

Physical activity interventions for fatigue in rheumatoid arthritis: a systematic review

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Physical activity interventions for fatigue in rheumatoid arthritis

Abstract

Background: Fatigue is a major symptom of rheumatoid arthritis (RA) and the need for effective interventions is evident. Programmes based upon physical activity (PA) have been shown to improve patient reported fatigue in other long term conditions.

Objectives: To investigate the effectiveness of PA interventions for reducing fatigue in adults with RA, and to identify key components of effective PA interventions.

Methods: Methods were based on a previous Cochrane systematic review for non-pharmacological interventions for fatigue in RA. The following electronic databases were searched up to October 2016: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; AMED; CINAHL; PsycINFO; Social Science Citation Index; Web of Science; Dissertation Abstracts International; Current Controlled Trials Register; The National Research Register Archive; The UKCRN Portfolio Database. Randomised controlled trials evaluating PA interventions in people with RA with self-reported fatigue as an outcome measure were included.

Results: Eight studies met the inclusion criteria. Results indicated a small beneficial effect of PA on RA fatigue. The type, frequency, duration and intensity of PA varied between studies. Delivery methods included supervised group programmes and unsupervised home exercise. Information regarding overall adherence to PA interventions was limited.

Conclusions: There is some evidence of the potential for PA to be effective in reducing symptoms of RA fatigue. However, few interventions in the included studies were designed to manage RA fatigue. These findings suggest that further work is needed to identify the optimal PA intervention for fatigue management that meets the needs of people with RA.

Keywords: rheumatoid arthritis, fatigue, physical activity, exercise, systematic review

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease, predominantly affecting peripheral joints¹. RA affects 1.16% of women and 0.44% of men in the United Kingdom². It is a progressive, systemic disease associated with considerable morbidity and increased mortality³⁻⁵.

Fatigue has been identified as an important symptom of RA, causing distress and disruption to patients' daily lives and affecting everyday tasks and leisure activities⁶⁻⁸.

Reported rates of fatigue in RA vary, possibly due to differences in definition and outcome measurement, but may be as high as 80%^{9, 10}. Many patients with RA report that they find it difficult to manage fatigue, and receive little professional support^{6, 11}.

The mechanisms and causality of fatigue in RA remain unclear due to its complex and multi-factorial nature. However, it has been suggested that interactions between RA disease processes (e.g. inflammation, pain, disability, muscle effort and deconditioning), thoughts, feelings and behaviours (e.g. illness beliefs, anxiety and depression), and personal life factors (e.g. work, health, support networks) might influence a person's fatigue experience¹². Recent multivariate analyses demonstrated that higher disease activity, poor sleep, depression and obesity are independent predictors of RA fatigue¹³.

Description of the intervention

Clinical guidelines for managing RA recommend non-pharmacological approaches to reduce the impact of physical and psychosocial factors associated with RA¹⁴⁻¹⁶. These approaches include physical activity (PA) interventions to enhance self-management and coping skills. PA interventions may also be used to manage RA fatigue, aiming to improve engagement in lifestyle PA, such as walking to work, or more formal prescribed exercise programmes. Interventions may specify PA components such as type, intensity, duration and frequency.

For example, some might specify aerobic exercise, such as walking or cycling, or other forms of exercise, such as resistance training or yoga. Prescribed PA or exercise programmes might specify a target duration, intensity and/or frequency. In addition the intervention might take place in a wide range of settings and may be land- or pool-based, such as hydrotherapy, and may or may not be supervised by a healthcare or exercise professional. Delivery may be one-to-one or in groups.

Programmes based upon physical activity (PA) have been shown to improve patient reported fatigue in other long term conditions, such as chronic fatigue syndrome¹⁷ and cancer-related fatigue¹⁸. Therefore the effectiveness of existing PA and exercise interventions for reducing RA fatigue warrants further exploration.

How the intervention might work

A previous Cochrane review¹⁹ suggested that PA interventions have the potential to reduce fatigue in RA. Physical inactivity has been significantly associated with RA fatigue, and its effects appear to be mediated by a range of non-RA-specific variables that are important predictors of fatigue, for example, poor sleep quality, depressive symptoms and obesity¹³. Therefore PA interventions may affect fatigue through their influence on RA disease processes and other psychosocial and lifestyle factors¹². For example, there is evidence that dynamic exercise programmes (aerobic capacity and/or muscle strength training) in RA have a positive effect on aerobic capacity²⁰. This type of PA might contribute to an improvement in RA fatigue through increased cardio-respiratory fitness and muscle strength. An improvement in physiological function could result in less effort required for specific tasks, thus reducing subsequent experiences of fatigue.

Given the multi-factorial nature of fatigue, improvements in physiological function alone are unlikely to have a large impact. Modified levels of PA might also improve psychosocial aspects of fatigue, for example, regular participation in PA might increase self-

efficacy and a sense of self-control for patients with RA^{21,22}. This could positively impact on cognitive and behavioural issues that might contribute to RA fatigue¹². Additionally, there is evidence that PA can address other predictors of fatigue that are not unique to RA, such as depression and anxiety²³. Regular participation in PA might reduce the impact of RA fatigue by moderating these associated risk factors¹³.

Why it is important to do this review

There are currently few published trials primarily investigating interventions for RA fatigue. The search conducted in a Cochrane review identified research reports up to October 2012¹⁹. The review presented in this paper aimed to identify evidence that has been published since this date, and to ascertain key components of PA interventions that might be used to manage RA fatigue.

Methods

Methods were based on a Cochrane review for non-pharmacological interventions for fatigue in RA¹⁷.

Criteria for considering studies for this review

Randomised controlled trials (RCTs) of interventions for adults with confirmed RA²⁴, with fatigue reported as a primary or secondary outcome measure and data reported separately for RA, were included. Where studies reported outcomes for rheumatic conditions or diseases as one population these data were excluded. In addition, included studies must have investigated a PA intervention.

Search methods for identification of studies

The search strategy for the Cochrane review was repeated with the addition of search terms to identify PA interventions (table 1). The following electronic databases were searched

between October 2012 and October 2016: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; AMED; CINAHL; PsycINFO; Social Science Citation Index; Web of Science; Dissertation Abstracts International; Current Controlled Trials Register; The National Research Register Archive; The UKCRN Portfolio Database.

Table 1. Search strategy

Data collection and analysis

Selection of studies

Titles and abstracts were screened for inclusion criteria by two reviewers (FC, VS). Full text reports were retrieved where studies appeared to meet these criteria, or where it was unclear whether a study should be excluded from the abstract or title alone. Potentially relevant reports were discussed between reviewers, one of whom was also first author on the Cochrane review (FC)¹⁹. Data from conference abstracts were not included in the current review unless corresponding full text articles were available. Abstract authors were not contacted.

Data extraction and management

Data were extracted from newly identified studies by one reviewer (VS) using a data extraction form modified from the original Cochrane review, and included: intervention details; participants' health status; assignment to study arm; outcome measures; timing of measurements; adherence to intervention and control; sample size; statistical analysis methods; results for fatigue outcomes; and long-term follow-up data.

Risk of bias

Risk of bias was assessed using the Cochrane risk of bias tool²⁵.

Measures of treatment effect

The Cochrane review used a meta-analysis to combine mean change scores from pre- to post-test for five of the included PA studies¹⁹. The Cochrane handbook advises that a new meta-analysis incorporating data from newly identified and included studies should only be performed if deemed appropriate by review authors²⁶. It was decided that data from additional studies would be incorporated into the meta-analysis if the size of the treatment effect, indicated by standardised mean difference (SMD), differed sufficiently that it would strengthen or alter the existing conclusions. If effect sizes were not available these would be calculated from the published data using methods described in the Cochrane handbook, section 7.7.3.3²⁶. Methodological quality of included studies would be considered when making this decision.

Results

Results of the search

Figure 1 illustrates the study selection process.

The six studies investigating PA in the original Cochrane review were retrieved²⁷⁻³². Following removal of duplicates an additional 44 studies were identified using the keyword search. After title screening 20 articles remained, with seven remaining after screening of abstracts. Of these seven, four were conference abstracts and were not included in this review³³⁻³⁶. Another study was not an RCT³⁷. Two studies were included^{38,39}.

Figure 1. Flow diagram showing study selection process

Description of studies

The eight included studies are described in table 2.

Table 2. Description of included studies

Participants

Data were available for 540 participants with RA (receiving a PA intervention: n=309; controls: n=231). The number of participants completing the studies ranged from 20 to 220. The mean age ranged from 28.5 to 60 years old. Average age was in the second decade for one study²⁸, fourth decade for four studies^{27, 29, 30, 32}, fifth decade for two studies^{31, 39} and sixth³⁸ decade for the remaining study. Both males and females were recruited in six studies, all with a higher percentage of females. Two studies only recruited female participants^{28, 30}. All studies reported disease duration with the mean ranging from 8 months to 16 years.

Interventions

Interventions are summarised in table 2.

Length of intervention

Six interventions were 12 weeks in length, one was six weeks²⁸ and another was 24 months²⁹.

Type of physical activity

The type of PA included in the interventions varied, and included aerobic exercise^{30, 31, 38, 39}, pool-based aerobic exercise²⁷, resistance training^{29, 31, 38}, range of movement exercises³⁸, yoga²⁸ and Tai Chi³². Control interventions included usual care²⁸, usual PA^{27, 30, 31, 39}, and advice and education^{32, 38}. In one study the control arm also performed range of movement and stretching exercises alongside usual recreational PA²⁹.

Frequency and duration of physical activity

Exercises were generally performed two to three times weekly for both class- and home-based interventions. Daily range of movement exercises and walking at least five times weekly was encouraged in one study³⁸. Another study encouraged aerobic PA five days per week³⁹. The duration of exercise sessions across the studies varied from 15 to 90 minutes.

One study²⁹ focussed on strength training, therefore the number of sets and repetitions were targeted rather than exercise duration.

Intensity of physical activity

Aerobic exercise intensity was targeted at 70-90% maximum heart rate in three studies^{27, 30, 31}. Two studies reported a more general target of light- to moderate-intensity walking, where participants felt moderately short of breath³⁸, or moderate- to vigorous-intensity aerobic PA³⁹. Interventions that included resistance training set a target intensity of either 40-50%³⁸ or 50-70%²⁹ repetition maximum. Of those studies reporting a prescribed aerobic intensity, two reported that adherence to the intensity was not known^{27, 31}. The remaining studies did not adequately describe adherence to PA intensity therefore this is unknown.

Intervention delivery

Exercise interventions were often supervised, although three studies investigated the effects of either an unsupervised home exercise programme^{31, 38} or tailored PA³⁹. One study reported that a physiotherapist guided initial exercises²⁹, but it was unclear whether ongoing exercise was performed with or without supervision. Not all studies described the professional background of the person delivering the intervention. Where reported, physiotherapists^{27, 29, 39}, a yoga instructor²⁸ or physical education graduate students³⁰ provided supervision.

Intervention adherence

Intervention adherence was reported in four studies. These included a mean attendance rate at sessions of 96%²⁸ and 78%²⁷, median number of sessions attended as 30 out of 36 for both class and home exercise groups³¹, and mean exercise frequency as 1.5 times weekly in months zero to 12, and 1.4 times weekly in months 13 to 24²⁹. Adherence data for this last study were collected via self-reported exercise diaries, therefore the authors acknowledged that they may be subject to recall bias and inaccurate reporting²⁹.

Outcome measures

A range of self-reported fatigue outcome measures was used. Three studies used two scales^{28, 32, 39}. Two studies reported fatigue as a primary outcome measure^{38, 39}. The primary outcome was not identified in three studies²⁹⁻³¹. No details were provided in relation to the design and development of PA interventions, although one study stated that the “goal of the intervention was, in partnership between participant and physical therapist, to devise a mutually agreed self-care plan that guided the participant in managing his or her fatigue”³⁹ (p. 29). Participants were selected for the presence of fatigue in only one study³⁹.

Adverse events

Only one study explicitly reported that there were no adverse events associated with the intervention³². None of the remaining studies reported adverse events. It is unclear whether this was due to a true absence of adverse events or poor reporting.

Risk of bias

Overall, four studies met three criteria^{27, 31, 32, 39}, three met two criteria^{28, 29, 38}, and one met one criterion³⁰ for low risk of bias (table 3). The percentage risk of bias for each domain across all studies is presented in figure 2.

Table 3. Risk of bias summary for included studies (n=8)

Figure 2: Risk of bias presented as percentages for included studies (n=8)

Random sequence generation and allocation concealment (selection bias)

Random sequence generation was adequately described in five studies. Randomisation was performed using computer-generated random numbers^{27, 32, 38, 39} or an *a priori* list of randomly generated permutations of three numbers³¹. Three studies adequately reported allocation concealment. Methods included patients independently choosing a time slot prior to randomisation³⁰ and use of sealed opaque envelopes^{32, 39}.

Blinding (performance and detection bias)

Blinding of participants, personnel and assessors was not reported in three studies^{29, 30, 38}. The remaining five studies reported blinding of outcome assessors only^{27, 28, 31, 32, 39}.

Incomplete outcome data (attrition bias)

The majority of studies (n=6) were considered at low risk of attrition bias, reporting all outcome data and giving reasons for missing data. The remaining studies either did not explain missing data for three participants who withdrew and no fatigue data were presented for controls³⁰, or no data were provided for withdrawals between randomisation and baseline³¹.

Selective outcome reporting (reporting bias)

Selective reporting was noted in four studies^{30-32, 39}. Outcome data for three intervention arms were combined in one study, thus providing insufficient detail regarding the effect of each intervention³⁰. One study reported collecting social support data³¹ and another collecting information about medications³⁹ but did not report these in the published article. The third study reported recording the number of and reasons for missing both intervention and control arm sessions, but did not present these data³².

Other sources of bias

Only one study was considered free from other sources of bias as specified for this review³¹. Of the remaining six studies, three were considered at high risk^{28, 29, 32} and four had unclear risk of bias from other sources^{27, 30, 38, 39} (table 4).

Table 4: Reasons for judgement of the risk of other sources of bias

Effect on fatigue

A statistically significant post-test improvement in fatigue scores was reported in the intervention arm compared with controls in five studies ($p < 0.05$)^{27, 28, 32, 38, 39}. The between-group difference in median change scores for the Visual Analogue Scale (VAS) for fatigue was reported to be clinically significant in one study³⁹ (minimal clinically important difference (MCID)⁴⁰: 10) although the difference in change in means of 8.2 did not reach the MCID. Information on the ability of fatigue scales to detect change⁴⁰ suggests that pre- to post-test between-group differences in change scores in three other studies were clinically significant^{28, 32, 38}. Changes in the 36 item Short Form Health Survey (SF-36) vitality scores in the remaining study²⁷ fell short of the MCID by 0.6 points⁴⁰. Although one study reported statistically significant changes in overall symptoms, the significance of changes in fatigue were not reported³¹. The fatigue change scores presented in the research report did not meet the criteria for MCID for the Multidimensional Assessment of Fatigue scale⁴⁰. The remaining two studies did not report statistically significant improvements, with one study only recording subjective improvements in fatigue³⁰.

Meta-analysis

In the Cochrane review mean change scores from pre- to post-test were combined in a meta-analysis for six comparisons from five of the six original RCTs^{27-29, 31, 32}. One study included two intervention arms enabling two comparisons³¹. Change data for fatigue were not available for the sixth study³⁰. Results from the six original comparisons indicated that PA was statistically more effective than control immediately post-intervention (SMD -0.36, 95% CI -0.62 to -0.10, $p = 0.0066$), indicating a small beneficial effect of PA on fatigue¹⁹.

In this updated review a summary effect size was not presented for one of the additional included studies³⁸. SMD for fatigue outcome was calculated as -0.47, unadjusted for baseline differences, indicating a small effect. When calculating SMD for the study, errors

in the data were noted making it difficult to trust the accuracy of the results. Therefore this study was not included in the meta-analysis. Although the SMD was slightly larger than that obtained in the Cochrane review, methodological concerns meant it would not strengthen or alter the original conclusions. The second study included in the updated review reported a summary effect size for VAS fatigue and the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAFF-MDQ)^{41, 42}. Where more than one fatigue outcome was reported for a study in the original Cochrane review VAS data were included in the meta-analysis¹⁹. The second study included in the updated review reported a summary effect size of 0.37 for VAS fatigue suggesting a small beneficial effect³⁹. As the size of the treatment effect was very similar to that of the original review it was decided that there was no need to repeat the meta-analysis.

Long-term follow-up

One study re-assessed outcomes two months after treatment²⁸. Significant post-treatment effects of the intervention on fatigue were not maintained at 2-month follow-up. In another study post-treatment effects of the intervention on VAS fatigue and BRAFF-MDQ total fatigue scores were no longer significant six months after baseline³⁹. However, significant improvements in the BRAFF-MDQ physical fatigue and living with fatigue subscales were maintained ($p < 0.05$). Follow-up data were not available for any other studies.

Discussion

This review investigated the effectiveness of PA interventions for reducing RA fatigue. Eight RCTs investigating PA interventions and including a fatigue outcome measure were included, providing data for 540 adults with RA. A previous meta-analysis incorporating data from five of the eight studies demonstrated a small significant effect for PA when compared with a control intervention, suggesting that PA may be useful for managing fatigue in RA in the

short-term¹⁹. This update identified two new RCTs that reported statistically significant changes in fatigue outcomes following a home exercise intervention ($p=0.04$)³⁸ and a person-centred physical therapy intervention focused on tailoring health-enhancing PA ($p<0.05$)³⁹ compared with controls. However, poor methodological quality and reporting errors, and similar effect sizes meant that inclusion of new data in the meta-analysis was not warranted. The limited follow-up data for included studies limits our understanding of any ongoing effects of PA on RA fatigue.

Components of PA interventions identified in this review included type of PA, mode of delivery, intervention length and duration, frequency and intensity of PA. Interventions were varied and included land- and pool-based aerobic exercise, yoga, Tai Chi and resistance training. Evidence from other long-term conditions suggests that aerobic exercise may be particularly beneficial for managing fatigue¹⁸. Delivery methods included supervised class programmes, unsupervised home exercise and individual person-centred physical therapy. Intervention length was reasonably consistent, with the majority lasting 12 weeks. This is similar to the length of PA interventions for managing fatigue in chronic fatigue syndrome¹⁷.

Several studies prescribed the intensity, duration and frequency of PA. These varied between interventions and it is unclear whether these parameters were successfully adhered to throughout the intervention period. Overall, there was insufficient information from these interventions to judge whether specific PA parameters are more or less likely to be effective for fatigue management in RA. This is a common issue, and data regarding dose response for exercise in general are rarely available. Considerable variation in the intensity, duration and frequency of PA sessions for fatigue management in other long-term conditions has also been reported^{17, 18}, although it has been suggested that commencing PA at a lower intensity might be more effective in the treatment of chronic fatigue syndrome⁴³.

Information regarding overall adherence to PA interventions was limited, making it difficult to determine reasons for participation or non-participation in these programmes. PA research relies on voluntary participation. Consequently, recruitment is often biased towards those who are interested in or motivated to perform PA⁴⁴. Self-selection of participants in PA trials also has implications for the control arm. As a sub-group of motivated participants, they might be more likely to engage in PA even if they have been asked not to, thus increasing the potential for contamination and reducing potential effect size for the PA intervention. This limits external validity of the findings.

Reasons for declining participation in the included studies were often not reported. Where they were, reasons included being busy, travel distance or disinterest²⁸. These reasons have been cited in other PA trials in RA^{44, 45}. An in-depth analysis of participants and non-participants in a recent PA trial in RA concluded that only 8% of the initial target population were assessed at baseline, despite 62% expressing interest prior to receiving information about location, timing and cost of the PA interventions⁴⁴. It is possible that PA interventions only reach a small minority of eligible participants in clinical practice.

The included studies were of moderate methodological quality, with small group sizes and lack of blinding being particularly problematic. Three studies reported a sample size calculation^{31, 38, 39} but only one was based upon fatigue as the primary outcome³⁹. It was unclear whether other studies reporting significant changes in fatigue were adequately powered to detect changes in these outcomes. Small samples and lack of statistical power limit the ability to generalise results to the wider RA population.

Blinding of participants is often not possible for PA interventions⁴⁶, and the use of self-reported questionnaires for measuring fatigue outcome negates the usefulness of blinding the outcome assessor. Therefore, risk of performance and detection bias is difficult to minimise for these interventions. Nonetheless, attempts to minimise this risk were only

reported in one study³⁹. Poor reporting was noted in several papers, making it difficult to determine the overall quality of the research. The majority of studies were at high risk of bias from sources such as contamination between groups, further limiting the internal validity of the research findings, for example, where control participants performed range of movement and stretching exercises alongside recreational PA²⁹.

Only two of the interventions specifically aimed to manage fatigue^{38,39}, although descriptions of intervention design and development processes were minimal for all studies. Similarly, only one study selected participants for the presence of fatigue³⁹, therefore this symptom may not have been a significant problem for participants in other studies. Consequently, these fatigue data are likely to underestimate the effectiveness of PA for RA fatigue management, as fatigue has been cited as a barrier to PA⁴⁷. Participants who withdrew from a recent PA trial between agreeing to take part and baseline assessment reported more fatigue than those who were assessed ($p=0.009$)⁴⁴. It is possible that eligible patients who experienced greater fatigue declined participation in studies included in this review and the resulting participants might be less representative of fatigued patients with RA. As a result, the true effectiveness of PA for reducing fatigue in RA is difficult to determine.

Variations in participant characteristics in included studies may further limit the external validity of the results. This includes imbalances in gender, with the inclusion of women only in two studies and fewer men included overall. Although RA affects more women than men², men tend to be under-represented in PA trials in RA^{44,48}. Also, men with RA may require different support strategies than women⁴⁹. As a result, recruitment of predominantly women to a PA intervention may not simply be indicative of gender differences in prevalence rates of RA, but may also reflect different coping styles and management preferences. It cannot be presumed, therefore, that these PA interventions would be effective for reducing fatigue in both men and women with RA.

The range of ages included in studies was also not representative of the general RA population. Peak age of incidence in the UK has been reported as 55-64 years old in women and 65-75 years old in men². However, only three studies reported the average age of participants as falling within the fifth and sixth decades, and none in the seventh decade. This may reflect other observations that participants in PA trials tend to be younger^{44, 45}.

Limitations of the review

There are several limitations to the current review. Conference abstracts were excluded, study authors were not contacted and grey literature was not searched. This may have resulted in omission of relevant data.

Only one reviewer (VS) completed data extraction and critical appraisal of the new studies in this update. However, overall results were discussed with a second reviewer (FC) who had been involved with the original review, and all authors were familiar with the eight papers and contributed to the review write-up. Similarly, the Cochrane meta-analysis was not revised to include data from additional studies. However, their inclusion is unlikely to have altered the current conclusions. Finally, the search was limited to RCTs in order to determine effectiveness of the interventions of interest. By limiting the search in this way potentially useful evidence from non-randomised and qualitative studies will have been missed.

Conclusions

Although there is some evidence from a previous meta-analysis of the potential for PA to be effective in reducing symptoms of fatigue in RA¹⁹, this evidence remains limited. Since publication of the original Cochrane review, two further RCTs have been published, also suggesting a positive effect of exercise on fatigue^{38, 39}. However, methodological flaws and poor reporting undermine the trustworthiness of these findings. Additionally, only two of the PA interventions in the included studies specifically aimed to manage RA fatigue, and few

participants were selected to take part in the studies based on their fatigue experience, making it difficult to establish the true effectiveness of these interventions for managing RA fatigue. Further research is needed to identify the optimal PA intervention, including key components and parameters such as type and intensity of PA, for managing fatigue for people with RA.

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Table 1. Example search strategy for use in MEDLINE

1	exp arthritis, rheumatoid/
2	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthrit\$ or artrit\$ or diseas\$ or condition\$ or nodule\$)).tw.
3	1 or 2
4	exp Fatigue/
5	fatigue\$.tw.
6	(tired\$ or weary or weariness or exhaustion or exhausted).tw.
7	((astenia or asthenic) and syndrome).tw.
8	((lack or loss or lost) adj3 (energy or vigo?r)).tw.
9	(apath\$ or lassitude or weak\$ or letharg\$).tw.
10	(feel\$ adj3 (drained or sleep\$ or sluggish)).tw.
11	vitality.tw.
12	or/4-11
13	randomized controlled trial.pt.
14	controlled clinical trial.pt.
15	randomized.ab.
16	placebo.ab.
17	drug therapy.fs.
18	randomly.ab.
19	trial.ab.
20	groups.ab.
21	or/13-20
22	(animals not (humans and animals)).sh.
23	21 not 22
24	and/3,12,23
25	exercise\$
26	resistance adj (train\$ OR prog\$)
27	strength adj (train\$ OR prog\$)
28	flexibility adj (train\$ OR prog\$)
29	endurance adj (train\$ OR prog\$)
30	aerobic\$
31	physical\$ activ\$
32	physical\$ therap\$

33	physical\$ exercise\$
34	interval training
35	sport\$
36	movement therap\$
37	stretching
38	dance therap\$
39	Tai Ji or Tai Chi or Tai-Ji or Tai-Chi
40	Walking
41	Yoga
42	Hydrotherap\$
43	or/25-42
44	and/24,43

\$=used to identify all words beginning with the stem

Table 2. Description of included interventions

Lead author, (year)	Bilberg, (2005) ²⁷	Durcan, (2014) ^{38*}	Evans, (2013) ²⁸	Feldthusen, (2016) ^{39*}	Hakkinen, (2003) ²⁹	Harkcom, (1985) ³⁰	Neuberger, (2007) ³¹	Wang, (2008) ³²
Primary outcome measure	Aerobic capacity, SF-36 physical	FSS, PSQI	HRQoL	VAS fatigue	Not identified	Not identified	Not identified	Attainment of ACR 20 response criteria
Fatigue scale	SF-36 vitality	FSS	SF-36 vitality, FACIT-F	VAS fatigue, BRAF MDQ	VAS fatigue	Likert scale rating of fatigue	MAF	VAS fatigue, SF-36 vitality
Type of PA	Aerobic capacity, dynamic and static strengthening and endurance exercises in a temperate pool	Home exercise programme (resistance exercise, ROM, walking)	Iyengar Yoga	Individually tailored aerobic PA	Dynamic strength training, using elastic bands and dumbbells, plus recreational PA, e.g. walking, cycling	Bicycle ergometer	Low-impact aerobics plus strengthening, Intervention arm I = class exercise, Intervention arm II = home exercise	Tai Chi
Duration and frequency of PA	45 min, 2 x weekly	30-60 min, Resistance training 3 x weekly, daily ROM, walking 5 x weekly	90 min, 2 x weekly	20-30 min, 3-5 x weekly	2 sets per exercise, 8-12 repetitions, 2 x weekly	15-35 min, 3 x weekly	60 min, 3 x weekly	60 min, 2 x weekly
Intensity of PA	75% HRmax	Resistance: 40-50% 1 RM; walking: light- to moderate-intensity (moderately short of breath on exertion)	N/A	Moderate to vigorous (not defined)	50-70% RM	70% HRmax	60-80% HRmax	N/A

Lead author, (year)	Bilberg, (2005) ²⁷	Durcan, (2014) ^{38*}	Evans, (2013) ²⁸	Feldthusen, (2016) ^{39*}	Hakkinen, (2003) ²⁹	Harkcom, (1985) ³⁰	Neuberger, (2007) ³¹	Wang, (2008) ³²
Length of intervention	12 weeks	12 weeks	6 weeks	12 weeks	24 months	12 weeks	12 weeks	12 weeks
Control intervention	Continue daily activities	Advice on benefits of exercise in RA	Usual care waitlist control	Continue usual physical and social activities, pharmacologic treatment and other treatments associated with care	ROM and stretching exercises 2 x weekly, continue recreational activity, no strength training	Continue daily activities	Continue baseline exercise levels	Stretching training and wellness education
Adherence to intervention and control	Mean attendance at intervention sessions = 78%	Not reported	96% intervention sessions attended	Not reported	Intervention group compliance: Months 0-12: Average 1.5 x weekly exercising; Months 13-24: average 1.4 x weekly	Not reported	Median of 30 of 36 sessions completed by both class and home exercise groups	Not reported

Lead author, (year)	Bilberg, (2005) ²⁷	Durcan, (2014) ^{38*}	Evans, (2013) ²⁸	Feldthusen, (2016) ^{39*}	Hakkinen, (2003) ²⁹	Harkcom, (1985) ³⁰	Neuberger, (2007) ³¹	Wang, (2008) ³²
Results for fatigue outcome	Significant between group difference at 12 weeks in favour of the intervention (p<0.05) Between-group difference in change scores = 10.1 (MCID: 10.7) ^a	Significant between-group difference in change in fatigue score at 12 weeks in favour of the intervention (p=0.04) Reported between-group difference in change scores = 11.3 (18%) (MCID: 15%) ^a	SF-36 significant post-treatment group differences in favour of the intervention (p<0.01) Between-group difference in change scores = 17 (MCID: 10.7) ^a FACIT-F significant changes (p<0.05) Between-group difference in change scores = 7.9 (MCID: 3-4) ^a	Significant between-group difference in change in mean VAS fatigue score at 12 weeks in favour of the intervention (p=0.042) Between-group difference in median change scores = 12 (MCID: 10) ^a BRAF MDQ significant changes (p=0.023), including subscales Physical fatigue (p=0.033), Living with fatigue (p=0.034) and Emotional fatigue (p=0.048)	No significant change	Subjective reporting of improvement in fatigue in intervention arm	Intervention arm I: Significant decrease in overall symptoms at 12 weeks in favour of the intervention (p<0.04) Between-group difference in fatigue change scores (class vs control) = 3.17 (significance not reported) (MCID: 5.0) ^a Intervention arm II: not significant	Significant between-group difference on SF-36 vitality in favour of the intervention (p=0.01) Between-group difference in change scores = 18 (MCID: 10.7) ^a

BRAF MDQ=Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire; FACIT-F=Functional Assessment of Chronic Illness Therapy Fatigue Subscale; FSS=Fatigue Severity Scale; HAQ=Health Assessment Questionnaire; HRmax=maximum heart rate; HRQoL=Health Related Quality of Life; MACTAR=McMaster Toronto Arthritis Patient Preference Disability Questionnaire; MAF=Multidimensional Assessment of Fatigue questionnaire; MCID=minimal clinically important difference; N/A=not applicable; PA=physical activity; PSQI=Pittsburgh Sleep Quality Index; RA=rheumatoid arthritis; RM=repetition maximum; ROM=range of movement; SF-36=36 item Short Form Health Survey; VAS=visual analogue scale

**Article identified in updated search*

^a*Data from Hewlett, Dures and Almeida, (2011)*⁴⁰

Table 3. Risk of bias summary for included studies (n=8)

Lead author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance and detection)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bilberg, ²⁷ (2005)	+	?	?	+	+	?
Durcan, ³⁸ (2014)	+	?	?	+	?	?
Evans, ²⁸ (2013)	?	?	-	+	+	-
Feldthusen, ³⁹ (2016)	+	+	-	+	?	?
Hakkinen, ²⁹ (2003)	?	?	?	+	+	-
Harkcom, ³⁰ (1985)	?	+	-	-	-	?
Neuberger, ³¹ (2007)	+	?	-	+	-	+
Wang, ³² (2008)	+	+	?	+	-	-

+ = low risk; ? = unclear risk; - = high risk

Table 4: Reasons for judgement of the risk of other sources of bias

Lead author, (year)	Risk of other sources of bias	Reason for judgement of risk of bias
Bilberg, ²⁷ (2005)	?	No reporting of monitoring of adherence of control arm to home exercise and daily activities
Durcan, ³⁸ (2014)	?	No reporting of adherence to physical activity or exercise in either arm
Evans, ²⁸ (2013)	-	\$10 travel expenses paid for intervention participants travelling more than 25 miles
Feldthusen, ³⁹ (2016)	?	No reported monitoring of access to treatment associated with care, e.g. physiotherapy, in control arm
Hakkinen, ²⁹ (2003)	-	Control group performed exercises, n=3 started exercising in a gym, monitoring by diaries not reported for control arm
Harkcom, ³⁰ (1985)	?	Control data for fatigue not reported so unable to determine baseline differences. Monitoring of adherence to physical

Neuberger, (2007) ³¹	+	activity not reported for either group No evidence of other sources of bias
Wang, (2008) ³²	-	Control group performed daily stretching exercises. Monitoring of adherence to physical activity not reported

+ = low risk; ? = unclear risk; - = high risk

Figure 1. Flow diagram showing study selection process

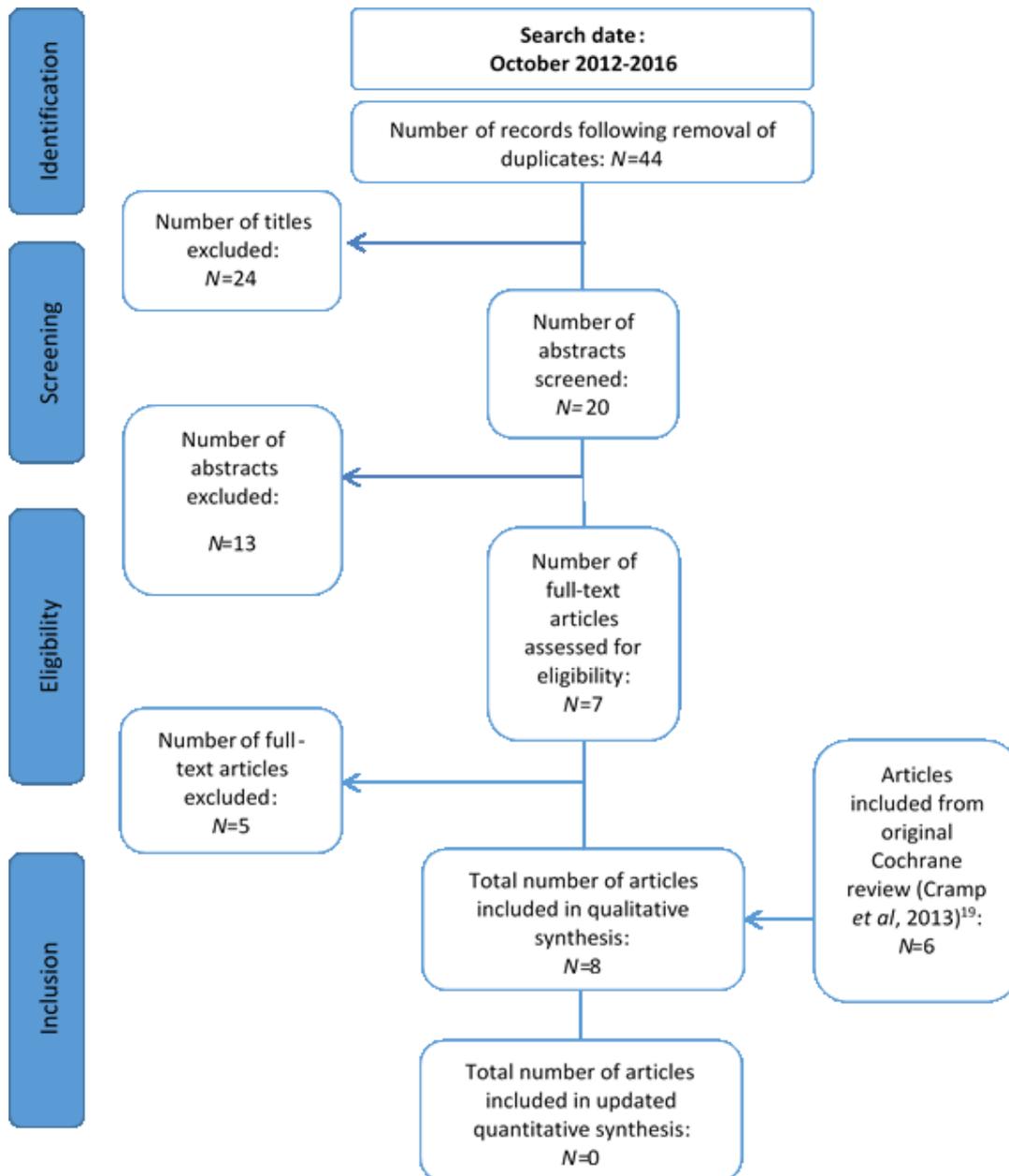


Figure 2: Risk of bias presented as percentages for included studies (n=8)

