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Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis

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Title: Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis

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Abstract

Fatigue is a common and highly debilitating symptom of multiple sclerosis (MS). This meta-analytic systematic review with detailed narrative synthesis examined randomised-controlled (RCTs) and controlled trials of behavioural and exercise interventions targeting fatigue in adults with MS to assess which treatments offer the most promise in reducing fatigue severity/impact. Medline, EMBASE and PsycInfo electronic databases, amongst others, were searched through to August 2018. Thirty-four trials (12 exercise, 16 behavioural and 6 combined; n=2,434 participants) met inclusion criteria. Data from 31 studies (n=1,991 participants) contributed to the meta-analysis. Risk of bias (using the Cochrane tool) and study quality (GRADE) were assessed. The pooled (SMD) end-of-treatment effects on self-reported fatigue were: exercise interventions (n=13) -.84 (95% CI -1.20 to -.47); behavioural interventions (n=16) -.37 (95% CI -.53 to -.22); combined interventions (n=5) -.16 (95% CI: -.36 to .04). Heterogeneity was high overall. Study quality was very low for exercise interventions and moderate for behavioural and combined interventions. Considering health care professional time, subgroup results suggest web-based cognitive behavioural therapy for fatigue, balance and/or multicomponent exercise interventions may be the cost-efficient therapies. These need testing in large RCTs with long-term follow-up to help define an implementable fatigue management pathway in MS.

Word count: 198

Key words: Fatigue; Multiple sclerosis (MS); Meta-analysis; Randomised controlled trials; Behavioural interventions; Exercise interventions.

Introduction

Multiple sclerosis (MS) is a chronic, incurable, demyelinating disease of the central nervous system, usually diagnosed during young adulthood (Compston & Coles, 2008). An estimated 2.3 million people worldwide have MS with a 2:1 ratio of women to men (Atlas of MS, 2013). Around 85% of people with MS (pwMS) are diagnosed with relapsing remitting MS (RRMS), which includes periods of remission, interspersed with symptom relapses. After 10 to 20 years, many patients with RRMS go on to develop secondary-progressive MS (SPMS), where impairment accumulates over time. Around 15% of pwMS are diagnosed with primary-progressive MS (PPMS) characterised by chronic-progressive worsening of symptoms and disability from onset (Compston & Coles, 2008; Reich, Lucchinetti, & Calabresi, 2018).

The disease causes a range of symptoms and associated disabilities, including loss of mobility, spasticity, sensory disturbances, impaired balance, slowed cognitive processing, incontinence, pain, and fatigue depending on the site of neuronal damage (Compston & Coles, 2008). Fatigue is one of the most common, reported by around 80% of pwMS. Two-thirds consider fatigue their most troubling symptom (Giovannoni, 2006). It is one of the most commonly cited reasons for stopping work and a predictor of poor quality of life even when controlling for disease severity (Branas, Jordan, Fry-Smith, Burls, & Hyde, 2000; Krupp, Serafin, & Christodoulou, 2010).

In the context of chronic medical illnesses, such as MS, fatigue is defined as a lack of energy, feeling of exhaustion or overwhelming sense of tiredness that can be physical or mental or both. This fatigue is not relieved by rest and may be unrelated to physiological exertion (Bleijenberg, 2003; Krupp, 2003; NICE, 2015). Fatigue is one of the least understood symptoms in MS. Evidence to date suggests that primary disease factors, such as demyelination, axonal loss or damage, and inflammatory disease activity only play a small part in MS fatigue (Krupp et al., 2010; van Kessel & Moss-Morris, 2006). According to older evidence significantly higher levels of fatigue were observed among people with progressive forms of MS compared to those with RRMS (Bergamaschi, Romani, Versino, Poli, & Cosi, 1997; Colosimo et al., 1995). However, more recent evidence suggests that there are no significant differences in fatigue by disease course after controlling for disability and duration of symptoms (Kroencke, Lynch, & Denney, 2000; Lerdal, Gulowsen Celius, Krupp, & Dahl, 2007; Patrick, Christodoulou, Krupp, & Consortium, 2009). Fatigue directly related to the disease mechanisms of MS can be referred to as primary fatigue (Langeskov-Christensen, Bisson, Finlayson, & Dalgas, 2017).

Recent systematic reviews suggest medications often used to treat MS fatigue, such as amantadine and aspirin, have low efficacy and that non-pharmacological interventions (both exercise and psychological/educational) may have more beneficial effects on reducing the severity of fatigue (Asano & Finlayson, 2014; Khan, Amatya, & Galea, 2014). This may be because a wide range of psychosocial and secondary factors contribute to fatigue in MS, including poor sleep, low mood, deconditioning, and unhelpful cognitive behavioural responses to fatigue (Krupp et al., 2010; van Kessel & Moss-Morris, 2006). Fatigue associated with these non-disease-specific factors is defined by some researchers as secondary fatigue which may be treatable through behavioural methods (Langeskov-Christensen et al., 2017). Clinical guidelines suggest behavioural methods and exercise be incorporated in treatments for MS fatigue, but the nature of these treatments is poorly specified (National Institute for Health and Care Excellence, 2014).

Meta-analytic systematic reviews of exercise and/or behavioural interventions for the management of fatigue in MS already exist. Two focused on the effects of exercise therapy only (Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015; Pilutti, Greenlee, Motl, Nickrent, & Petruzzello, 2013), one on yoga (Cramer, Lauche, Azizi, Dobos, & Langhorst, 2014), three on behavioural interventions, including energy conservation (EC; Blikman et al., 2013), cognitive-behavioural therapy (CBT; van den Akker et al., 2016), and patient education (Wendebourg et al., 2017). Only Asano and Finlayson (2014)'s systematic review included pharmacological, exercise and behavioural interventions, but no consideration was given to the heterogeneity of interventions within the exercise and behavioural categories. Except for three systematic reviews (Asano & Finlayson, 2014; van den Akker et al., 2016; Wendebourg et al., 2017), none of the other reviews specified fatigue as a primary outcome. Furthermore, van den Akker et al. (2016)'s review found variability in intervention content, suggesting that even CBT is not one entity.

The combined evidence from these reviews has shown small to moderate effects of exercise and behavioural interventions on fatigue in MS; however, given the heterogeneity and complexity of such interventions, this evidence fails to unravel differences in efficacy by subtypes of exercise or behavioural interventions, limiting the clinical utility of the evidence syntheses. Firstly, previous reviews have not focused exclusively on interventions aimed at fatigue, and instead pooled outcomes across fatigue-specific and non-specific interventions. Although, improvements in mood or self-management are likely to lead to secondary benefits in fatigue, essential differences in content of therapeutically-similar interventions based on intervention target are overlooked. For instance, CBT for depression focuses on thoughts and behaviours relevant to low mood, while fatigue-specific thoughts and behaviours need to be addressed in CBT aimed at fatigue. In fact, according to a systematic review in cancer, psychosocial interventions were only superior to exercise interventions when aimed specifically at fatigue (Kangas, Bovbjerg, & Montgomery, 2008). Inevitably this also limits the consideration of treatment mechanisms pertinent to fatigue. Another important caveat of this is that trials evaluating interventions not aimed at fatigue specifically are less likely to screen patients for fatigue, which is likely to introduce a ceiling effect, again doing little to discern what therapeutic approaches need to be considered in the management of fatigue.

It is also still unclear which exercise and behavioural interventions are likely to have the greatest clinical utility, as an in-depth analysis of intervention components is not presented in the current reviews and interventions are often pooled in meta-analyses without any clear indication of how similar or different these interventions may be, making the relative effectiveness hard to determine. For example, whereas CBT for fatigue involves establishing balance in activity and rest by often gradually increasing activity (Chalder, 2014), energy conservation involves a systematic assessment of all daily activities and identifying ways of reducing energy expenditure (Packer, Brink, & Sauriol, 1995). This clearly highlights that pooling behavioural interventions without consideration of the potentially conflicting mechanisms of action specific to each approach may not be appropriate. Issues such as intervention delivery, dose, and homework practice are often not elucidated. Therefore, although a number of meta-analytic reviews are already available, key research questions remain unanswered. Hoffman and colleagues have recently argued for methods of reviewing complex intervention studies which enhance the clinical utility of the reviews (Hoffmann et al., 2017; Hoffmann & Walker, 2015). These include using the Template of Intervention Description and Replication (TIDieR) to extract and summarise the contextual factors relevant to an intervention (Hoffmann et al., 2014) and establishing the key components of complex interventions. The current systematic review incorporates these elaborated methods alongside meta-analysis of treatment efficacy. The overall aim was to provide a detailed description of all behavioural and exercise interventions for MS fatigue trialled to date against their relative potential efficacy and future treatment utility. The specific objectives are to:

(1) Provide a narrative synthesis of all the exercise and behavioural interventions explicitly designed to treat fatigue in MS, including a breakdown of the treatment components of each intervention, the delivery methods, and acceptability of the interventions (uptake and adherence).

(2) Calculate the effect size for outcomes of self-reported fatigue for each intervention based on the primary post-randomisation end-point (defined as being within two months following the stated duration of the intervention) and summarise risk of bias for each study.

(3) Create subgroups within the exercise and behavioural interventions based on key intervention components and conduct meta-analyses of post-treatment effect sizes of self-reported severity or impact of fatigue across each of these intervention subtypes.

(4) Where possible conduct meta-analyses of effect sizes of longer-term follow-up of self-reported fatigue outcomes across each of these intervention subtypes[1].

(5) Compare the overall standardised intervention effect sizes of the exercise and behavioural interventions.

(6) If possible, conduct exploratory moderator and sensitivity analyses to explore how treatment effects vary according to whether interventions were guided by theory or not, different levels of health care professional contact, types of MS, comparators used, and study quality.

Method

The review protocol was registered on PROSPERO (2016: CRD42016033763) and contains details of the methodology employed (Moss-Morris et al., 2016).

Eligibility Criteria

Studies were included if they (a) were randomised controlled trials (RCT) or quasi-randomised controlled clinical trials (CCT) (b) delivered behavioural and/or exercise interventions where the primary focus of the intervention was explicitly stated as reducing

[1] Our original protocol also aimed to explore treatment effects on measures of physical or cognitive/mental fatigability (A. M. Harrison, das Nair, & Moss-Morris, 2016). Fatigability has been defined as "the magnitude or rate of change in a performance criterion relative to a reference value or given time of task performance or measure of mechanical output" (Kluger, Krupp, & Enoka, 2013). As none of the studies included in the review included a measure of fatigability, this aim was dropped from the review (A. M. Harrison et al., 2016).

fatigue[2] (c) recruited adults (aged 18 and over) with a confirmed diagnosis of MS (McDonald et al., 2001; Polman et al., 2011; Polman et al., 2005) (d) used any comparator (no intervention. usual care, standard medical care, placebo treatment or another active intervention); and (e) measured self-reported fatigue severity and/or impact of fatigue, or vitality as an outcome using a validated scale. Studies including pwMS alongside people with other conditions were included if at least 50% of the sample comprised pwMS, and if data for the MS subgroup were reported separately or provided by the author on request. Trials were excluded if they evaluated pharmacological and dietary interventions, except where diet was included as part of a broader behavioural approach. No language restrictions were applied.

Search Strategy

Studies were identified though a systematic online search of AMED, CINAHL, EMBASE, LILACS, Medline, PEDro, PsycInfo, SPORTDiscus, and Web of Science core collection databases to December 2015 using search terms in Appendix A. AH and RS screened all titles/online abstracts independently. Relevant full-text published and unpublished articles were read and assessed for eligibility. Forward citation searches and screening of reference lists were conducted of included articles and previous MS fatigue reviews and key authors contacted for unpublished studies. Trial databases (Cochrane Library, WHO ICTRP, NIHR, ClinicalTrials.gov, Controlled trials) and grey literature online databases were also searched (Dissertation Abstracts International World Cat, Greylit.org, and Open Grey). The search was updated using the same strategy on the online databases in August 2018 by MvdL and a research assistant (see flow-chart Figure 1).

INSERT FIGURE 1 ABOUT HERE

[2] Generic interventions like CBT or Mindfulness-based Stress Reduction (MBSR) were not deemed eligible, unless specifically targeting fatigue and a clear mechanism postulated by authors.

Data Extraction

Trial data were double extracted independently using tables developed *a priori* based on the Cochrane Handbook recommendations (Higgins et al., 2011). Data extracted for the calculation of treatment effect sizes were sample sizes, means, and standard deviations per arm at each post-randomisation assessment. Where this was not available, related information (e.g. standard errors, confidence intervals and test statistics) were recorded. The details of the intervention delivery were single-extracted using TIDieR (Hoffmann & Walker, 2015). Where possible, manuals of the interventions were obtained from authors. Details of the key intervention components or techniques were extracted either from these manuals or article descriptions alongside background theory, if available.

Data Synthesis Methods

A narrative synthesis of all interventions was conducted (Popay et al., 2006), including a breakdown of the key treatment components and the acceptability of the interventions (uptake and adherence). Because of the multicomponent nature of many of the interventions, the key components of each of these were described and where relevant, linked to behaviour change taxonomies (Hardcastle, Fortier, Blake, & Hagger, 2017; Michie et al., 2013).

Grouping of Interventions: There has been a recent trend for reviews to group interventions based on the use of specified behaviour change techniques (BCTs; French, Olander, Chisholm, & Mc Sharry, 2014; Michie, Abraham, Whittington, McAteer, & Gupta, 2009) as defined in the Behaviour Change Taxonomy (Michie et al., 2013). However, the context in which BCTs were delivered varied substantially across interventions included in this review (e.g. goal setting to conserve energy versus goal setting to increase activity) and the BCT approach failed to differentiate between type of intervention. Therefore, interventions were sub-categorized under three broad groupings: exercise, behavioral or mixed behavioral/exercise interventions based on similar intervention features and theoretical backgrounds rather than use of BCTs. Behavioural interventions focused on behaviour change, cognitive/attitudinal changes and/or emotional changes. Behavioural interventions included physical activity unless clearly defined as exercise. Physical activity was defined as any bodily movement produced by skeletal muscles that requires energy expenditure and includes activities which are done as part of playing, working, active transportation, house chores and recreational activities (WHO, 2018). Exercise interventions included exercise defined as a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness (United States Department of Health and Human Services, 2008).

Mixed interventions included a clearly defined exercise component (as opposed to general physical activity) alongside a clearly defined behavioral intervention (i.e. a defined intervention not just use of BCTs to enhance the exercise uptake).

Risk of Bias: Risk of bias for all included studies was assessed independently by AH and RS according to the Cochrane Handbook for Systematic Reviews of Risk of Bias tool (Higgins et al., 2011). Overall studies were considered to be 'low risk' of bias in relation to treatment effects when: i) participants were randomly assigned to groups (selection bias); ii) group allocation was concealed to study personnel at both randomisation and outcome assessment (selection & detection bias); iii) analyses followed the intention to treat principle with levels of incomplete outcome data unlikely to introduce bias (attrition bias); and iv) there was no evidence of selective outcome reporting for fatigue (reporting bias). It is important to note that all studies are at risk for performance bias, as whilst it is possible to blind participants to the study's hypotheses, it is not possible to blind participants or health care professionals to group allocation in behavioural and exercise interventions (Page & Persch, 2013). Therefore, performance bias was ignored in the overall assessment of bias for each study, but is included in the summaries per study. Discrepancies between raters were resolved by discussion with all authors until consensus was reached.

Meta-Analysis: Individual effect sizes were calculated for each study based on data extracted. Treatment effect estimates were pooled in pairwise random-effects meta-analyses conducted using *metan* in Stata 14.1 (Harris, 2008), stratifying interventions into their subgroups under (1) exercise, (2) behavioural and (3) mixed. The treatment effect on the primary fatigue outcome was expressed as the standardised mean difference (SMD) between groups at the primary post-randomisation end-point, calculated as Hedge's *g* with correction for small degrees of freedom (White & Thomas, 2005). In trials with more than one intervention group, the standard error of the SMD compared to a common control arm was calculated accounting for the non-independence of the control arm across the comparisons (Borenstein, 2009). Data were combined into a single control group where studies included multiple control groups. Statistical heterogeneity, representing the variability in effect sizes between studies, was quantified using the I^2 statistic within each intervention group and subgroup. Heterogeneity was considered important when I^2 was greater than 40% and the significance test indicated $p<.05$ (Higgins et al., 2011).

Where available, data for fatigue at subsequent longer-term follow-up assessments (>2months) were extracted to allow for examination of maintenance of treatment effects. Data from 7 studies were provided for the behavioural intervention group at mid-term follow-up (3-6 months) and 3 studies at longer-term follow-up (7-12 months). Only one exercise (Heine et al., 2017) and four mixed interventions (Hugos, Cameron, Chen, Chen, & Bourdette, 2018; Hugos et al., 2019; Nedeljkovic et al., 2016; Rietberg, van Wegen, Eyssen, & Kwakkel, 2014; Turner et al., 2016) had long-term follow-up.

Where sufficient studies in each subgroup existed, planned sensitivity analysis was conducted omitting studies where the risk of bias assessment was either high or unclear for three key domains. Exploratory analyses of potential moderators, including total contact hours with a healthcare professional (none or limited, defined as ≤ 80 minutes, versus other), type of MS (relapsing remitting versus progressive), and type of control condition (no treatment or usual care versus active comparators) were also conducted where possible.

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Assessment

RS, SN and AH conducted GRADE assessments to provide an overview of the quality of evidence for each intervention subtype. Trial data were assessed according to the five GRADE domains, including risk of bias, inconsistency, indirectness, imprecision and publication bias (Guyatt et al., 2008). Because these were behavioural and exercise interventions the risk of bias domain was not downgraded due to either detection or performance biases.

Results

Study Characteristics

The combined online searches yielded 2,659 abstracts after removing duplicates, and six additional studies were identified through contacting authors and forward citation/manual searches (see figure 1). Thirty-four studies were identified as meeting inclusion criteria for this review and are summarised in Table 1 including demographics of the samples (including disability), fatigue screening and primary outcome measures, post-intervention follow-up point, attrition at follow-up and long-term follow-up if present. All but one of the studies were RCTs and 31 studies had sufficient data to be included in the meta-analysis including 34 active interventions.

Twelve studies evaluated exercise, 16 behavioural, and six combined exercise and behavioural interventions, comprising a total of n=2,434 pwMS. Eight (67%) of the 12 exercise studies had treatment group sizes of less than 20, 4 of the behavioural studies (25%) and 2 of the combined studies (33%). All but one of the studies were RCTs, and two published articles provided separate one-year follow-up analyses (Mathiowetz, Matuska, Finlayson, Luo, & Chen, 2007; P. W. Thomas et al., 2014). Twenty-four studies included people with both RRMS and progressive MS (71%), although the majority tended to be RRMS. Three included people with RRMS only and seven failed to report type of MS. Twenty-two studies provided Expanded Disability Status (EDSS) scores (a measure of severity of MS; Kurtzke, 1983) for their sample. Mean EDSS scores ranged from 2.4 to 5.5 suggesting on average patients had mild to moderate disability and most patients had some level of mobility impairment. Six studies comprised all female samples. Two studies included only pwMS with limited standing balance. None of the studies screened for anxiety, while 12 studies included depression as an exclusion criterion and five studies excluded patients with substance abuse problems. Different definitions were utilised to define presence of depression or substance abuse problems across the studies.

Twenty-four studies (71%) had a screening cut-off for fatigue before entry into the study. Only six (18%) studies reported assessing treatment fidelity, four of these were behavioural studies and two mixed behavioural and exercise studies. Adherence was assessed in 19 studies (56%) including 5 exercise studies, 10 behavioural and 4 combined (Tables B.1 and B.2, Appendix B). In the narrative synthesis below, loss to follow-up in the intervention arm at end of treatment is taken as a proxy measure of acceptability of the intervention, as the methods to assess adherence were varied across studies and almost half did not assess adherence.

Component Analysis and Grouping of Exercise Interventions

Tables B.1 (Appendix B) and C.1 (Appendix C) provide a summary of the exercise intervention subgroups, physical fitness components, delivery details, and key BCTs. Interventions were initially grouped according to key physical fitness components i.e. aerobic, muscle strengthening, balance and flexibility, or combined exercise consisting of more than one fitness component (see Table 2 for descriptors of these components).

INSERT TABLE 2 HERE

Six of the 15 exercise interventions focussed on a fitness component which fitted into one of these discrete categories, two focusing on balance and four on aerobic exercise (one of these was designed as the active control group for the balance intervention). The aerobic interventions included: twelve 15-minute treadmill sessions at an intensity of 11-12 RPE (Gervasoni, Cattaneo, & Jonsdottir, 2014), group exercises involving walking at a comfortable pace for 45 minutes three times a week for three weeks (Dettmers, Sulzmann, Ruchay-Plossl, Gutler, & Vieten, 2009), 30 minute aerobic interval training at 40%, 60% and 80% of peak power on a cycle ergometer, three times a week, for 16 weeks (12/48 sessions were supervised in an outpatient setting while the remaining 36 were home-based using identical equipment) (Heine et al., 2017).

Both Heine et al. (2017) and Dettmers et al. (2009) provided a rationale for their interventions but only Heine et al (2017) described progression of the exercise intensity. In terms of loss to end of treatment follow-up in the aerobic groups, two studies reported zero drop-out but follow-up was short: 2 weeks (Gervasoni et al., 2014) and 6 weeks (Hebert, Corboy, Manago, & Schenkman, 2011), whilst Dettmers et al. (2009) reported 44% drop-out (follow-up 3 weeks) and Heine et al (2017) 21% (16 weeks). Hebert et al. (2011) and Heine et al. (2017) reported on adherence. Participant daily diaries suggested significantly better adherence to the vestibular home exercise group (mean 60.5 days) compared to the aerobic exercise group (mean 42.7 days; Hebert et al., 2011), while 74% of patients completed all sessions in Heine et al. (2017).

The balance studies used vestibular rehabilitation delivered by a physical therapist twice a week for up to an hour over six weeks (Hebert et al., 2011; Hebert, Corboy, Vollmer, Forster, & Schenkman, 2018). Only people with balance impairments were included. The authors postulated that balance exercises could alleviate fatigue through improvement in upright postural control. Following the six-week supervised training, participants in both exercise groups completed daily home-based exercises lasting 40 to 60 minutes over an 8- to 10-week period. There was 92% adherence to the supervised training and 88% adherence to the home-based exercises (Hebert et al., 2018).

The remaining interventions reviewed were multi-faceted targeting between three to four of the key physical fitness components, but without explicit reference to a dominant physical fitness component or established exercise principles (i.e. specificity, overload, progression, initial values, reversibility and diminishing returns (Ammann, Knols, Baschung, de Bie R, & de Bruin, 2014). Eight interventions were therefore grouped as 'general exercise' and further divided into two types: general aquatic and general land-based (see Table B.1 for the components included in each intervention). The five general aquatic programmes were delivered in a group format and included eight to 12 weeks of exercise, three times a week. Although none of the interventions was guided by theory per se, buoyancy of water, resistance against movement and the cooling effect of the aquatic environment were considered important. End of treatment drop-out for the general aquatic group ranged from 0 to 37%.

The three land-based general exercise interventions used yoga and pilates. The two yoga interventions were delivered in groups, led by an experienced/certified instructor. In the yoga interventions, sessions lasted 10-15 minutes, twice a week over 6 weeks (Karbandi, Gorji, Mazloum, Norian, & Aghaei, 2015) and 60 minutes, three times a week over 8 weeks (Razazian, 2016), respectively. The Pilates intervention sessions were 60 minutes, three times a week over 12 weeks (Shanazari, Marandi, & Minasian, 2013). None of the land-based general exercises were guided by theory. End of treatment loss to follow-up for these exercise groups ranged from 0 (Razazian, 2016) to 31% (Karbandi et al., 2015). Of these three studies, only Shanazari et al., (2015) reported the inclusion of a progression in the level of exercise.

Adherence for the general exercise interventions was only reported by Karabandi et al. (2015) with an average of 10.6 out of 12 sessions completed.

Only one study belonged to the category of combined exercise (Escudero-Uribe, Hochsprung, Heredia-Camacho, & Izquierdo-Ayuso, 2017), consisting of a combination of exercise components: aerobic, resistive, flexibility, and balance, delivered by a neurologic physical therapist twice weekly over 12 weeks for 60 to 100 minutes, with the duration of sessions increasing by 5 minutes every week. The exercises were delivered either via a Whole-Body Vibration (WBV) or Balance Trainer (BT) mechanical devices. In the treatment groups, 16% and 22% of participants were lost at follow-up, respectively.

Component Analysis of the Behavioural Interventions

Table 3 provides descriptors and authors of the key behavioural intervention types. Most of the studies could be divided into energy conservation (EC; n=8) and cognitive behavioural therapy (CBT; n=5). One study combined CBT and EC (labelled energy effectiveness) and two were relaxation interventions. Tables B.2 (Appendix B) and D.1 (Appendix D) provide a summary of the interventions under each subgroup, delivery details, intervention components and summary of key BCTs across the behavioural studies.

INSERT TABLE 3 ABOUT HERE

All eight EC interventions focused primarily on analysing and modifying activities to reduce energy expenditures or to use energy more efficiently (S. Harrison, 2007). Other methods are included in Table 3. No specific theory was provided but one study referred to general self-efficacy theory (Mathiowetz, Finlayson, Matuska, Chen, & Luo, 2005). In terms of BCTs, most studies included a psychoeducational focus. Six of the EC interventions included goals setting to change behaviour. However, only one specified monitoring and reviewing of these goals (Daphne Kos et al., 2016).

Six of the EC interventions were delivered face-to-face in a community group format, by a range of HCPs (occupational therapist, doctor, psychologist, physiotherapist) with occupational therapist being the most common. Groups were held weekly and ranged from three to 16 weeks' duration (6 weeks being the most common) with sessions lasting from 45 to 180 minutes. The two remaining six-week energy conservation interventions utilised home-based web delivery with an online forum for pwMS (Ghahari, Packer, & Passmore, 2010), and group-based teleconferencing (Finlayson, Preissner, Cho, & Plow, 2011). Some, but not all, energy conservation interventions included weekly homework. Where reported, loss to follow-up at end of EC treatment ranged from 14% to 28% with one of the web-delivered interventions having the highest rate (see Table 1).

The five CBT interventions were based on a theoretical and empirical model of MS fatigue (see Table 3 for details). In terms of BCTs, all CBT interventions asked pwMS to set and review specific, measurable, activity-related, realistic, and time-specified or time-limited goals. Goals focused on setting a baseline of activity that can be achieved even on a bad day or when tired, or increasing activity if under-active, and once achieving consistency when over or under active, increasing activity gradually over time by pre-planned graded increments if needed. Self-monitoring of goal progress was a key component. CBT also used therapy techniques not clearly identified in the BCT such as identifying and managing unhelpful thoughts in relation to fatigue and high personal expectations, and reattributing symptoms to reduce somatic focus.

CBT interventions ranged from 8 to 16 weeks' duration, with individual weekly or fortnightly sessions lasting up to 60 minutes plus weekly homework. They differed with respect to delivery methods. Two included weekly one-to-one sessions with registered psychologists (van den Akker et al., 2016; van Kessel et al., 2008) with one also including a participant manual (van Kessel et al., 2008). Loss to follow-up at the end of CBT for these two studies was 2% and 7%, respectively. The remaining three CBT interventions were delivered through tailored interactive websites that pwMS worked through at home; one with three hours of individual telephone support sessions with an assistant psychologist (Moss-Morris et al., 2012), one with 10 minutes a week of email support from a clinical psychologist (van Kessel, Wouldes, & Moss-Morris, 2015) and one with no additional support (Pöttgen et al., 2018). Loss to follow-up was higher for the web-based than therapist-delivered CBT ranging from 13% with telephone support, 21% with email and 26% with no support.

Only one intervention combined CBT with EC methods (S. Thomas et al., 2013). The aims of the treatment were to normalise the experience of fatigue, support learning of strategies to manage energy more effectively and to explore different, more helpful ways of thinking about fatigue. Whilst the programme drew upon EC principles the overall aim was not to limit activity but rather to provide individuals with strategies to enable them to do more of the things that matter to them. It included one 2-hour session and five 105-minute sessions over six weeks. The manualised programme was delivered by either occupational therapists, physiotherapists or MS nurse. Loss to follow-up in the treatment group at the end of treatment was 15%.

The relaxation interventions were not theory-based. Limited information was provided about the intervention evaluated in Nazari, Shahreza, Shaygannejad, and Valiani (2015), it consisted of twice weekly relaxation sessions of 40 minutes over 4 weeks. In Sgoifo et al. (2017), participants received Jacobsen relaxation exercises biweekly over the course of 8 weeks, with sessions lasting between 40 and 60 minutes delivered by one psychotherapist. At the end of treatment, 4% attrition was observed in the treatment group.

Component Analysis of the Combined Exercise/Behavioural Interventions

The components of the combined interventions are listed in Appendix B; Tables B.1 (exercise components) and B.2 (behavioural components). Three tested EC and aerobic exercise (Hugos et al., 2019; Hugos et al., 2010; Rietberg et al., 2014), one motivational interviewing (MI) and physical activity promotion (Turner et al., 2016), one aerobic exercise and autogenic relaxation training (Zalisova & Havrdová, 2001) and one a multidisciplinary rehabilitation programme with an embedded aerobic exercise programme (Nedeljkovic et al., 2016).

Rietberg et al. (2014)'s EC and high intensity aerobic exercise intervention combined group- and individual-based sessions delivered by a physical therapist, lasting for up to 45 minutes twice a week over 12 weeks. Participants set general goals related to lifestyle changes to use energy more efficiently. Attrition from the treatment group was at 9%. The "Fatigue: Take Control" intervention included several additional elements including educating pwMS on how depression can impact negatively on sleep, and helping them to set realistic and achievable goals (Hugos et al., 2019; Hugos et al., 2010). There were six weekly 2-hour group sessions. The intervention also included low intensity exercise delivered in 20-30 minutes 3 to 5 times a week for seven weeks. Attrition from the treatment group was at 25% and 9%, respectively.

Turner et al. (2016) evaluated a six-week telephone-supported treatment delivered by a trained therapist, using MI techniques, such as values identification, to feed into personal goals and choice related to participating in exercise of preference. Weekly sessions were around 40 minutes. Homework consisted of working on physical activity (not always exercise) with goals guided by a DVD and booklet. End of treatment loss to follow-up was 3%.

Zalisova and Havrdová (2001) combined group- and individual-based sessions which consisted of thirty-six hours of relaxation-based techniques with thirty hours of aerobic, resistive and balance exercises and education. All activities were instructed by two physiotherapists, and intensity of aerobic exercise was set at 60% VO_2 maximum load. There was no attrition at the end of treatment.

Finally, one study offered a 3-week multi-disciplinary rehabilitation programme, delivered after a 5-day course of intravenous methylprednisolone, which is a corticosteroid medication used to suppress the immune system and decrease inflammation (Nedeljkovic et al., 2016). The rehabilitation programme was conducted in an outpatient clinic, and included provision of mobility aids, bladder management, instruction on basic physical exercises (not specified) performed at home for 5 days. It also included two 30-minute sessions with a rehabilitation physician who encouraged patients to create their own fatigue management strategy focused on organising their activities of daily living.

Meta-Analysis of Exercise Interventions

Two exercise studies with active comparators did not provide sufficient data to be included in the meta-analysis (Dettmers et al., 2009; Karbandi et al., 2015). Figure 2a presents the individual and pooled effect sizes for the remaining exercise interventions at the end of treatment. The meta-analysis of the overall effect of all exercise interventions on fatigue included 13 exercise interventions from ten studies providing a pooled SMD of -0.84 (95% CI -1.20 to -.47; I^2=73%). The substantial heterogeneity observed means inferences are potentially unreliable. Kargafard et al. (2012) provided the greatest contribution to heterogeneity, which was likely due to substantial worsening in self-reported fatigue at post-intervention in the control arm. When this study was removed the pooled SMD estimate decreased to -.75 (95% CI: -1.09 to -.40; I^2=69%). This suggests that the effect of exercise interventions overall is moderate to large and though statistically reliable the 95% confidence interval indicates considerable uncertainty in the effect size.

Subgroup analyses using the five categories derived from the narrative synthesis indicated that general exercise in an aquatic environment involving five studies had a pooled SMD of -1.02 (95% CI: -1.72 to -.32; I^2=74%) with substantial heterogeneity. Excluding Kargarfard et. al. (2012) decreased heterogeneity and lowered the pooled estimate to -.74 (95% CI: -1.29 to -.18; I^2=57%). The three aerobic studies had a pooled SMD of -.29 (95% CI: -.69 to .12;

I^2=26%) with low heterogeneity suggesting aerobic exercise on its own in these three studies only had a small and potentially non-significant effect. There were too few studies to draw inferences about the pooled effects for subgroups relating to balance (2 studies), general land-based exercise (2 studies), and combined exercise (1 study). The effects of these subgroups were generally large, but potentially non-significant.

Exploratory sensitivity and moderator analyses of exercise interventions

The RoB graph for the exercise studies is presented in Figure 2b. Five studies were considered to have a low RoB. The pooled SMD of low RoB studies was -1.01 (95% CI: -1.45 to -.56; I^2=72%), while the pooled SMD of high RoB studies was -.63 (95% CI: -1.23 to -.02; I^2=72%). Planned moderator analyses were not possible as all studies except two (Escudero-Uribe et al., 2017; Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012) included a mixture of MS types or failed to specify subtype (Atri, Saeedi, Sorouri, & Sokhangooy, 2012; Hebert et al., 2018; Shanazari et al., 2013). HCP contact time was always more than 80 minutes, and only one of the control groups was considered an active comparator.

[INSERT FIGURE 2 ABOUT HERE]

Meta-Analysis of Behavioural Interventions

Figure 3a shows the individual and pooled effect sizes for each of the behavioural interventions at end of treatment. These 16 interventions from 16 studies provided a pooled SMD of -.37 (95% CI -.53 to -.22; I^2=42%), indicating small to moderate effects on fatigue, but with moderate and statistically significant heterogeneity.

Subgroup analysis of the narrative review categories showed an SMD of -.20 (95% CI -.36 to -.03; I^2=0%) for the eight EC studies with low heterogeneity. This suggests that the effect on fatigue is small but statistically reliable with the 95% confidence interval indicating large effects are unlikely. The pooled SMD for the five CBT studies was -.66 (95% CI: -.94

to -.38; I^2=47%), however, heterogeneity was high and the width of the 95% confidence interval wide indicating considerable uncertainty in the effect size. Other subgroups included too few studies to allow for meta-analyses. The mixed CBT+EC study had a non-significant end of treatment effect and the two relaxation studies a medium to large effect.

Exploratory sensitivity and moderator analyses of behavioural studies

Figure 3b shows that ten out of the 16 behavioural studies had a low risk of bias. When including only studies with low risk of bias the pooled effect size reduced to -.33 (-.48 to -.18; I^2=30%), but did not make any substantive difference to the interpretation of the treatment effect. Considering only low risk of bias studies in subgroup analysis was only possible for EC interventions. Including the four low risk of bias EC interventions the effect size remained stable at -.23 (95%CI: -.41 to -.06; I^2=0%), indicating a small treatment effect with low heterogeneity.

[INSERT FIGURE 3 ABOUT HERE]

Moderator analysis by MS type was not possible as all behavioural studies included mixed samples. Because most of the heterogeneity in terms of CIs and delivery types was in the CBT category, we conducted moderator analysis by HCP contact dose for this category only.

The two studies with <80mins contact had a pooled effect size of -.57 (95% CI: -1.14 to .00) whereas the three with >= 80 mins contact time had a pooled effect of -.76 (95% CI: -1.05 to -.47). The CBT effect is lower with less contact time, but the confidence intervals overlap considerably so no real inference can be drawn.

Moderator analysis by control group type for the total behavioural intervention category provided no robust indication that the type of control used impacted on treatment efficacy. Studies with a treatment as usual or waitlist control arm (n=14) had a pooled SMD of -.34 (95% CI: -.51 to -.18; I^2=43%) whereas studies with an active control group (n=2), specifically relaxation, had a pooled SMD of -.66 (95% CI: -1.08 to -.25; I^2=0%).

Treatment effects at longer-term follow-up for the behavioural studies

In addition to the primary post-randomisation assessments, seven behavioural interventions provided data at longer-term assessment ranging between 3 and 6 months post-randomisation (see Figure 4 for list of studies and individual follow-up treatment effects). The overall pooled effect for behavioural interventions at this time was reduced to -.35 (95% CI: -.53 to -.16; I^2=0%). In terms of subgroups, four studies investigating EC provided a pooled SMD of -.24 (95% CI: -.55 to .06; I^2=0%), which was equivalent to the effect post-treatment. There were too few studies to allow for the examination of the other subgroups at 3 to 6 months follow-up. However, the individual SMDs suggested that the combined CBT+EC study and the CBT studies had similar medium size effects at follow-up (see Table 4).

Data from three behavioural studies was available for a point greater than 6 months post-randomisation (Blikman et al., 2017; Thomas et al., 2014, van den Akker et al., 2017). The pooled effect for these three behavioural studies was SMD=-.23; 95%CI -.47 to .01; I^2=0%.

[INSERT FIGURE 4 ABOUT HERE]

Combined Exercise and Behavioural Interventions

Figure 5a shows the individual and pooled end of treatment effect sizes for the combined interventions. The pairwise meta-analysis assessing the efficacy of mixed interventions comprising aerobic exercise, physical activity and behavioural components included five studies (Hugos et al., 2019; Hugos et al., 2010; Nedeljkovic et al., 2016; Rietberg et al., 2014; Turner et al., 2016). The pooled effect was SMD=-.16 (95% CI: -.36 to

.04; I^2=0%). Statistical heterogeneity was unlikely to be important, but the estimate may not be reliable due to the small number of studies. Four of the studies had low risk of bias (see Figure 5b). Subgroup and moderator analyses were not possible due to the small number of studies.

Four combined intervention studies provided 3 to 6 months follow-up data, with a pooled SMD of -.09 (95% CI: -.30 to .12; I^2=0%). Only two studies (Heine et al., 2017; Hugos et al., 2018) reported follow-up data for a point greater than 6 months post-randomisation.

[INSERT FIGURE 5 ABOUT HERE

GRADE Assessment

The GRADE assessment for exercise, behaviour and combined interventions is summarised in Table 4. As with RoB, due to the nature of the interventions, the quality of evidence was not downgraded based on lack of blinding to minimise performance and detection biases in the included studies. The quality of evidence was ‘very low’ for overall exercise and land-based general exercise, because most information is from studies with inadequate allocation concealment or incomplete accounting for outcome data (limitation), large differences between studies in the magnitude of point estimates and minimal overlap of corresponding CIs (inconsistency) and small total sample size and relatively wide CI (imprecision). Quality of evidence was rated as ‘low’ for general exercise in aquatic environment due to ‘limitation’ and ‘imprecision’. Kargarfard et al. (2012) was excluded from GRADE assessment so as not to downgrade the quality of general aquatic exercise further for the ‘inconsistency’ domain. The GRADE rating for aerobic exercise and balance exercise was moderate, downgraded from high because of imprecision.

The overall GRADE rating for the broader behavioural group was moderate, downgraded for inconsistency. In terms of subgroups, CBT evidence was downgraded to moderate due to ‘imprecision’, while relaxation was rated as ‘low’ quality due to ‘limitation’ and ‘imprecision’. EC was the only subgroup rated as ‘high’ quality evidence. Evidence was rated as ‘moderate’ quality for combined exercise behaviour, due to imprecision.

INSERT TABLE 4 ABOUT HERE

Discussion

Thirty-four studies (33 RCTS and one CCT) of exercise and behavioural interventions specifically targeting MS fatigue were included in this review. In terms of exercise, the meta-analysis of the 13 exercise interventions suggested that at the end of treatment, exercise on average has a large effect on fatigue. However, heterogeneity within the broader exercise category was high and the overall quality of the evidence was very low so we have no certainty in this estimate. The overall effect size was larger here than the estimate reported in a previous meta-analysis of exercise studies for fatigue in MS (SMD =.53, 95%; CI: .73 to -.33), but with similar heterogeneity (Heine et al., 2015). This disparity is likely due to Heine et al. (2015) including all exercise studies which measured fatigue as an outcome, whereas the current review only included interventions with a primary focus on fatigue reduction.

In terms of exercise subcategories, based on the three studies included in the meta-analysis, we have moderate quality evidence that the effect size for aerobic exercise on its own is small, not retained at follow-up (Heine et al., 2017) and accompanied by high drop-out, suggesting poor acceptability of this approach. Therefore, this tentatively suggests aerobic exercise on its own may not be the best form of exercise for MS fatigue, although this may depend on programme content and delivery as well as study quality.

The effect size for general exercise (a mixed combination of aerobic, flexibility, strength and balance) was large, but quality of the evidence was poor and the exercise principles were generally inadequately specified, in contrast to aerobic exercise.

There was some preliminary evidence in favour of a balance intervention (vestibular rehabilitation) when compared to a waitlist control based on two trials (Hebert et al., 2011; Hebert et al., 2018), but not against an aerobic exercise group (Hebert et al., 2011). Drop-out from the balance intervention was low (Hebert et al., 2011; Hebert et al., 2018), and better adherence to home practice than the aerobic exercise group was observed (Hebert et al., 2011). Hebert et al., (2011) postulated that balance training in vestibular rehabilitation may condition central sensory processing for efficient upright postural control. It is noteworthy that all but one of the aquatic general exercise interventions in this review included balance exercises as part of the interventions (Kargarfard et al., 2012; Kooshiar et al., 2015; Razazian, 2016; Shanazari et al., 2013) and all three land-based general exercise programmes were either yoga or Pilates interventions that target maintenance of upright postures (Karbandi et al., 2015; Razazian, 2016; Shanazari et al., 2013). Many patients with MS, even those minimally affected with MS have balance impairments (Martin et al., 2006) and over 50% are at risk of falling (Finlayson, Peterson, & Cho, 2016). Poor balance is likely to make navigating the environment more effortful, and thus a mechanistic argument can be developed for improvement in balance leading to reductions in fatigue (Cameron & Lord, 2010). Whilst it is not possible to make recommendations based on the quantity and quality of evidence currently available, this suggests that vestibular rehabilitation and other balance interventions warrant further investigation.

In terms of behavioural interventions, 16 interventions were included in the meta-analysis most of which were either EC or CBT. The overall end of treatment estimate for the behavioural category was small, but heterogeneity was high, so we cannot be confident in this estimate. Effect sizes differed across the two intervention types. There was good quality evidence that EC has a small non-significant positive effect on fatigue at the end of treatment and at follow-up. Therefore, at this stage, we believe no further evidence is needed for EC. Although a small effect may be better than no effect, EC requires a reasonable time commitment from patients and has moderate drop-out in many studies, ranging from 14 to 28% (possibly because most of the EC interventions were group-based). Future trials could use EC as a better and more matched control condition than wait-list or treatment as usual groups for either exercise or CBT (Moss-Morris & Norton, 2017).

CBT for fatigue showed a moderate to large effect. However, heterogeneity was high and quality of the evidence only moderate, with small to moderate effects maintained up to 6 months follow-up, but not at 12 months follow-up as identified by one study (van den Akker et al., 2016). There was only some attenuation of the effect in the web-delivered CBT subgroup, but the confidence intervals were large, possibly because one web-based trial had no guided support (Pöttgen et al., 2018), whilst others offered minimal support by telephone or email (Moss-Morris et al., 2012; van Kessel et al., 2015). Although one-to-one CBT delivered by a psychologist appears to have high acceptability with little drop-out (van den Akker et al., 2016; van Kessel et al., 2008), it is unlikely to be an approach that can be rolled out to all patients with MS fatigue. Web-based CBT with some guided support from a HCP shows some promise with the suggestion this may be a cost-effective option, but the evidence is preliminary and no follow-up data are available (Moss-Morris et al., 2012; van Kessel et al., 2015). Further high-quality studies on web-based CBT are warranted which focus on optimal levels of clinical and cost-effective HCP support.

To date, none of the EC trials have published mediation analyses of the potential mechanisms of the treatment effect. According to available mediation analyses of CBT, changes in negative perceptions of fatigue were key mediators of the reduction in fatigue severity, rather than changes in anxiety and depression (Knoop, Van Kessel, & Moss-Morris, 2012; van den Akker et al., 2018). Although these data support the need for CBT protocols to focus on symptom perceptions rather than changing mood, these were small RCTs and larger powered mechanistic studies are needed to test the cognitive-behavioural theory of fatigue and to accordingly refine CBT.

A limited number of combined interventions was identified, which mainly consisted of EC and aerobic exercises, with a small effect size. Statistical heterogeneity was low, but the estimate may not be reliable due to the small number of studies and moderate quality of evidence. These preliminary data suggest that combining exercise and behavioural interventions does not have any added benefit. This closely resonates with the findings of a recent meta-analysis of exercise and CBT interventions for depression, anxiety, fatigue, and pain in adults with chronic illness, where no additive benefit of combined CBT and exercise interventions was identified on any of the outcomes (Bernard et al., 2018). However, none of the studies here combined CBT and exercise so drawing firm conclusions in relation to combined interventions is premature. Therefore, it would be valuable to explore the additive benefits of combined interventions, such as CBT and exercise, taking into account that their benefits may extend beyond treatment effects on fatigue, but also lead to improved adherence and maintenance of benefits over time; and identify moderators of treatment effect, such as disease course.

A number of common issues are evident across intervention subgroups. Other than in the CBT for fatigue and balance studies, the underlying theory or mechanisms of the interventions are seldom considered, particularly in exercise interventions. Yet, this is essential to maximise the efficacy of interventions by activating the desired chain of events. A recent scoping review describes more than 30 potential pathophysiological mechanisms contributing to primary and secondary fatigue in MS (Langeskov-Christensen et al., 2017). Future studies, particularly evaluating exercise interventions, should aim not only to reduce fatigue, but to design programmes that target proposed mechanisms. Nested process analysis of potential mediators of change are needed to build a more evidence-based theoretical model of the pathophysiology of MS fatigue which will help improve treatments downstream.

Exercise and behavioural studies need to focus on improving adherence to the interventions and sustaining behavioural change in the face of unpredictable and increasing symptoms, and disability progression. Longer-term treatments or booster treatment sessions may be necessary. If exercise is to reduce fatigue in the longer-term, it needs to be presented as a way of developing a lifestyle habit rather than a treatment for a short-defined period of time. To do this, exercise needs to consider personal preference (enjoyment) of type of exercise, tailoring of exercise during times of symptom fluctuation or more serious relapse, and ways of adapting exercise as the disease progresses. Therefore, programmes which provide equipment only for the duration of the study, and only a single exercise regardless of patient preference are unlikely to succeed in the longer-term (Moss-Morris & Norton, 2017). Similarly, the benefits of pool-based exercise programmes can only be sustained if patients have ongoing access to these facilities. This needs to be considered alongside implementation and cost-effectiveness and may mean matching type and level of intensity of intervention to the complexity and severity of fatigue and other patient needs and circumstances.

Overall, to address these issues, clearly defined screening to not only ensure that participants meet diagnostic fatigue thresholds, but also to assess co-morbidities, such as the presence of depression, anxiety, and substance abuse problems; is necessary as these may influence engagement with and adherence to treatment, as well as the mechanisms of change underlying improvement. Some researchers have dealt with this by excluding based on co-morbidities. The disadvantage of this approach is that the results are not generalisable across people with MS as rates of depression and anxiety are high, and may also be a consequence of the fatigue. A better approach would be to measure these factors and then to explore whether they moderate or predict treatment effects. If they do – then treatment may need to be specially tailored for these groups.

Additionally, in the context of complex interventions, assessment and monitoring of treatment fidelity is fundamental to the interpretation of treatment effects in relation to the delivered intervention. However, treatment fidelity is often under-reported in studies (O'Shea, McCormick, Bradley, & O'Neill, 2016), as also evident here with only six studies assessing treatment fidelity. Comprehensive assessment and monitoring of treatment fidelity in future trials will enhance the quality of evidence and optimise the translation of interventions into clinical practice (Bellg et al., 2004).

Limitations of this review need to be noted. First, although substantial effort was made to categorise the interventions through obtaining treatment manuals, few manuals were available, particularly in the exercise category, consequently some of the interventions were categorised based on limited descriptors provided in the papers. To offset this limitation, authors were contacted with queries to obtain more detail where possible and the majority of authors replied. Second, the registered protocol for this review (Moss-Morris et al., 2016) specified a handful of *a-priori* subgroup analysis and exploratory sensitivity and moderator analysis which could not be conducted due to the small number of studies in many of the subgroups and substantial design and statistical heterogeneity.

This is the first systematic review to combine both a very detailed narrative synthesis and meta-analysis of all the behavioural and exercise studies conducted to date with a primary focus on treating fatigue in MS. The review suggests that web-based CBT and mixed or balance-based exercise interventions may be the most promising areas to pursue in future research although conclusions are very tentative due to the moderate to poor quality of sporadic evidence. There is a clear need for adequately powered trials of these treatments with a focus on ensuring the interventions are designed in a way that they are easily implementable in the future. This requires pragmatic trial designs and evaluation of cost-effectiveness. EC could be used as an active comparator to control for HCP time and attention as there is good evidence of small non-significant effects for EC. Trials need to include longer-term follow-up and methods to maintain gains obtained at end of treatment. Clear mechanisms of action to reduce fatigue need to be specified in interventions. Studies need to be large enough to embed mediation and moderation analysis of treatment effect to address how interventions lead to fatigue reduction and how to personalise treatments. These data can then be used to improve and tailor treatments further. The findings of this review provide a valuable foundation for future research to define a sorely needed routine fatigue management pathway in MS. There is moderate quality evidence that both CBT for fatigue and balance interventions are most promising and poor-quality evidence that mixed exercise interventions have large effects in the short-term and may be worthy of further study. RCTs comparing these treatments would aid in the development of a treatment pathway which provides informed choice for patients to manage fatigue.

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Disclosure

Professor Rona Moss Morris and Dr Sarah Thomas have published RCTs of behavioural interventions for fatigue in Multiple Sclerosis which were included in the current review. However, preliminary searches, formal screening of search results against eligibility criteria, data extraction, risk of bias assessment and data analysis were conducted independently of these individuals. Remaining authors declare no financial or other conflicts of interest.

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Table 1: Studies included in the systematic review (studies in bold were significantly effective at post-treatment in the meta-analysis)

Study reference	**Country**	**Study Design**	**Participants**		**Type**		**Demographic and Disease Factors** (RRMS (%); Age years M (SD); Female (%); Level of disability M (SD) / Mdn (Q1-Q3 / Min to Max); Time since diagnosis months/years M (SD) / Mdn (Q1-Q3).		**Screened for Fatigue** (cut-off score/ measure)	**Fatigue Outcome** (primary or secondary)	**End of intervention time-point** (wks)	**Lost to post-treatment follow-up** (%)		**Final follow-up time-point** (wks post end intervention)
			Exp n.	Ctrl n.	Exp.	Ctrl.	Exp.	Ctrl.				Exp.	Ctrl.	
Exercise studies														
1. **Atri et al. 2012^**	IR	RCT	14	12	General (Aquatic)	NR (TAU)	NR; 36.3 (7.81); 100%, EDSS: 2.4 (1.1); NR.	NR; 31.50 (7.96); 100%; EDSS: 2.8 (1.5); NR.	No	FSS (NR)	8	NR	NR	NR
2. Dettmers et al. 2009*	DE	RCT	15	15	Aerobic	General exercise (Active control)	86.86 %; 45.8 (7.9); 66.66 %; EDSS: 2.6 (1.2); 8.0 (5.9) yrs.	66.66 %; 39.7 (9.1); 73.33%; EDSS: 2.8 (0.7); 6.1 (4.3) yrs.	Yes (NR)	MFIS (S)	3	44%	33%	NR
3. Escudero-Uribe et al. 2017 (1)^	ES	RCT	19	18	Whole body vibration (combined)	Waitlist (TAU)	100%; 43.1 (10.2); 62.5%; EDSS: 3.0 (1.0); 10.5 (8.8) yrs.	100%; 43.0 (9.3); 77.7%; EDSS: 3.2 (1.1); 8.0 (5.4) yrs.	Yes (FSS ≥4) & clinical history of impairment in daily living due to fatigue	FSS (P) MFIS (P)	12	16%	0	NA
4. Escudero-Uribe et al. 2017 (2)^	ES	RCT	18	18	Balance trainer (combined)	Waitlist (TAU)	100%; 40.3 (8.9); 64.2%; EDSS: 3.2 (1.1); 7.4 (5.0) yrs.	100%; 43.0 (9.3); 77.7%; EDSS: 3.2 (1.1); 8·0 (5.4) yrs.	Yes (FSS ≥4) & clinical history of impairment in daily living due to fatigue	FSS (P) MFIS (P)	12	22%	0	NA
5. Gervasoni et al. 2014^	IT	RCT	15	15	Aerobic (Treadmill training)	Conventional training	37.5%; 49.6 (9.4); 40%, EDSS^{+}: 5.0 (3 to 6.5); 14.5 (9.7) yrs.	54.6%; 45.7 (8.6); 40%, EDSS^{+}: 5.5 (3.5 to 6); 15.5 (10.3) yrs.	No	FSS (S)	2	0	0	NR

6. Hebert et al. 2011(1)^*◊	US	RCT	12	13	Balance (Vestibular rehabilitation)	Waitlist	92%; 46.8 (0.5); 75%; 6MWT (ft): 1,335.6 (320.3); 6.5 (5.6) yrs.	92%; 50.2 (9.2); 85%; 6MWT (ft): 1,049.2 (328.9); 9.1 (7.3) yrs.	Yes (MFIS ≥ 45)	MFIS (P)	6	0	7%	10
7. Hebert et al. 2011(2)^*◊	US	RCT	13	13	Aerobic and stretching	Waitlist	85%; 42.6 (10.2); 85%; 6MWT (ft): 1,066.1 (335.9); 5.1 (3.2) yrs.	92%; 50.2 (9.2); 85%; 6MWT (ft): 1,049.2 (328.9); 9.1 (7.3) yrs.	Yes (MFIS ≥ 45)	MFIS (P)	6	0	8%	10
8. Hebert et al. 2018^◊	US	RCT	44	44	Balance and Eye-Movement Exercises for People with Multiple Sclerosis (Balance)	Waitlist	NR; 46·5 (8·8); 84%; EDSS: 3.50 (1.1); 8.34 (5.7) yrs.	NR; 43·0 (10·8); 86%; EDSS: 3.34 (1.1); 8.54 (7.6) yrs.	Yes (MFIS ≥ 22)	MFIS (S)	14	14%	14%	NR
9. Heine et al. 2017^*	NL	RCT	43	46	Aerobic interval training	MS nurse consultations	72.1%; 43.1 (9.8); 74.4%; EDSS: 2.5 (2.0-3.5); 7.0 (2.0-10.0) yrs.	73.9%; 48.2 (9.2); 71.7%; EDSS: 3.0 (2.0-4.0); 12.0 (2.0-19.0) yrs.	Yes (CIS20r fatigue ≥35)	CIS20r fatigue subscale (P)	16	21%	15%	36
10. Karbandi et al. 2015	IR	RCT	41	44	General (Group Yoga)	Individualised Yoga	NR	NR	No	MFIS (NR)	6	31%	34%	NA
11. Kargarfard et al. 2012^	IR	RCT	16	16	General (Aquatic)	TAU	100%; 33.7 (8.6); 100%; EDSS: 2.9 (0.9); 4.9 (2.3) yrs.	100%; 31.6 (7.7); 100%; EDSS: 3.0 (0.7); 4.6 (1.9) yrs.	No	MFIS (NR)	8	37%	31%	NA
12. Kooshiar et al. 2015^▼	IR	RCT	20	20	General (Aquatic)	No intervention	75.7%; 29.2 (8.0); 100%; EDSS: 2.5 (1.1); NR.		No	FSS (NR) MFIS (NR)	8	10%	5%	NA
13. Razazian et al. 2016 (1) ^*▲	IR	RCT	18	18	General (Aquatic)	TAU	61.1%; 35.39 (6.89); 100%; EDSS: 3.44 (0.95); 7.11 (0.90) yrs.	66.6%; 33.11 (6.60); 100%; EDSS: 3.25 (1.24); 6.78 (0.65) yrs.	No	FSS (NR)	8	0	0	NA
14. Razazian et al. 2016 (2) ^*▲	IR	RCT	18	18	General (Group Hatha Yoga)	TAU	72.2%; 33.33 (7.40); 100%; EDSS: 3.89 (1.02); 6.90 (0.90) yrs.	66.6%; 33.11 (6.60); 100%; EDSS: 3.25 (1.24); 6.78 (0.65) yrs.	No	FSS (NR)	8	0	0	NA
15. Shanazari et al. 2013 (1)^	IR	RCT	19	19	General (Aquatic)	TAU	NR; NR; 100%; EDSS <4.5; NR.	NR; NR; 100%; EDSS <4.5; NR.	No	MFIS (P)	12	16%	16%	NA
16. Shanazari et al. 2013 (2)^	IR	RCT	19	19	General (Pilates)	TAU	NR; NR; 100%; EDSS <4.5; NR.	NR; NR; 100%; EDSS <4.5; NR.	No	MFIS (P)	12	16%	16%	NA

Behavioural studies

1. Blikman et al. 2017^*	NL	RCT	36	40	EC	MS nurse consultations	76.2%; 47.7 (11.0); 81%; EDSS: 2.5 (2-4); 6.5 (3.7-17.3) yrs.	72.7%; 46.6 (11.5); 68.1%; EDSS: 1.8 (1-4); 7.5 (3-14) yrs.	Yes (CIS20r ≥35)	CIS20r Fatigue subscale (P)	16	14%	9%	36
2. Finlayson et al. 2011^	US	RCT	94	96	EC	Waitlist	52%; 56 (9); 79%; NR; 15 (9) yrs.		Yes (FSS ≥4)	FSS (P)	7	28%	27%	24
3. Ghahari et al. 2010 (1)^**	A	RCT	25/ 24	23/ 20	EC	No intervention	65%; NR; 96%; NR; 102.22 (83.38) mo.	57.1%; NR; 72%; NR; 92.59 (69.466) mo.	Yes (FSS ≥ 4)	FIS (P)	7	NR	NR	12
4. Ghahari et al. 2010 (2)^**	A	RCT	19/ 23	26/ 20	EC	No intervention	77.8%; NR; 82%; NR; 116.00 (85.56) mo.	57.1%; NR; 72%; NR; 92.59 (69.466) mo.	Yes (FSS ≥ 4)	FIS (P)	7	NR	NR	12
5. Garcia-Burguillo Aguila-Maturana 2009^	E	CCT	9	5	EC	NR	66.7%; 44.7 (NR); 88.9%; EDSS: 2,5 (1.2); 9.5 (NR) yrs.	60%; 44.4 (NR); 80%; EDSS: 2.6 (1.3); 8 (NR) yrs.	Yes (FSS ≥ 3.5)	FIS Physical (NR)	10	NR	NR	NA
6. Garcia Jalon et al. 2012^*	IE	RCT	13	10	EC	Peer support (Active control)	15%; 45.85 (9.93); 76%; RMI: 12.77 (2.12); 11 (7.01) yrs.	30%; 52 (7.01); 60%; RMI: 13.1 (1.44); 14.22 (11.94) yrs.	Yes (FSS ≥ 4)	FIS (S) FSS (S)	6	23%	0%	12
7. Kos et al. 2007^*	BE	RCT	28	23	EC	Education	72%; 42.9 (9.1); 8%; MSFC: 0.13 (0.6); 6.1 (4.9) yrs.	61%; 44.5 (9.9); 8%; MSFC: 0.16 (0.7); 8.2 (9.0) yrs.	Yes (≥ 3 fatigue subscale GNDS)	MFIS (P) FSS (S)	7	14%	31%	42
8. Kos et al. 2016^	BE	RCT	17	14	EC + goals for physical activity	Relaxation therapy	NR; 37 (8.2); NR; EDSS: 3 (2.5-3.25); NR.	NR; 44 (8.9); NR; EDSS: 3.5 (3.5-4); NR.	Yes (VAS ≥ 60)	MFIS (NR)	3	18%	21%	12
9. Mathiowetz et al. 2005 / 2007^	US	RCT	78	91	EC	Waitlist	61.5%; 48.3 (8.4); 83%; 33% unable to work; 9.5 (7.4) yrs.		Yes (FSS ≥ 4)	FIS (P)	7	21%	25%	58
10. Moss-Morris et al. 2012^	GB	RCT	23	22	CBT	TAU	43.5%; 40.14 (17.76); 69.6%; S-EDSS: 39.1% = 4; 21 (9.05) yrs.	70.6%; 41.81 (11.43); 94.1%; S-EDSS: 58.8% = 4; 16 (7.88) yrs.	Yes (CFS >4)	CFS (P) MFIS (P)	10	13%	27%	NA

11. Nazari et al. 2015^*****	IE	RCT	25	25	Relaxation	No intervention	NR any subtype defined in the inclusion criteria; 33.90 (5.60); 100%; NR; 5.18 (4.69) yrs.	NR any subtype defined in the inclusion criteria; 34.40 (7.70); 100%; NR; 4.78 (3.36) yrs.	Yes (FSS ≥ 4)	FSS (NR)	4	0	0	8
12. Pöttgen et al. 2018^	DE	RCT	139	136	CBT	No intervention	70.5 %; 40.80 (11.12); 82%; DS: 54% ≥ moderate; 8.91 (7.47) yrs.	75%; 41.90 (9.36); 79%; DS: 53% ≥ moderate; 9.19 (7.43) ys.	Yes (FSMC≥42)	CFS (P)	12	26%	11%	24 (not yet available)
13. Sgoifo et al (2017)^	I	RCT	24	24	Integrated Imaginative Distention Therapy (bio/neurofeedback training)	Waitlist (TAU)	83%; NR; NR; EDSS: 3·15 (1·97); 8·2 (7·3) yrs.	91%; NR; NR; EDSS: 3·44 (2·01); 10·5 (8·5) yrs.	No	MFIS (P)	8	4%	0%	NA
14. Thomas et al. 2013 / **2014^▲**	GB	RCT	84	80	CBT & EC	Current local practice / TAU	43%; 48.0 (10.2); 73%; APDDS: 78% ≥ 4; 40% 1 to 5 yrs.	51%; 50.1 (9.1); 73%; APDDS: 81% ≥ 4; 27% 1 to 5 yrs.	Yes (FSS >4)	GFS (P)	10	15%	6%	52
15. Van den Akker et al. 2017^*	NL	RCT	44	47	CBT	MS nurse consultations	72.7%; 50.6 (8.3); 70.5%; EDSS: 3.0 (2.8; 3.6); 8.2 (2.9-14.2) yrs.	74.5%; 46.4 (11.6); 83%; EDSS: 2.5 (2.3; 3.0); 5.2 (2.1-1.5) yrs.	Yes (CIS20r fatigue ≥35)	CIS20r fatigue (P)	16	7%	17%	36
16. van Kessel et al. 2008^	NZ	RCT	35	37	CBT	Relaxation (placebo intervention)	66%; 42.89 (9.92); 80%; EDSS: 3.04 (1.78); 5.54 (4.80) yrs.	49%; 47.03 (9.45); 70%; EDSS: 3.86 (1.53); 6.65 (5.91) yrs.	Yes (CFS ≥4)	CFS (P) WSAS (S)	8	2%	5%	24
17. van Kessel et al. 2015^	NZ	RCT	19	20	CBT	CBT without email support	79%; 42.95 (8.16); 58%; EDSS: 42% ≥ 4.5; 4.78 (4.36) yrs.	55%; 45.70 (8.39); 90%; EDSS: 50% ≥ 4.5; 5.12 (4.29) yrs.	Yes (CFS ≥ 4)	CFS (P) MFIS (P)	10	21%	55%	NA

Combined studies

1. Hugos et al. 2010^*	US	RCT	21	20	Fatigue: Take Control (EC & exercise)	Waitlist	NR; 55.41 (9.10); 87%; EDSS: 4.9 (1.2); 14.24 (7.04) yrs.	NR; 55.41 (9.10); 73%; EDSS: 5.5 (0.8); 15.54 (6.52) yrs.	No	MFIS (P) FSS (S)	8	25%	25%	13
2. Hugos et al. 2018 / 2019^*¤	US	RCT	109	109	Fatigue: Take Control (EC & exercise)	MS: Take Control (education)	61%; 53·9 (9·8); EDSS: 5.1 (1.1); 12·3 (7·6) yrs.	55%; 53·6 (10·5); EDSS: 5.3 (1.1); 12·7 (9·3) yrs.	Yes (MFIS ≥ 25)	MFIS (P)	6-10	9%	9.5%	24

3.	Nedelikovic et al. 2016^▲	RS	RCT	19	20	Methylpred. & Aerobic exercise & MDR	Methylpred. & TAU	100%; 41.7 (9.5); 63.2%; EDSS: 4.4 (1.3); 8 (3-13) yrs.	100%; 39.7 (10.5); 70%; EDSS: 4.2 (0.7); 5 (2-10.8) yrs.	No	FSS (NR)	4	13.6%	17%	12
4.	Rietberg et al. 2014^*▲	NL	RCT	23	25	Aerobic exercise & EC	Nurse consultation / TAU	70%; 45 (9.9); 61%; EDSS+: 3 (3); 7 (6.6) yrs.	48%; 47 (8.6); 68%; EDSS+: 4 (2); 8 (6.1) yrs.	Yes (according to MSCCPG definition)	CIS-20R (P) FSS (S) MFIS (S)	12	9%	8%	24
5.	Turner et al. 2016^▲	US	RCT	31	33	General (land-based) exercise & MI	Exercise DVD & booklet / TAU	70%; 53.6 (13.1); 42%; Mobility PF: 2.73 (1.35) 11.85 (10.41) yrs.	65%; 52.7 (11.6); 29%; Mobility PF: 2.35 (1.50) 11.33 (9.00) yrs.	Yes (MFIS ≥ 20)	MFIS (P)	6	3%	0	18
6.	Zalisova et al. 2011	CZ	RCT	9	9	Aerobic exercise & Relaxation	No intervention	NR; 36.6 (6.64); 6%; AI: 3.27 (1.71); 6.8 (6.19) yrs.	NR; 38.87 (6.98); 0%; AI: 3.5 (1.65); 17.1 (3.8) yrs.	Yes (self-report)	MFIS (NR)	6	0	0	NA

*Participants were excluded if they had major depression, or were under psychiatric treatment for depression, or had high levels of depressive symptomatology,

◊Participants with limited standing balance were included

▲ Participants with addiction problems were excluded

▼ Participants who had experienced severe stress during four weeks prior to recruitment were excluded**MS Subsample data provided by author.

¤Long-term follow-up (12 months) data provided for one site

^Included in the pairwise meta-analyses

+Median (range)

Abbreviations: AI (Ambulation Index); APDDS (Adapted Patient Determined Disease Steps); CCT (Controlled Clinical Trial); CIS-20R (Checklist Individual Strength Fatigue total score); Ctrl (Control group); DS (Disease Steps); EC (Energy Conservation); EE (Energy Effectiveness); EDSS (Expanded Disability Status Scale); Exp (Experimental group); GNDS (Guy's Neurological Disability Scale); MDR (multidisciplinary rehabilitation); Mobility PF (Mobility item of the Performance Scales); MSCCPG (The Multiple Sclerosis Council for Clinical Practice Guidelines); MSFC (MS-Functional Composite score); NR (Not reported); NA (not applicable to the study hypotheses); RCT (Randomised Controlled Trial); RMI (Rivermead Mobility Index); RR (Relapse-Remitting MS); S-EDSS (Self-report Expanded Disability Status Scale); TAU (Treatment as usual/standard care); WSAS (Work and Social Adjustment Scale).

Self-report Fatigue Scales:

1. CFS: Chronic Fatigue Scale
2. FIS: Fatigue Impact Scale
3. GFS: Global Fatigue Severity subscale of the Fatigue Assessment Inventory
4. FSMC: Fatigue Scale of Motor and Cognition
5. FSS: Fatigue Severity Scale
6. MFIS: Modified Fatigue Impact Scale
7. WSAS: Work and Social Adjustment Scale

Table 2. Descriptors of key physical fitness components for the exercise intervention subgroups

***Aerobic fitness.** Main fitness component in exercise in which the body's large muscles move in a rhythmic manner for a sustained period of time. Aerobic activity, also called endurance activity, improves cardiorespiratory fitness. Examples include walking, running, cycling and swimming
***Muscle strength/power.** Main physical fitness component in exercise aiming at increasing skeletal muscle strength, power, endurance, and mass (e.g. progressive resistance training (PRT) – fixed weights; PRT-free weights; resistance training; body-weight-resistance exercise)
***Flexibility.** Main fitness component in exercises aimed at increasing the range of motion possible at a joint. Flexibility is specific to each joint and depends on specific variables, including but not limited to the tightness of specific ligaments and tendons.
***Balance:** Main fitness component in static and dynamic exercises that are designed to improve individuals' ability to withstand challenges from postural sway or destabilizing stimuli caused by self-motion, the environment, or other objects.
General Exercise (aquatic and land-based). Exercise involving combination of two or more of the above components, no dominant fitness component focus provided.
Combined Exercise. Exercise explicitly aimed at more than one of the exercise components listed above, often using a progressive overload principle.

*Adapted from: United States. Dept. of Health and Human Services (2008) Physical activity guidelines for Americans: be active, healthy, and happy! US Government Printing Office pp61

Table 3. Descriptors of the key behavioural intervention types/ subgroups.

Energy Conservation:

Energy effectiveness strategies or Energy Conservation (EC) education is defined as the "the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home and leisure activities in all relevant environments" p.592, (Mathiowetz et al., 2005). Energy conservation strategies include analyzing and modifying activities to reduce energy expenditures; taking frequent rests; prioritizing activities; planning; delegating some activities, using the body efficiently, organising tools, materials and work area, using assistive technologies to conserve energy; adopting good posture; leading a healthy lifestyle (regular exercise, healthy diet and stress management, examining and modifying standards and priorities).

Cognitive Behaviour Therapy (CBT) for MS fatigue:

CBT is founded on the premise that physiological, cognitive (thinking), emotional, and behavioural responses influence one another in a reciprocal way within the context of the social environment, where change in any one of these responses may produce changes in others (Beck, 1991). The cognitive behavioral model of fatigue in MS proposes that primary disease factors trigger the initial symptom of fatigue in MS, but fatigue is perpetuated or worsened by environmental factors such as stress and how people react cognitively, emotionally, and physiologically to their fatigue (van Kessel et al., 2008). CBT for fatigue is based on guided discovery where individuals identify which perpetuating factors may be relevant to them and are provided techniques to alter or manage these behavioral, cognitive, emotional and external factors (van Kessel et al., 2008). Protocols vary but tend to include creating consistent activity routines (including sleep wake cycles), identifying and managing unhelpful thoughts in relation to fatigue and high personal expectations, reattributing non-MS symptoms to reduce somatic focus, managing stress, accessing social support, and relapse prevention.

Motivational Interviewing (MI) (only included in mixed exercise and behavioural interventions:

MI comprises "several techniques used by practitioners to evoke motivation and behaviour change in clients. A key feature of MI is that it comprises techniques that differ in function. Some MI techniques focus on *content* of the intervention, which reflect the information and knowledge provided to intervention recipients to promote behaviour change (e.g., exploration of pros and cons). MI also comprises [*relational*] techniques that reflect the interpersonal style of delivery in which the content-based techniques are presented by the practitioner to increase their effectiveness (Miller & Rollnick, 2013)." (p. 3) (Hardcastle et al., 2017).

Relaxation:

Relaxation techniques include "a number of practices such as progressive relaxation, guided imagery, biofeedback, self-hypnosis, and deep breathing exercises. The goal is similar in all: to produce the body's natural relaxation response, characterized by slower breathing, lower blood pressure, and a feeling of increased well-being" (NCCIH, accessed 2017)

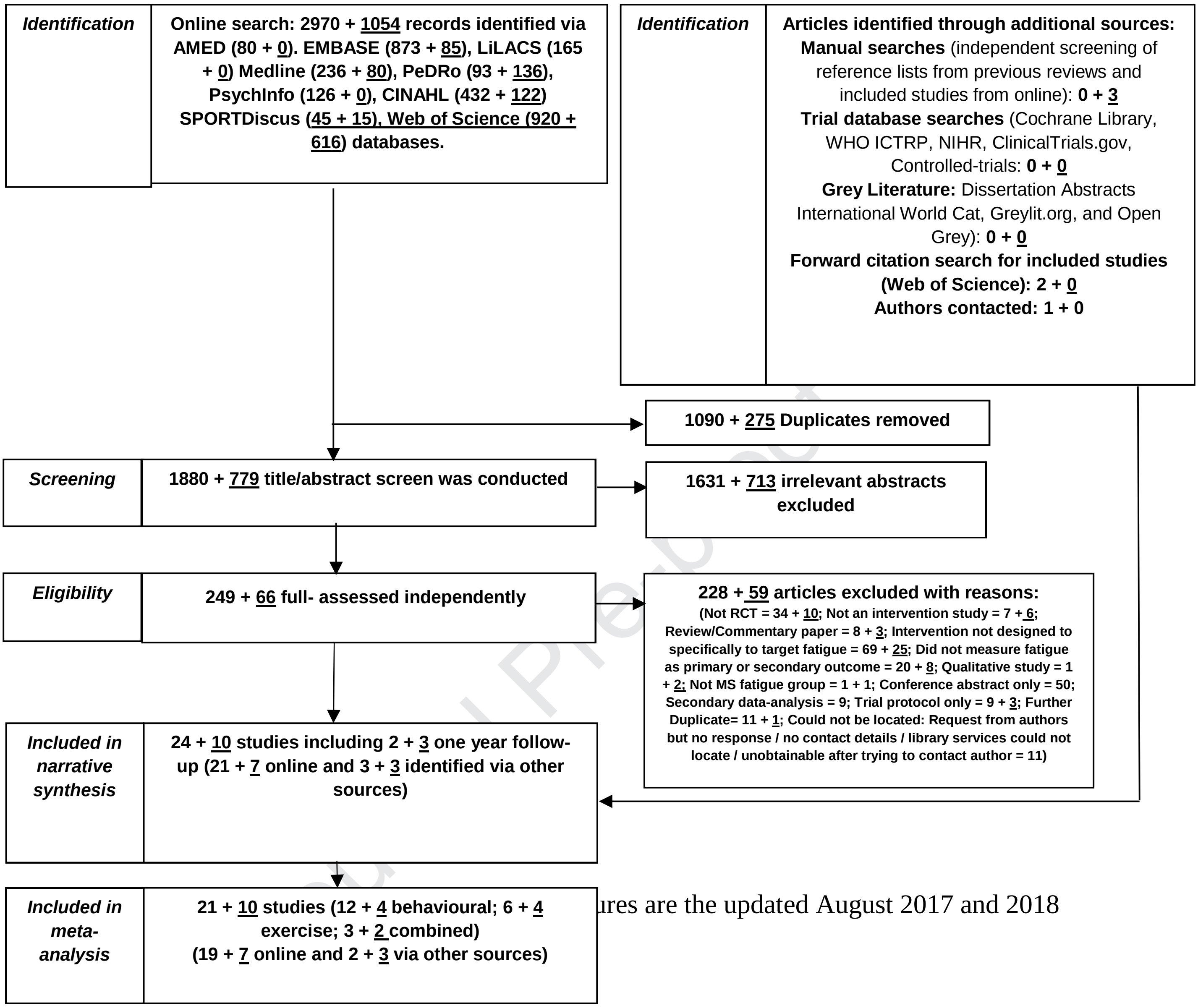
Table 4. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Assessment.

Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Intervention**			
Fatigue (Overall Exercise vs Control) FSS, MFIS and CIS-20R Follow-up: 2-16 weeks	No risk assumed	The mean fatigue (overall exercise) in the intervention groups was **0.75 standard deviations lower** (1.09 to 0.40 lower)	445 (9 studies[1])	⊕⊖⊖⊖ **very low**[2,3,4,5]	Limitation (-1) Inconsistency (-1) Imprecision (-1)
Fatigue (General, aquatic vs Control) FSS and MFIS Follow-up: 8-12 weeks	No risk assumed	The mean fatigue (general, aquatic) in the intervention groups was **0.74 standard deviations lower** (1.29 to 0.18 lower)	113 (4 studies)	⊕⊕⊖⊖ **low**[2,3,5]	Limitation (-1) Imprecision (-1)
Fatigue (General, land-based vs Control) FSS and MFIS Follow-up: 8-12 weeks	No risk assumed	The mean fatigue (General, land-based) in the intervention groups was **1.22 standard deviations lower** (2.94 lower to 0.50 higher)	50 (2 studies)	⊕⊖⊖⊖ **very low**[2,4,5,6]	Limitation (-1) Inconsistency (-1) Imprecision (-1)
Fatigue (Aerobic vs Control) MFIS, FSS and CIS-20R Follow-up: 2 - 16 weeks	No risk assumed	The mean fatigue (aerobic) in the intervention groups was **0.29 standard deviations lower** (0.69 lower to 0.12 higher)	139 (3 studies)	⊕⊕⊕⊖ **moderate**[5]	Imprecision (-1)
Fatigue (Balance vs Control) MFIS Follow-up: 6–14 weeks	No risk assumed	The mean fatigue (balance) in the intervention groups was **1.26 standard deviations lower** (1.69 to 0.84 lower)	95 (2 studies)	⊕⊕⊕⊖ **moderate**[5]	Imprecision (-1)
Fatigue (Overall Behaviour vs Control) MFIS, FSS, CFS, FIS, CIS-20R Follow-up: 4-16 weeks	No risk assumed	The mean fatigue (overall behaviour) in the intervention groups was **0.37 standard deviations lower** (0.53 to 0.22 lower)	1334 (16 studies)	⊕⊕⊕⊖ **moderate**[4]	Inconsistency (-1)
Fatigue (CBT vs Control) CFS, CIS-20R Follow-up: 8 - 16 weeks	No risk assumed	The mean fatigue (CBT) in the intervention groups was **0.66 standard deviations lower** (0.94 to 0.38 lower)	512 (5 studies)	⊕⊕⊕⊖ **moderate**[5,6]	Imprecision (-1)
Fatigue (EC vs Control) FSS, FIS, CIS-20R and MFIS Follow-up: 6 - 16 weeks	No risk assumed	The mean fatigue (EC) in the intervention groups was **0.20 standard deviations lower** (0.36 to 0.03 lower)	578 (8 studies)	⊕⊕⊕⊕ **high**	
Fatigue (Relaxation vs Control) FSS and MFIS Follow-up: 4 - 8 weeks	No risk assumed	The mean fatigue (Relaxation) in the intervention groups was **0.68 standard deviations lower** (1.09 to 0.27 lower)	98 (2 studies)	⊕⊕⊖⊖ **low**[2, 5]	Limitation (-1) Imprecision (-1)
Fatigue (Overall combined Behaviour & Exercise vs Control) MFIs, FSS and CIS-20R Follow-up: 6 - 12 weeks	No risk assumed	The mean fatigue (overall combined behaviour and exercise) in the intervention groups was **0.16 standard deviations lower** (0.36 to 0.04 higher)	380 (5 studies)	⊕⊕⊕⊖ **moderate**[5]	Imprecision (-1)
Fatigue (Combined EC & Aerobic vs Control) MFIs and CIS-20R Follow-up: 6 - 12 weeks	No risk assumed	The mean fatigue (EC and Aerobic) in the intervention groups was **0.15 standard deviations lower** (0.38 lower to 0.09 higher)	278 (3 studies)	⊕⊕⊕⊖ **moderate**[5]	Imprecision (-1)

*The argumentation for downgrading the grades of evidence is provided in the footnotes.
CBT: Cognitive Behaviour Therapy
CI: Confidence interval;
EC: Energy Conservation

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Twelve exercise interventions from nine studies
[2] Most information is from studies with inadequate allocation concealment or incomplete accounting for outcome data.
[3] Kargarfard (2010) was excluded from summary of finding and GRADE tables due to possible overestimation of the effect size..
[4] There is difference in magnitude of point estimates and CIs show minimal overlap.
[5] Total sample size is small.
[6] Total effect size has wide CIs.



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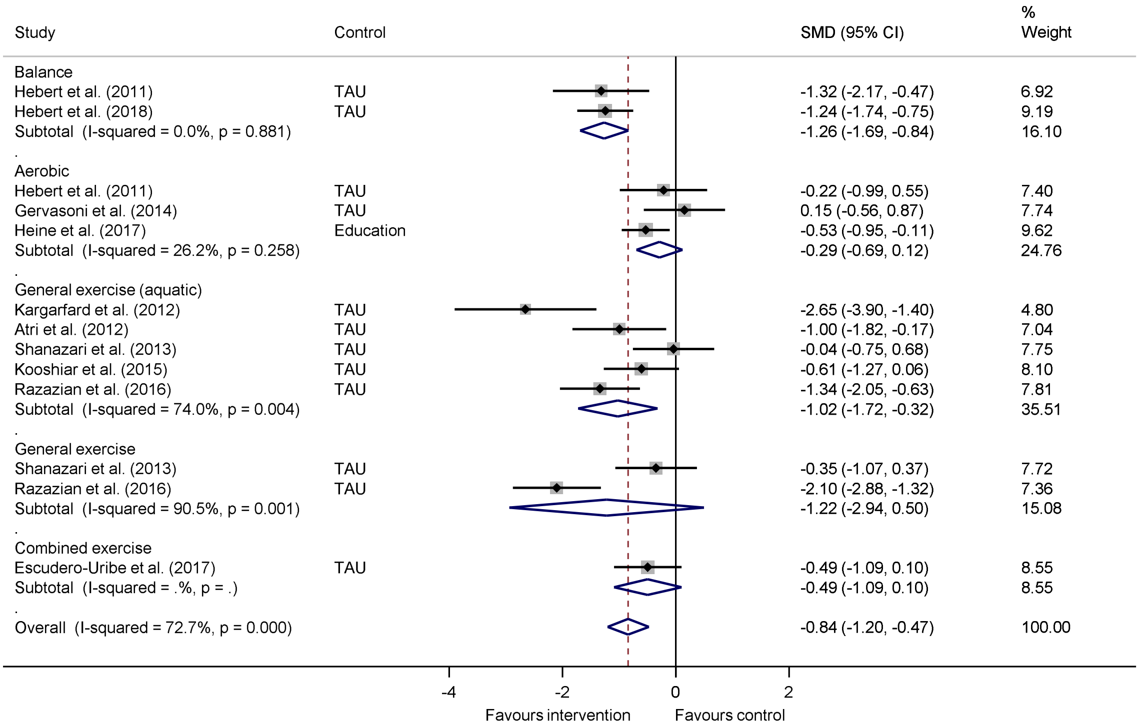

Figure 2a. End of treatment effects on self-reported fatigue for the exercise interventions, grouped by type.

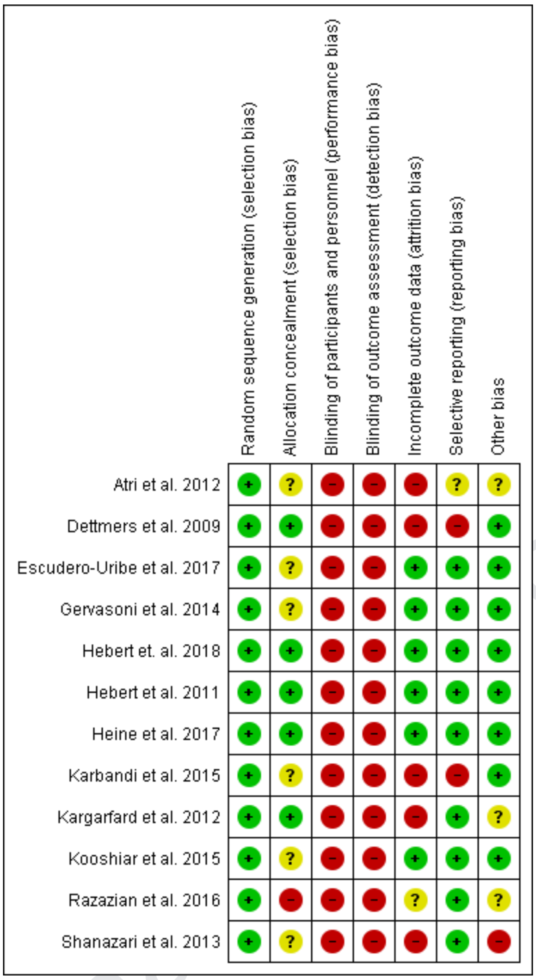

Figure 2b. Risk of Bias (RoB) for each of the exercise intervention studies.

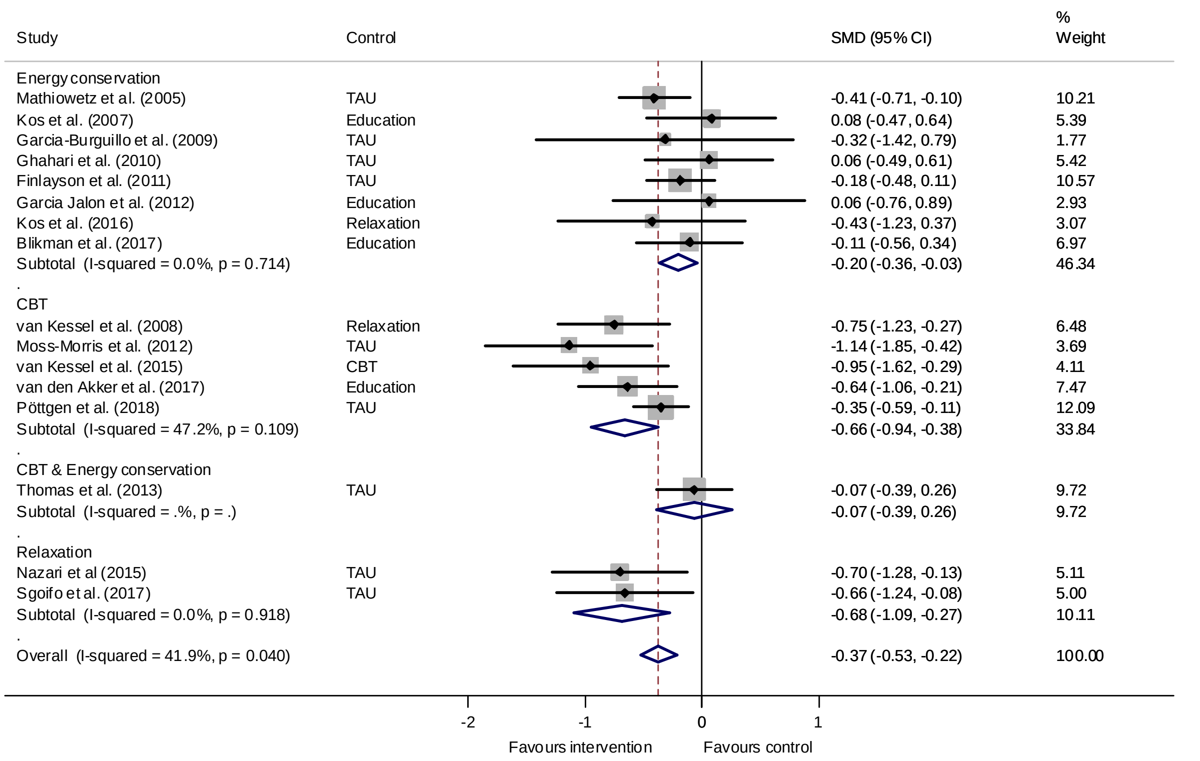

Figure 3a. End of treatment effects on self-reported fatigue for the behavioural interventions, grouped by type.

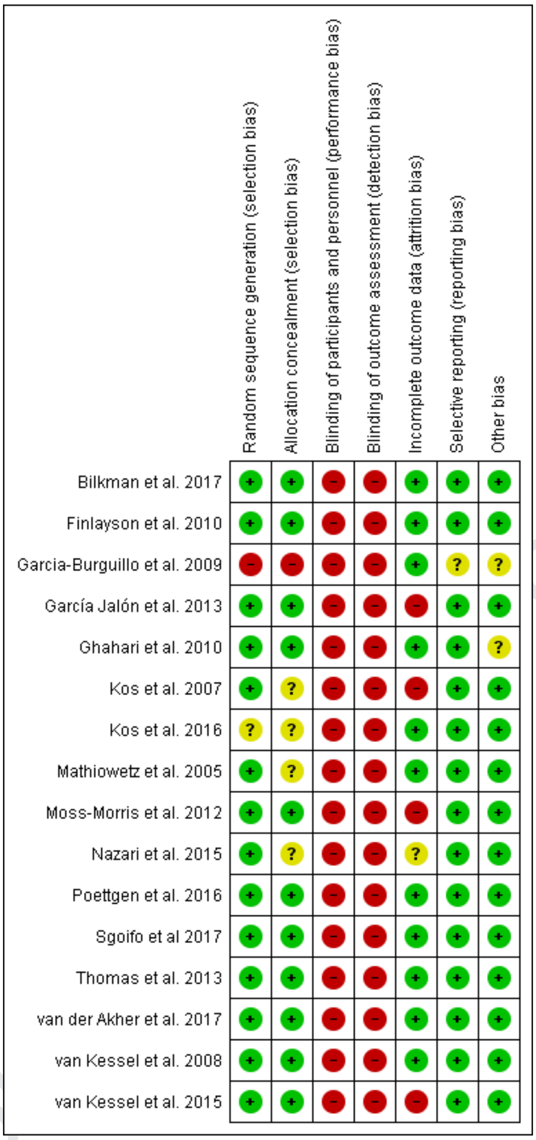

Figure 3b. Risk of Bias (RoB) for each of the behavioural intervention studies.

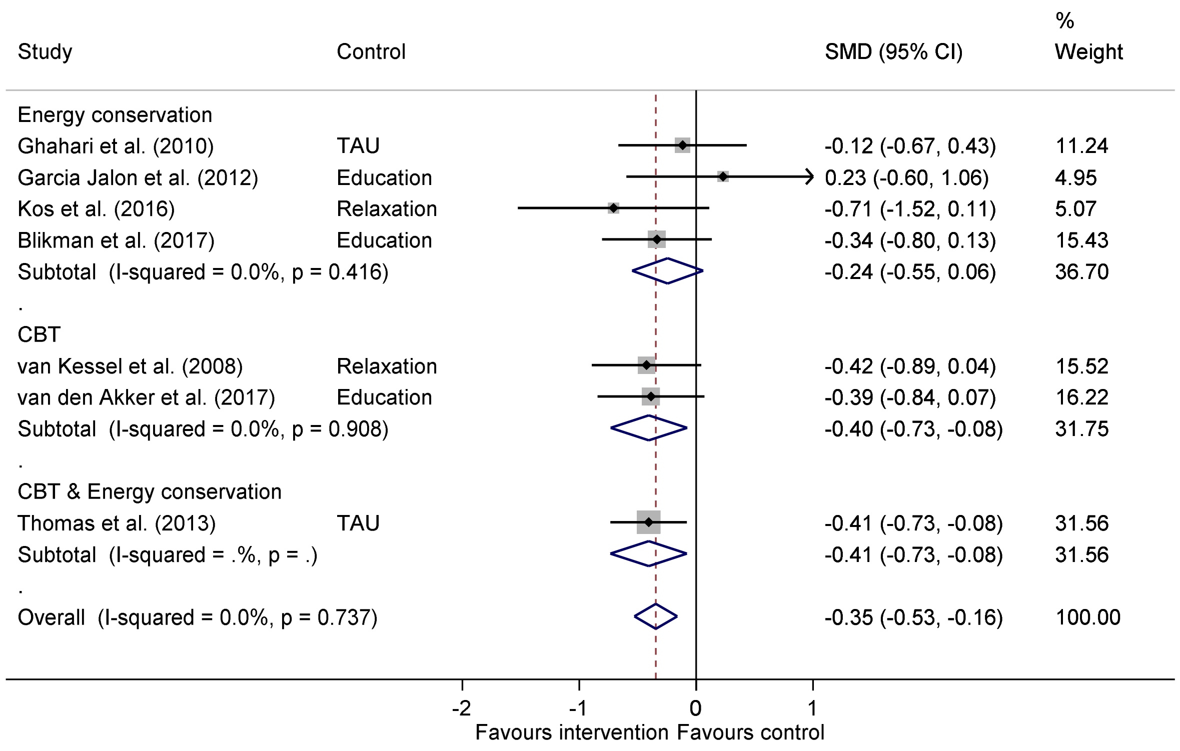

Figure 4. Longer term (3-6 months) treatment effects of behavioural interventions on self-reported fatigue, grouped by type.

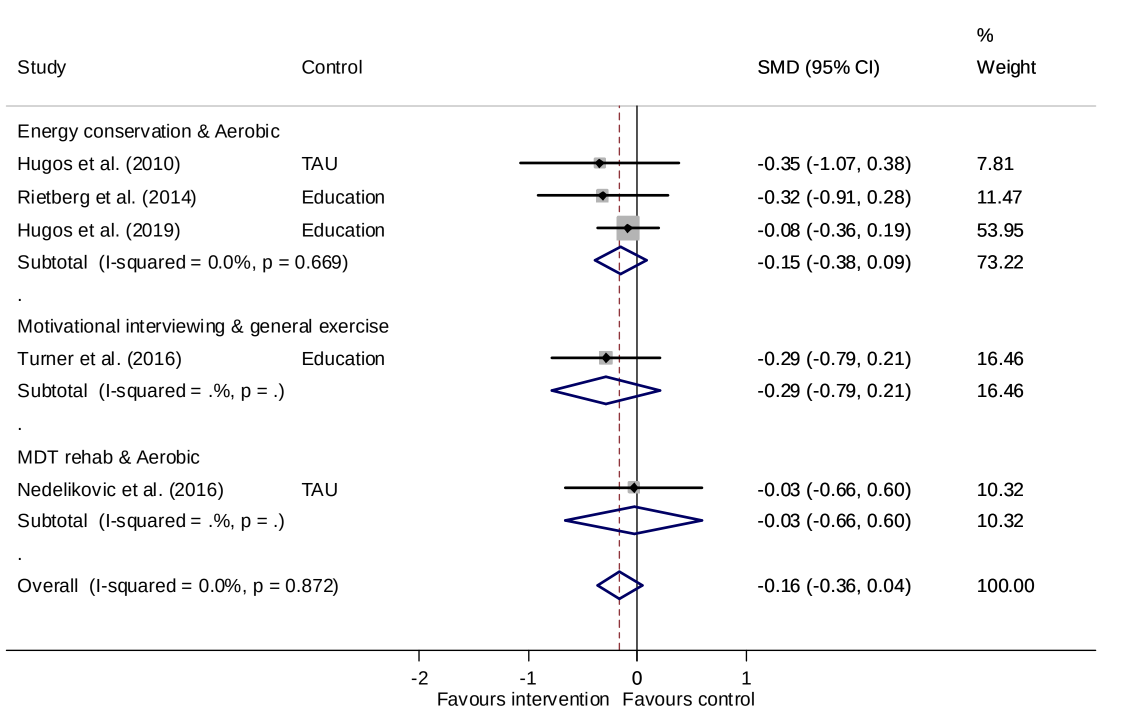

Figure 5a. End of treatment effects on self-reported fatigue of combined exercise and behavioural interventions, grouped by type.

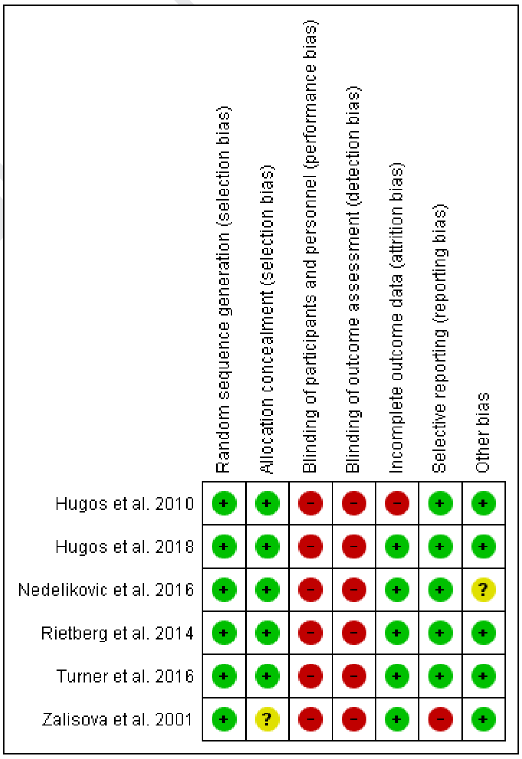

Figure 5b. Risk of Bias (RoB) for each of the combined intervention studies.

Highlights

- Exercise and behavioural interventions had moderate to large effects on MS fatigue
- The quality of evidence was moderate for behavioural but poor for exercise studies
- There was good quality evidence of non-significant effects of energy conservation
- Web-based CBT and balance interventions showed promise but require large trials
- Based on limited evidence, combined interventions did not show added benefits