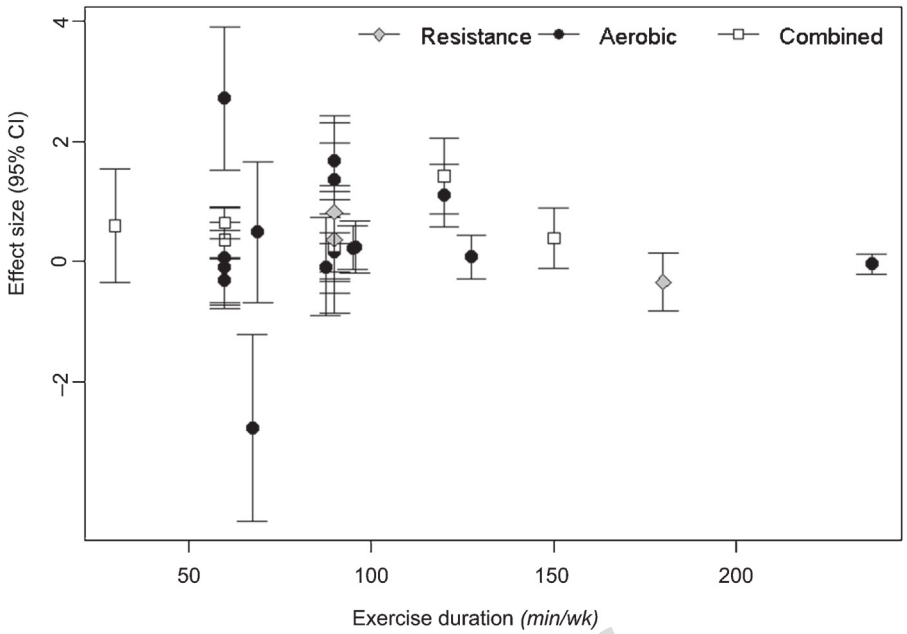

Figure 5. Meta-regression scatter plot of 26 trials showing the relationship between exercise duration (minutes per week) and the effect on fatigue (effect size, 95% CI).

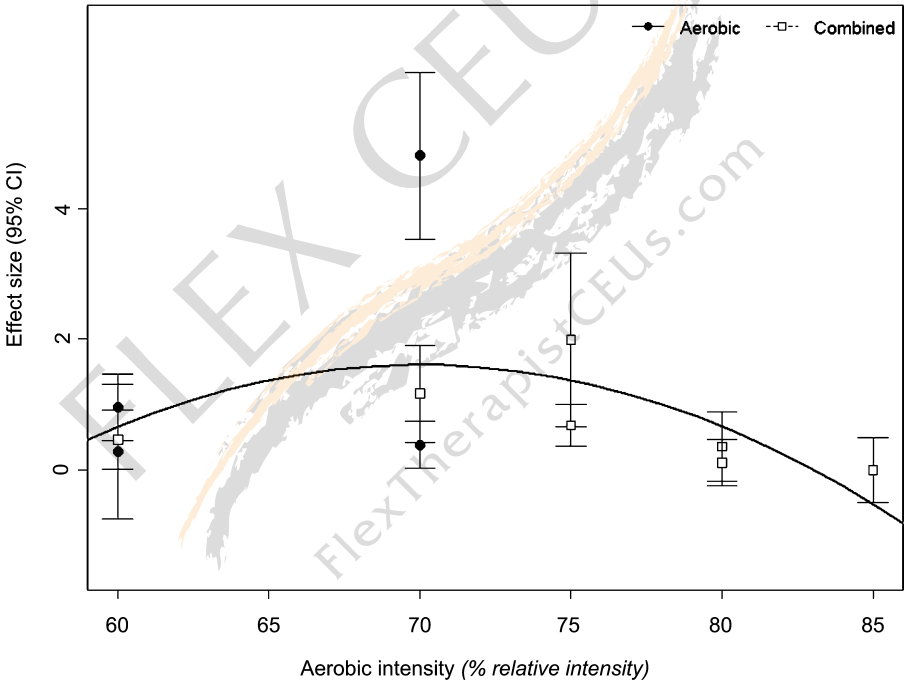

Figure 6. Meta-regression scatter plot of 12 trials showing the relationship between aerobic exercise intensity (% relative intensity) and the effect on walking endurance (effect size, 95% CI), fitted with quadratic regression line.

influence the effectiveness of high-intensity training, which this review was unable to assess. It should also be noted that there were no trials included in this review that assessed low-intensity exercise. So, while there is evidence that moderate-intensity exercise may reduce fatigue and improve mobility more effectively than high-intensity, it cannot be concluded that moderate-intensity exercise is superior to low-intensity exercise for improving these outcomes.

A dose-response relationship for exercise in relation to inflammatory markers was unable to be established. Previous literature has suggested that inflammatory biomarkers' response to exercise is dependent on the volume of mechanical work completed. [117] There were too few trials to establish a dose-response relationship and a lack of variation in exercise intensity levels in the trials that measured inflammation. There is evidence that high-intensity or prolonged exercise duration can cause immune suppression and increase susceptibility to infection in healthy people. [115] This is a major consideration, given that people with cancer are often immunocompromised.

The current recommendations for exercise for people with cancer are that they complete at least 150 minutes of moderate-intensity exercise per week. [6] It is also recommended that people with cancer complete a combination of aerobic and resistance exercise to achieve this goal. Results from this review support the recommendation to complete moderate-intensity exercise, particularly in relation to aerobic exercise and the benefits of combined aerobic and resistance exercise programs for improving cancer-related fatigue. [19,38–40] The recommendation for the amount of exercise required to achieve benefits for fatigue and activity is less clear. As such, cancer survivors should follow the recommendation

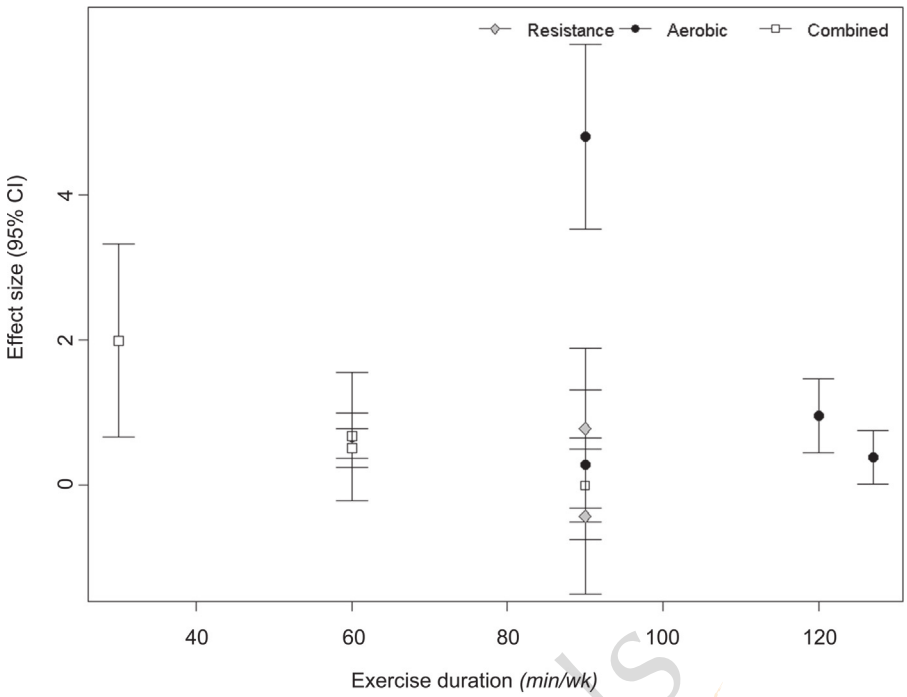

Figure 7. Meta-regression scatter plot of 11 trials showing the relationship between exercise duration (minutes per week) and the effect on walking endurance (effect size, 95% CI).

to avoid inactivity [6] and complete as much moderate-intensity exercise as tolerated.

It is believed that this was the first review that analysed the effect of dose on fatigue in cancer survivors using meta-regression analysis across exercise modalities. It was also the first to investigate the effects of exercise on inflammatory biomarkers in people with cancer using meta-analysis. It included only randomised, controlled trials, which reduced the risk of selection bias and increased confidence in the results.

There were some limitations to this review. The search strategy included only four databases and was restricted to the English language, which posed some risk of publication bias. However, relatively few articles were located through additional methods and forest plots were analysed for publication bias. The results for activity outcomes were based on trials where fatigue and/or inflammation were also measured among the outcomes, so the results for activity may not be based on a complete set of available trials. However, previous reviews on exercise interventions for adults with cancer have reported similar results in relation to activity outcomes such as walking endurance. [5,7] The overall quality of the evidence was moderate to high, but there were high levels of unexplained heterogeneity in the meta-analyses; this is consistent with previous meta-analyses. [5,19,38–40] This may have limited the confidence in the size of the pooled effect. To account for this, subgroup and sensitivity analyses were completed based on tumour stream and treatment phase. There was also evidence of unequal variances between groups, which influence the way in which the differences of means should be standardised; Glass' D effect size was used to overcome this. The analyses were also conducted using Cohen's d and the main findings remained intact. Combining a number of relative-intensity measures (eg, maximum heart rate, VO_{2max} and Borg) may also be a limitation. However, since these are effective measures ofintensity and standardised effects were used, this was unlikely to be an issue.

In conclusion, this review of 42 randomised, controlled trials supports the growing body of evidence that exercise is a safe and effective intervention for reducing fatigue and improving mobility in adult cancer survivors. It was also able to establish a dose-response relationship ofintensity for aerobic exercise, supporting current recommendations emphasising moderate-intensity aerobic training in exercise programs for cancer survivors. These findings demonstrated greatest effect in people with solid tumours, with no significant effect evident for people with haematological malignancies.

What is already known on this topic : For people with cancer, exercise has beneficial effects on strength, cardiovascular function, fatigue and quality oflife. However, the ideal mode and intensity of exercise for people with cancer is unclear.
What this study adds : Exercise is safe and reduces fatigue and increases endurance in cancer survivors. Moderate-intensity exercise appears to be the most appropriate aerobic exercise for benefits on fatigue and walking endurance.

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